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BIOLOGY

Mammalian Synthetic Biology: Foundation and Therapeutic Applications

Ron Weiss

Synthetic biology is revolutionizing how we conceptualize and approach the engineering of biological systems. Recent advances in the field are allowing us to expand beyond the construction and analysis of small gene networks towards the implementation of complex multicellular systems with a variety of applications. In this talk I will describe our integrated computational / experimental approach to engineering complex behavior in a variety of cells, with a focus on mammalian cells. In our research, we appropriate design principles from electrical engineering and other established fields. These principles include abstraction, standardization, modularity, and computer aided design. But we also spend considerable effort towards understanding what makes synthetic biology different from all other existing engineering disciplines and discovering new design and construction rules that are effective for this unique discipline. We will briefly describe the implementation of genetic circuits and modules with finely-tuned digital and analog behavior and the use of artificial cell-cell communication to coordinate the behavior of cell populations. The first system to be presented is a multi-input genetic circuit that can detect and destroy specific cancer cells based on the presence or absence of specific biomarkers in the cell. We will also discuss preliminary experimental results for obtaining precise spatiotemporal control over stem cell differentiation for tissue engineering applications. We present a novel approach for generating and then co-differentiating hiPSC-derived progenitors with a genetically engineered pulse of GATA-binding protein 6 (GATA6) expression. We initiate rapid emergence of all three germ layers as a combined function of GATA6 expression levels and tissue context. We ultimately obtain a complex tissue that recapitulates early developmental processes and exhibits a liver bud-like phenotype that includes haematopoietic and stromal cells, as well as a neuronal niche. This complex organoid can be used for drug development and potentially for tissue transplantation.

SREBPs in the control of intestinal homeostasis and tumorigenesis

Luke Engelking, Yanchao Xu, Min Ding, Shili Li, Jing Liu, Emily Richmond

Lipids are key regulators of the growth and differentiation of intestinal epithelial cells, including intestinal stem cells (ISC). High-fat diets and obesity are serious risk factors for gastrointestinal cancers in humans. Sterol regulatory element-binding proteins (SREBPs) are transcription factors that control lipid synthesis and uptake in the intestine. Our recent studies have shown that SREBPs and their major products, sterols (from SREBP-2) and unsaturated fatty acids (from SREBP-1) have a critical role in sustaining growth of the intestinal epithelia: (1) The loss of Scap, which controls intracellular cleavage events

required for SREBP activation, reduces lipid synthesis and causes a lethal intestinal injury in mice characterized by a loss of intestinal crypts, which house ISCs. (2) When SREBP-2 is inactivated in intestinal epithelium, hyperplasia of intestinal crypts and hypertrophy of the intestine results. In SREBP-2 knockouts, sterol synthesis falls while unsaturated fatty acid synthesis does not, owing to an increase in SREBP-1. (3) Despite this overgrowth phenotype, ablation of SREBP-2 in intestinal epithelia of mice blocks the formation of adenomas caused by mutant APC. These findings indicate that SREBPs govern intestinal epithelial homeostasis in complex ways. SREBPs maintain homeostasis of intestinal epithelia by producing specific, yet-to-be identified lipid metabolites that sustain the proliferation of ISCs. These pathways control intestinal organ size and malignant potential, which bears on human diseases of under- or over-proliferation of the intestine, such as short gut syndrome and colorectal cancer, the 3rd most common cause of cancer death in the U.S.

Towards a Periodic Table Equivalent for Animal Viruses

Jan Slingenberg

The world's main livestock viruses may be broadly grouped into three categories. Firstly, strictly epithelial viruses cause an acute, transient infection. Secondly, viruses colonizing also the internal organs cause both acute and persistent infections. Thirdly, strictly inner-body viruses cause persistent infections. When the individual viruses, 36 in total, are accordingly lined up the virus organ system tropism shifts from respiratory to alimentary tract, to skin, epithelia, including the distal urogenital tract, plus peripheral nerves & ganglia, the reproduction organs system, the immune plus circulatory systems, to just the blood circulation system. The horizontal transmission modes of the epithelial viruses gradually give way to the vertical modes of the internalized viruses. The virus distribution across the acute, outer- to persistent, inner-body continuum matches the host availability. Hence, the organ system bound virus transmission ecology may be applied to categorize viruses on ecological grounds.

Magnetic nano-pulling: A New Methodology for Exploring the Role of Force as a Messenger of Axonal Growth

Alessandro Falconieri, Sara De Vincentiis, Valentina Cappello, Domenica Convertino, Samuele Ghignoli, Sofia Figoli, Frederic Català-Castro, Laura Marchetti, Ugo Borello, Michael Krieg, Vittoria Raffa

The axon is the projection that emerges from the neural cell body and establishes synaptic contacts with its partner. In developing neurons, the growth cone is a fine sensor that integrates mechanical and chemical cues and transduces these signals through the generation of a traction force that pushes the tip and pulls the axon shaft forward. The axon shaft, in turn, senses this pulling force and transduces this signal in an orchestrated response, coordinating cytoskeleton remodeling and intercalated mass addition to sustain and support the advancing of the tip. Extensive research suggests that the direct application of active force is per se a powerful inducer of axon growth, potentially bypassing the contribution of the growth cone. This mechanism is generally referred to as "stretch growth". Unfortunately, the molecular mechanisms underlying the stretch growth process and how axonal growth is coupled in time and space to intercalated mass addition

are largely unknown. Recently, we have validated a nanotechnology-based biophysical tool to mechanically manipulate hippocampal neurons at the axon level. The technique is based on the magnetic labeling of the axons via magnetic nanoparticles (MNP) and the magnetic nano-pulling by the application of a magnetic field gradient. We focused our investigation at the axon level and we used Axon-Seq to segregate the local response from the somatic one. Our data support the idea that the force induces a local response consisting in axonal cytoskeleton remodeling, axonal transport modulation and local translation activation, which, in turn, transduces a cellular response consisting in axon outgrowth and synapse maturation. This knowledge could also have practical implications in terms of potential novel therapies for re-wiring the nervous system.

Biocompatible Cryopreservation of Blood, Corneas and Skin Grafts

Xu Han, Peter Koulen, Andrew Huang, Henry White

Cryopreservation is a slowly progressing field due in large part to limitations in understanding mechanisms associated with intracellular ice formation at nanoscale dimensions, plus a lack of efficient measures to control ice formation on a cellular scale. Practical cryostorage began in 1940's when it was serendipitously discovered that animal semen could be cryopreserved using glycerol-rich media [1]. Ever since that discovery, based on rationale of prevention of lethal intracellular ice formation by modifying intracellular components, all existing cryopreservation technologies for cells (except those rarely and solely used for red blood cells and a few cell types with unique biophysical features [2-4]) and tissues, as well as all existing products in the marketplace, have remained dependent on the use of various types and concentrations of biologically incompatible (i.e., cell permeating and reactive) small molecule cryoprotectants. Such cell permeating cryoprotectants generally include, but are not limited to, dimethyl sulfoxide (DMSO), glycerol, and ethylene glycol. However, inclusion of these small molecule reagents in cryopreservation media cause numerous technical, practical and regulatory issues. More importantly, numerous cell types and nearly all tissue types survive poorly from these traditional cryopreservation protocols, and that low survival rate is a long-existing unsolved issue in current biobanking practices, and until solved would definitely continue to impair the operation of numerous existing or emerging biomedical industries. With the support of National Institute of Health and Coulter Foundation, we recently discovered a novel mechanism of action that is based on the use of biocompatible polysaccharides to promote nano-scale cubic ice formation in extracellular solutions [5] and simultaneously prevent damaging intracellular ice formation without the need for cell permeating processes [6]. Based on this breakthrough discovery, CryoCrate developed a novel cryopreservation medium, trademarked as OdinSol[®], which no longer requires the inclusion of a cell permeating chemical for the cryoprotection of mammalian cells and tissues. The OdinSol[®] technology also allows for effective cryostorage in standard laboratory freezers at -80°C, thereby eliminating the need for expensive and hazardous liquid nitrogen facilities. We also demonstrated the efficacy of OdinSol[®] in significantly increasing post-thaw viability and function of various blood cell types and donor tissue types:

- For red blood cells, this technology successfully removes the need for high concentration (typically 30% v/v) of glycerol for storage in regular deep freezers and significantly simplifies the operation procedures by eliminating the time-consuming glycerization and deglycerization procedures.

- For T cells, CAR-T and NK cells, the OdinSol® technology significantly increases the post-thaw cytotoxicity by preventing the functionality damaging effects (e.g., the oxidative and osmotic stress) generated by the traditional use of DMSO for cryopreservation.
- For corneal limbal tissues, the OdinSol® technology enables eye banks to efficiently cryostorage limbal tissues to facilitate limbal stem cell transplantation. And we are working the local Organ Procurement Organization to establish the first limbal tissue bank in the US.
- For human skin graft, the OdinSol® technology removes the need for the high concentration of glycerol and complicated cooling procedures for these large tissues, and more importantly, enhances the post-thaw tissue mechanical properties by improving tight junction of keratinocytes and reduces cell apoptosis.

We are now extending the applications of this novel platform technology in cryopreservation of bioartificial tissues and xenogeneic tissues to pave a path to the future industrialization of regenerative medicine and xenotransplantation technologies.

Reverse Epitomics: A Novel Approach with Applications to Design Vaccines And Diagnostic Kits

Sukrit Srivastava, Michael Kolbe

Coronaviruses are causative agents of different zoonosis including SARS, MERS, or COVID-19. The high transmission rate of coronaviruses, the time-consuming development of efficient anti-infectives and vaccines, the quick evolutionary adaptation of the virus to conventional vaccines are the major reasons that made it challenging to avoid coronaviruses outbreaks. Although, a plethora of different approaches are being followed to design and develop vaccines against coronaviruses, most of them target subunits, full-length single, or only a very limited number of proteins. A vaccine targeting multiple proteins or even the entire proteome of the coronavirus is yet to come.

In the present talk, we propose and discuss the novel “reverse epitomics” approach to identify ‘Antigenic Patch’ (Ag-Patch) from the entire proteome of SARS-CoV-2 and their further utilization in diagnostic kits and Multi-Patch Vaccines (MPV). The ‘Ag-Patch’ based diagnostics and MPV utilize highly conserved and potentially immunogenic stretches of SARS-CoV-2 proteins. The utilized Ag-Patch arise from a large number of coronavirus proteins, covering these proteins as immunogenic targets, thus enhance the neutralization potential of the Ag-Patch based diagnostics and MPVs. Taken together, we propose here a reverse epitomics approach for diagnostics and vaccine to combat SARS-CoV-2 and its frequent evolutionary adaptation.

Key words: Coronavirus, SARS-CoV-2, COVID-19, Epitopes, Ag-Patch (Antigenic Patch), Reverse epitomics, Multi-Patch vaccine

Host and bacterial biomarkers to predict bacteraemia

Thomas S Wilkinson

Bloodstream infections cause significant mortality across the World. Extra-intestinal pathogenic *Escherichia coli* (ExPEC) are an important cause of bloodstream infections. There are numerous reasons why ExPEC are such successful bloodstream pathogens, which

include i) presence as a resident member of the gut microbiota; ii) expression of important virulence factors; iii) expression of multiple genes associated with antimicrobial resistance (AMR); iv) strategies to evade and resist the host immune system. Significant correlations exist between the time to antimicrobial therapy and death. This work aimed to identify novel biomarkers associated with host and pathogen that predict bacteraemia.

Blood culture positive *E. coli* isolates (~150) with clinically defined origin of infection (e.g urinary, gut, biliary) were collected and archived. DNA was isolated for next generation sequencing and bioinformatic analysis and the bacterial strains were assessed for their ability to generate immune responses in infection models using human whole blood and THP-1 monocytes. Ethics applications allowed the access of medical records to identify risk factors.

Bioinformatic pipelines confirmed the diversity of *E. coli* isolates in the collection, confirmed their ExPEC nature and identified numerous isolates from ST131. Isolates had numerous AMR genes and phenotypic resistance profiles. *Ex vivo* virulence, assessed in healthy volunteer whole blood, confirmed serum resistance in a subgroup of isolates that could be associated with increased inflammatory cytokine output. Genome wide association mapping also confirmed association between some *E. coli* genes and origin of infection, serum resistance and cytokine output.

These results are important because they implicate new genes in the pathogenesis of ExPEC infection and suggest future targets to predict bacteraemia and sepsis. Early detection of *E. coli* genes by simple PCR strategies may be a cost-effective way to further improve the clinical toolkit to predict future risk form ExPEC infections.

High-Throughput Selection of Aptamers for Medical Applications

Alissa Drees

Aptamers are synthetically produced, single-stranded nucleic acid oligomers that form defined three-dimensional structures through intramolecular interactions and thus can bind target molecules. These oligomers, which consist of up to 100 nucleotides, are comparable to antibodies in terms of affinity and specificity, as well as in terms of their potential applications in bioanalysis, and in some cases can even be considered as more effective.

Aptamers offer many advantages over antibodies and are suitable as receptors in detection systems or also for therapeutic purposes. There are a number of issues in medicine where inhibition of protein/protein or other interactions would be of therapeutic benefit. However, conventional selection of aptamers by Systematic Evolution of Ligands by Exponential Enrichment (SELEX) is laborious and has a low success rate, which significantly limited the application of aptamers so far. The High-Throughput Sequencing-Fluorescent Ligand Interaction Profiling (HiTS-FLIP) experiment has the potential to change this. This strategy is the first to enable both high-throughput screening and quantitative measurement of the affinity of DNA-protein interactions, and therefore represents a promising method for selecting high-affinity and specific aptamers.

BIOMARKERS

Mechanical Biomarkers of Medial Compartment Knee Osteoarthritis Diagnosis and Severity

Grading: Discovery Phase

Neila Mezghani

Objectives: The aim of this study is to investigate, as a discovery phase, the use of machine learning and 3D knee kinematics assessment parameters as mechanical biomarkers. More specifically their efficiency such a diagnostic biomarker and burden of disease biomarkers, as defined in the Burden of Disease, Investigative, Prognostic, Efficacy of Intervention and Diagnostic classification scheme for osteoarthritis (OA) (Altman et al., 1986). These biomarkers consist of a set of biomechanical parameters discerned from 3D knee kinematic patterns, namely, flexion/extension, abduction/adduction, and tibial internal/external rotation measurements, during gait recording.

Methods: 100 medial compartment knee OA patients and 40 asymptomatic control subjects participated in this study. OA patients were categorized according to disease severity, by the Kellgren and Lawrence grading system. The proposed biomarkers were identified by incremental parameter selection in a regression tree of cross-sectional data. Biomarker effectiveness was evaluated by receiver operating characteristic curve analysis, namely, the area under the curve (AUC), sensitivity and specificity.

Results: Diagnostic biomarkers were defined by a set of 3 abduction/adduction kinematics parameters. The performance of these biomarkers reached 85% for the AUC, 80% for sensitivity and 90% for specificity; the likelihood ratio was 8%. Burden of disease biomarkers were defined by a 3-decision tree, with sets of kinematics parameters selected from all 3 movement planes.

Conclusion: The results demonstrate that machine learning method identified efficiently a set of 3D knee kinematic parameters that have the potential to serve as diagnostic and burden of disease biomarkers of medial compartment knee OA.

Identification of Biomarkers for Glaucomatous Blindness Prevention. Where do we Come from and Where are We Going?

Zanon-Moreno Vicente

Glaucoma is one of the leading causes of blindness worldwide. Primary open angle glaucoma (POAG) is the most common of all types of glaucoma, accounting for 60-70% of all cases. It is a degenerative eye disease characterized by high intraocular pressure, a progressive loss of optic nerve fibers and a decrease in the visual field. The cause of POAG is not known. Vision loss is progressive and, if not stopped, causes irreversible blindness. Early diagnosis is essential for the prevention of blindness caused by this disease. To do this, research is focused on the search for new biomarkers, which are physiological, biochemical or molecular alterations that can be measured and are associated with a particular state, whether normal or pathological. There are different biological samples that can be used for the identification of biomarkers for the diagnosis or prognosis of glaucoma. However, not all are equally useful. Classically, aqueous humor (AH) was used for this type of study. And, although it is a fluid that provides a lot of information, it is not valid for this purpose of identifying biomarkers, mainly due to the method used to obtain this fluid. Different molecules have been studied in AH as potential POAG biomarkers: oxidative stress markers, apoptotic molecules, cytokines... None of these biomarkers has been validated nor can be used today in the clinic to diagnosis. And some of them will hardly be used for this purpose, such as oxidative stress markers, for example. Another biological sample that we can use is the trabecular meshwork, especially useful for studying DNA methylation since methylation is tissue-dependent. However, these samples cannot be obtained from all people, but only from those who have glaucoma and are going to

undergo trabeculectomy surgery. Therefore, they are also not useful for the identification of biomarkers. Human tears are recently being used for researchers, a sample that is very easy to obtain and suitable for biomarker identification. In these studies, metabolites, microRNAs and other molecules have been identified as potential biomarkers for glaucoma. For example, our research group has identified 8 miRNAs that could be used for the diagnosis of POAG. These are very promising results and, without a doubt, they will help to prevent glaucomatous blindness. Nevertheless, it is necessary to continue the research and validate the results.

Is reduced expression of the lncRNA NRON a potential hallmark of the CMV-amplified CD8+ T cell accumulations commonly seen in older humans ?

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Subclinical cytomegalovirus (CMV) seropositivity is very prevalent in general humans. Its subclinical repetitive activation in bone marrow had ongoing accumulated clonal explosions of late-stage differentiated CD8+ T cells lifelong. Therefore, it is commonly seen CMV-amplified CD8+ T cell in older humans. However, it is challenging to screen for subclinical biomarkers of T cell immune aging in the elderly. Here we systematically identified differentially expressed long noncoding RNAs (lncRNAs) as potential biomarkers in CD28^{null}CD8+ T cell in 14 elderly CMV carriers over 80 years of age. By overtaking CD28 as immunosenescence biomarker of CD8+ T cells, we sorted the CD28^{null}CD8+ T cell subset and its CD28^{bearing}CD8+ counterpart in five nonagenarians. We profiled the differential expression of lncRNAs and genes in CD28^{null}CD8+ T cells via array detection. We focused on 11 differentially expressed antisense lncRNAs and cross-referenced them with previously identified age-accumulated lncRNAs to create a set of candidates in CD28^{null}CD8+ T cells. We performed intracellular validation on the age-accumulated candidate lncRNAs paired with their antisense target genes using quantitative polymerase chain reaction (qPCR). Simultaneously, we sorted the CMV_{pp65-specific} CD8+ T cell subset and its counterpart from participant cells with the HLA-A-*0201 genotype. The validated age-accumulated lncRNAs in CD28^{null}CD8+ T cells were intracellularly cross-validated in CMV_{pp65}CD8+ T cells. Finally, we identified the immunity-related gene(s) that acted as potential target(s) to the cross-validated age-accumulated lncRNA(s), using bioinformatics techniques. The potential regulation of the final identified lncRNA-gene pair(s) was simultaneously predicted in two pathway-integrated networks. Using such stepwise analysis, we revealed that expression of lncRNA (NRON) was decreased, whereas that of its immunity-related target gene (NFAT) was increased, in both CD28^{null}CD8+ T cells and CMV_{pp65}CD8+ T cells of elderly individuals harboring CMV seropositivity. We supposed that NRON might be a potential biomarker contributing substantially to CMV-enhanced CD28^{null}CD8+ T cell aging by modulating phosphorylation and/or IL-4-dependent NFAT signaling.

CARDIOLOGY

Genetic Variants in Calcium Calmodulin Pathway in Association with Cardiovascular Disease: Focus on the Potential Role of Camkk1 in Heart and Vessels

Sofia Beghi

Cardiovascular disease (CVD) is the leading cause of death all over the world and it affects an increasing number of people annually. Numerous risk factors are involved in the etiology of this complex disease. In addition to an unhealthy lifestyle, environmental factors, and other comorbidities, genetics also plays a role. The study of genetic variants associated with CVD is one of the main areas of interest nowadays. This is because it can aid in the identification of genetic biomarkers for prevention, prediction and treatment of patients affected by CVD.

Regulation of calcium signalling through calmodulin (CaM) is a key pathway involved in the physiology and molecular biology of the heart. CaM binds calcium and regulates calcium, playing a crucial role in several processes, such as cellular excitation-contraction coupling.

Research has shown that genetic variants, such as polymorphisms, can be factors predisposing to complex diseases. Thus, I hypothesized that studying and characterizing polymorphisms in the components of the CaM pathway could unravel how genetic traits influence CVD predispositions. In this thesis I focused on polymorphisms in 3 isoforms of CaM (CaM1, 2, 3) and proteins involved in its signalling, NOS (nitric oxide synthases) and CaMKs (calcium/calmodulin dependent protein kinases), in CVD. The analysis of the polymorphisms was performed on a cohort of 300 cardiopathic patients; a blood sample was collected and spotted on FTA cards. DNA was isolated and RLFP-PCR was performed in order to analyse the single nucleotide polymorphisms (SNP) of interest. The comparison of the genetic and allelic frequencies between the group of interest and the European reference group, used as control, showed interesting results in increasing the risk to develop a specific CVD, specifically for the SNP rs1549758, rs61202009 in NOS3 and mainly for the SNP rs7214723 in CaMKK1. The significant and interesting results of this last SNP in the cardiopathic Italian population, I analysed it also in a dutch cohort population and carried out an in-depth study of the role of CaMKK1 (calcium calmodulin-dependent protein kinase kinase I) in the heart and blood vessels, through in vitro studies on human vascular smooth muscle cells. In this in vitro experiment I found that CaMKK1 is a novel regulator of phenotypic switching of hVSMC towards synthetic VSMCs, thereby providing CaMKK1 as a new therapeutic target to reduce vascular remodeling, as well as a new potential genetic biomarker in the contest of cardiovascular diseases.

Aspirin use to decrease the risk of sudden cardiac death during marathons**Arthur J. Siegel**

Regular physical exercise is cardioprotective, reducing the life-time risk of sudden cardiac death in a dose-dependent relationship. The evidence is in, however, that "exercise is known to acutely, albeit transiently, increase the relative risk for sudden cardiac death and acute myocardial infarction" (1). An increasing frequency of sudden cardiac deaths have been occurring since 2000 in middle-aged males during recreational endurance sports including marathons and triathlons. As evidence-based in a randomized controlled prospective study to reduce first heart attacks by 44% in middle-aged men (2), low-dose aspirin use is prudent to minimize the risk for exertional cardiac events in same-aged males (3-8).

Clinical Significance:

- Endurance exercise has been associated with a greater density of calcium in the coronary arteries. Calcium scores over 100 A units independently confer a greater than 7.5% 10-year risk of acute cardiac events.
- Inflammation due to exertional rhabdomyolysis in asymptomatic marathon runners elevates C-reactive protein levels, which independently predict greater risk for cardiac events.
- Low-dose aspirin is evidence-based to reduce first heart attacks in middle-aged men by 44% in a randomized prospective primary prevention trial.
- Aspirin use is a Class 1A recommendation for pre-hospital administration in cases of acute coronary syndrome. Pre-race use is pre-emptive and prudent to protect susceptible athletes (*) from exertional cardiac arrest due to exercise-induced activation of atherothrombosis. (*) Coronary calcium scores > 100 A units and/or elevated C-reactive protein levels.

End tidal CO₂ and cerebral oximetry for the prediction of return of spontaneous circulation during cardiopulmonary resuscitation

Brian O'Neil

Background: Current guidelines for the treatment of cardiac arrest suggest that the infusion of medications and fluids directly into the circulation of cardiac arrest victims may improve the likelihood of return of spontaneous circulation (ROSC), survival to hospital discharge, favorable neurological outcomes, and other important clinical outcomes. Consequently, increased awareness of the utility of various methods for emergent vascular access in the setting of cardiac arrest may help to enhance providers' ability to care for these patients. Various routes for the infusion of resuscitative medications and fluids exist for cardiac arrest patients, including direct peripheral intravenous access, central venous access, and intraosseous access. Each technique for accessing the central circulation has its own advantages and disadvantages, which should be considered when planning a strategy for emergent vascular access in this population.

Specific Aims for the Session: Upon completion of this session, learners will have an increased understanding of:

- The various routes for emergent vascular access available to providers in the treatment of cardiac arrest
- Factors to be considered in determining the optimal vascular access technique for cardiac arrest patients
- The relative advantages and disadvantages of each technique for emergent vascular access
- Existing evidence on the importance of immediate vascular access, including areas of controversy and inadequate data as it relates to important clinical outcomes for cardiac arrest patients

Endoplasmic Reticulum Stress, Inflammation, Oxidative Stress And Neutrophil Extracellular Traps In Cardiovascular Diseases

Chiara Mozzini

The talk is intended primarily to summarize the understanding of the interrelated roles of endoplasmic reticulum (ER) stress, oxidative stress and inflammation in cardiovascular diseases. Insults interfering with ER function lead to the accumulation of unfolded and

misfolded proteins in the ER. An excess of proteins folding in the ER is known as ER stress. This condition initiates the unfolded protein response (UPR). When the UPR fails to control the level of unfolded and misfolded proteins, ER-initiated apoptotic signalling is induced. Moreover, the role of the protective nuclear erythroid-related factor 2 (Nrf2)/antioxidant-related element (ARE) and the activation of the pro-inflammatory nuclear factor-kappa B (NF- κ B) are analysed. Oxidative stress, inflammation and ER stress are closely entwined phenomena. They are involved in the pathogenesis of different cardiovascular diseases. Current literature data are presented, focusing on three topics of related pathologies: atherosclerotic plaque, coronary artery disease and diabetes. This talk will provide a basic platform for study and application to several other conditions in which oxidative stress, ER stress and inflammation are key features. Future studies in this area may identify the most promising molecules to be investigated as common targets for cardiovascular diseases.

Optimizing emergent vascular access for the treatment of cardiac arrest

James H. Paxton, MD MBA FACEP FAHA

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Hyperbaric Oxygen: A Potential Target for Cerebral Edema After CPR

Qiang Sun, Yuxin Yin, Qing Sun

Cardiac arrest (CA) is a common sense of death and disability around the world. Although wide spread education on cardiopulmonary resuscitation (CPR) and high availability of automated external defibrillators have improved survival following CA, the neurologic injury caused by CA remains an enormous source of morbidity. As a result, cerebral edema, which is a cardinal feature of brain injury as well as a powerful prognosticator of neurologic

outcome, became an appropriate therapeutic target for neuro-protection in patients who survived CPR.

There exist many newest progresses towards treating edema. Hyperbaric oxygen therapy (HBOT) is one of the candidates, which has long been used clinically for neuro-protective purposes by reducing cerebral edema on both animals and human beings. Roland et al has proved that intra-ischemic HBOT reduced early and delayed postischemic blood-brain barriers (BBB) damage and edema after focal ischemia in rats and mice. And in 2022, Wu et al has also published an article concerning that HBOT could reduce brain and pulmonary edema and cognitive deficits in rats. On a molecular level, HBOT could lead to an activation of ion channels, inhibition of hypoxia inducible factor-1 α , up-regulation of Bcl-2, inhibition of MMP-9, decreased cyclooxygenase-2 activity, decreased myeloperoxidase activity, up-regulation of superoxide dismutase and inhibition of Nogo-A. Therefore, an early induction of HBOT on clinical management of neurologic injury after CPR/CA is essential to promote the growth of neurons, protection of BBB integrity and inhibition of a cascade inflammation after the initial ischemic stroke. We herein propose the critical care society to conduct more scientifically-designed, double blind, placebo-controlled trials to prove the significance of HBOT in deducing cerebral edema after CA, therefore bettering the outcome of the surviving patients after CA/CPR.

Keywords: HBOT; hyperbaric oxygen; edema; CPR; cardiac arrest

Cardio-Rheumatology: A Journey from Myositis to Myocarditis

Risheen Reejhsinghani, MD, FACC

Cardio-Rheumatology is an emerging sub-specialty, focused on cardiac diseases among patients with underlying rheumatologic conditions including rheumatoid arthritis (RA), systemic lupus erythematosus, scleroderma, and ankylosing spondylitis, and several others. By developing a cardio-rheumatology program at our institution, we have gained clinical experience in utilizing evidence-based diagnostic and therapeutic interventions to manage the cardiac manifestations of autoimmune disease. Our program is built upon multidisciplinary collaboration with our rheumatology and immunology colleagues, to manage this often-complex population of patients.

Clinical challenges in the cardio-rheumatology arena include diagnostic cognizance of cardiac involvement in autoimmune disease, recognizing the effects of systemic inflammation on cardiovascular risk, and early detection of patients at highest risk for cardiovascular complications. For instance, the cardiovascular risk in RA approaches that of diabetes mellitus, yet patients with RA are often not treated with the same aggressive cardiac risk-reduction measures as patients with diabetes would be. Additionally, understanding the role of immunomodulator therapy in this population, and developing targeted preventive strategies are of key importance while managing cardio-rheumatology patients.

Through this talk, we first aim to describe the cardiac manifestations of common rheumatologic/autoimmune diseases from a clinico-pathologic and diagnostic standpoint. We will then review the current literature and guidelines for cardiovascular disease management and screening recommendations among the rheumatology patient population. Finally, we explore clinical, research, and educational strategies to develop cardio-rheumatology into a collaborative, multi-disciplinary sub-specialty, relying on expertise from both cardiologists and rheumatologists.

Dynamic Conduit Function and Systems Integration in the Microcirculation

Arif Somani, MD.

The microcirculation is an active conduit for red cell transport, nutrient and gas exchange, and contributes to the multiple processes involved in the maintenance of metabolic homeostasis and optimal end-organ function. It's angio-architecture and surface properties influence conduit function and flow dynamics influencing resistance and vascular tone over a range of pathological and organ-specific scenarios. This overview will provide a description of these varied and intricate functions of the microvasculature in relation to contributions of the endothelium, Nitric oxide pathways, adhesion molecule expression, red cell rheology, and balanced systems integration.

Diagnostic Performance of Cardiac Magnetic Resonance Imaging and Echocardiography in Evaluation of Cardiac and Paracardiac Masses

Barbara Srichai Parsia

Cardiac masses are rare, often incidental findings on cardiovascular imaging studies performed for other indications. Echocardiography is the preferred initial imaging method for assessment of cardiac masses. Cardiac magnetic resonance (CMR) imaging, with its excellent tissue characterization and wide field of view, provides additional unique information important for patient management. Specific echocardiographic and CMR characteristics provide predictive value in distinguishing tumor versus nontumor and malignant versus nonmalignant lesions. Both modalities demonstrate high diagnostic accuracy in diagnosis of non-neoplastic and benign tumors, approximately 70-80%. Parameters associated with tumor include location outside the right atrium, T2 hyperintensity, and contrast enhancement. Parameters associated with malignant tumors include location outside the cardiac chambers, nonmobility, associated pericardial effusion, myocardial invasion and contrast enhancement. CMR more commonly identifies masses missed on echocardiography, particularly paracardiac masses, and provides significantly more correct histopathologic diagnoses compared to echocardiography, particularly for malignant tumors although accuracy is limited, reported in the 60-70% range. Pathology remains the gold standard in accurately determining the histopathologic diagnosis. CMR offers the advantage over echocardiography of identifying paracardiac masses and providing crucial information on histopathology of cardiac masses.

The "Down-under" repair for ischaemic mitral regurgitation

Michael Yii MS, FRCS (Eng), FRACS (CTS)

There remain a divergent of opinions on the surgical management of ischaemic mitral regurgitation (IMR). Underpinning this area of controversy is the inability to accurately quantify the mitral regurgitation and the broad grouping of IMR into a single homogenous entity, rendering direct comparison of treatment strategy and outcome challenging.

We present the "down-under" repair for IMR. Adherence to this principle results in effective and durable mitral valve repairs associated with significant tethering of the mitral valve leaflets.

Optimizing Emergent Vascular Access for The Treatment of Cardiac Arrest

James H. Paxton, MD MBA FACEP FAHA

Background: Current guidelines for the treatment of cardiac arrest suggest that the infusion of medications and fluids directly into the circulation of cardiac arrest victims may improve the likelihood of return of spontaneous circulation (ROSC), survival to hospital discharge, favorable neurological outcomes, and other important clinical outcomes. Consequently, increased awareness of the utility of various methods for emergent vascular access in the setting of cardiac arrest may help to enhance providers' ability to care for these patients. Various routes for the infusion of resuscitative medications and fluids exist for cardiac arrest patients, including direct peripheral intravenous access, central venous access, and intraosseous access. Each technique for accessing the central circulation has its own advantages and disadvantages, which should be considered when planning a strategy for emergent vascular access in this population.

Specific Aims for the Session: Upon completion of this session, learners will have an increased understanding of:

- The various routes for emergent vascular access available to providers in the treatment of cardiac arrest
- Factors to be considered in determining the optimal vascular access technique for cardiac arrest patients
- The relative advantages and disadvantages of each technique for emergent vascular access
- Existing evidence on the importance of immediate vascular access, including areas of controversy and inadequate data as it relates to important clinical outcomes for cardiac arrest patients

Clinical Evaluation of Anomalous Aortic Origin of a Coronary Artery

Hitesh Agrawal, MD, MBA

Anomalous aortic origin of a coronary artery (AAOCA) is a congenital abnormality of the origin or course of a coronary artery that arises from the aorta. This is the second leading cause of sudden death in young athletes in the US. Diagnosis of AAOCA presents significant complexity in clinical decision making. Clinical symptoms may not be present consistently and do not usually correlate with anatomic findings. Sudden cardiac death can be the first manifestation of this disease. There is limited consensus on the evaluation and management of AAOCA and long-term data is not available. A standardized approach towards evaluation and management across institutions can help to uncover the unknowns surrounding AAOCA, and provide a framework for quality improvement and long-term data for this population.

Hence, a multi-disciplinary team of specialists including cardiologists, cardiovascular surgeons, radiologists, psychologists, anesthesiologists and research/outcomes staff came together at our institution to collaborate on this disease.

Fine specificity of antibodies to citrullinated antigens in patients with coronary heart disease and in patients with type II diabetes with and without associated cardiovascular events

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Introduction: Increased cardiovascular risk in patients with Rheumatoid arthritis (RA) is associated with high levels of serum anti-citrullinated protein antibodies (ACPA). ACPA are detected using citrulline-containing peptides (CCP) in ELISA. In an earlier retrospective study, we investigated whether anti-CCP were associated with coronary heart disease

(CHD), in the absence of RA. Using samples from the Second Northwick Park Heart Study (NPHSII), we found a strong association with the development of CHD (odds ratio (95% CI) = 3.26 (1.36-7.80), $p = 0.008$), remaining significant after adjustment for smoking and CRP (4.23 (1.22-14.61) $p = 0.02$) (1,2).

Aim: To test whether ACPA are associated with CHD in other clinical settings such as Type II Diabetes and to determine their fine specificity.

Methods: Serum IgG and IgM antibodies to 30 citrullinated and 7 uncitrullinated antigens were measured using multiplex bead array (MBA). Results were expressed in mean fluorescence intensity (MFI), Z-normalised to compensate for the number of binding sites per antigen with a cut-off point of Z score ≥ 1 (Lahey, L; Stanford University).

Patients: Cohort 1: 26 patients with CHD (including 15 with positive anti-CCP) and 46 age matched controls, all male (aged 50-64) from NPHSII. Cohort 2: Subjects from the University College London Diabetes and Cardiovascular Study (UDACS), with data on CVD presence/absence (including positive coronary angiography, angioplasty, coronary artery bypass, cardiac thallium scan, exercise tolerance test, myocardial infarction or symptomatic/treated angina).

Results: Cohort 1: There was considerable variability between patient profiles but Z scores in MBA comparing CHD patients with controls showed significantly higher levels ($p < 0.05$) of IgG against 60% (18/30) of cit-antigens; no differences were seen to same uncitrullinated antigens. Most significant were cit-ApoA1 ($p = 0.005$), cit-Histone2A ($p = 0.0009$) and cit-Histone2Acyclic1-20 ($p = 0.007$). IgM antibodies to only one antigen were increased, cit-FibrinogenA 211-230 sm cyclic ($p \leq 0.05$); none against uncitrullinated antigens.

Cohort 2: 3.3% (14/430) samples were positive for IgG-anti-CCP and 4.2% (18/430) for IgM-anti-CCP. There were no significant differences between Type II Diabetic subjects with or without CVD for either IgM or IgG antibodies against citrullinated/uncitrullinated antigens, with the exception of higher IgG anti-uncitrullinated ApoA1 ($p = 0.04$) in those with CVD.

Discussion: We showed an association between antibodies to an extended array of citrullinated antigens and CHD in the absence of rheumatoid arthritis and in the absence of Type II Diabetes. The CHD patients (NPHSII) had significantly higher levels of autoantibody levels to citrullinated but not uncitrullinated antigens but individual antibody specificities varied widely. This novel finding in CHD patients should be validated in a larger cohort and investigated for causality. Antibody profiles in patients with Type II Diabetes were not different in those with or without clinical evidence of CVD. The lack of such an association of ACPA with CVD in Diabetic patients is consistent with recognised differences in associations with CVD versus CVD in the setting of Type II Diabetes.

Presentation on: New insights into Cardio-Renal interactions – Role of NGAL

Professor Yacov Shacham

Neutrophil gelatinase-associated lipocalin (NGAL) is an early marker of renal tubular damage. We investigated the incidence and possible implications of elevated NGAL levels (suggesting renal damage) compared to both functional and damage markers (manifested as serum creatinine (sCr) elevation) and no NGAL/sCr change, among ST elevation myocardial infarction patients (STEMI) treated with primary coronary intervention (PCI). We included 131 patients with STEMI treated with PCI. Blood samples for plasma NGAL were drawn 24 hours following PCI. We used the terms NGAL(-) or NGAL(+) with levels ≥ 100 ng/ml suggesting renal tubular damage and the terms sCr(-) or sCr(+) to consensus

diagnostic increases in sCr defining acute kidney injury. Patients were also assessed for in hospital-adverse outcomes.

Of the study patients (42%) were NGAL(-)/sCr(-), (44%)NGAL(+)/sCr(-), and 14% were both NGAL(+)/sCr(+). According to the three study groups there was a stepwise increase in the proportion of left ventricular ejection fraction $\leq 45\%$ (43% vs. 60%. Vs. 72%; $p=0.04$), in-hospital adverse outcomes (9% vs, 14% vs. 56%; $p<0.001$) and their combination. Specifically, more NGAL(+)/sCr(-) patients developed the composite endpoint when compared to NGAL(-)/sCr(-) patients [64% vs.46%; OR 2.1 (95% CI 1.1–4.5), $P=0.05$]. A similar and consistent increase was observed in peak sCr, length of hospital stay and C-reactive protein levels. Similarly NGAL level aid in the early identification of acute kidney injury. In conclusion, elevated NGAL levels suggesting renal tubular damage, increased inflammation, or both, are common among STEMI patients and are associated with adverse outcomes even in the absence of diagnostic increase in sCr.

Exploring Medical Data by Sonification. Applications in Cardiology

Minodora Andor, George Mihalas

Introduction. Sonification is defined as “the use of non-speech audio to convey information or perceptualize data”. For medical applications the data space comprises all types of data, but those related to dynamic processes (like biological signals – ECG, EEG etc.) or structured data (like molecular sequences – DNA, proteins) are most appropriate.

Methods. The central paradigm of sonification, called “parameter mapping” is to establish a correspondence between the parameters of the input data and the characteristics of the audio display as output. There are several sonification techniques classified on various taxonomic axes. We have used a “three level approach”: level A (acoustic) – with a continuous spectrum of frequencies, level S (sonic) – with a discrete scale of frequencies and durations and level M (musical) –adding harmony and rhythm. Most of our studies have been focused on the S level. Data: both our own recordings as well as data from Physiobank have been used – ECG, heart rate (HR) and pulse wave from both health subjects or patients with various CVD (arrhythmia, atrial fibrillation, ventricular extrasystolae, obstructive sleep apnea) or during exercise test. Algorithms: a simple natural mapping was chosen: sound pitch (frequency) to be a discrete function of normalized signal amplitude. For sound duration we have introduced tempolenses for dilating or compressing the signal, including an original tempolens with variable magnification, for ECG. Software: a MATLAB set of programs has been done for all operations – preprocessing (normalization), parameter mapping, tempolenses and producing the audio display.

Results. For ECG the results were modest: easy to recognize the obstructive episodes and some ischemic modifications (flat T wave), but insufficient discriminant power for other cases. Much better perception of deviations was shown by HR sonification and still better for HR monitoring during the exercise. For the latter application a warning software module was added and a couple of warning designs was tested.

Discussions refer to potential directions of medical applications and the limits of the method.

Conclusions Sonification is a new way to represent medical data, still insufficiently explored, but with high potential to complement the present list of investigation methods.

Contemporary Data in Infectious Endocarditis and Importance of a Multidisciplinary Approach

P. Paolisso, MD, G. Van Camp, MD

Aim: To investigate the value of prospective in-hospital registry data and the impact of an infectious endocarditis heart team approach (IEHT) on improvement in quality of care and monitor outcomes in hospitalized patients with IE.

Methods: Between December 2014 and the end of 2019, 160 patients were hospitalized in one center with the definite diagnosis of infectious endocarditis (IE) and entered into a prospective registry. From 2017, an IEHT was introduced. Propensity score matching was used to assess the impact of an IEHT approach on clinical outcomes.

Results: Median age was 72.5 y (62.75-80.00), diabetes was present in 33.1%, chronic kidney disease in 27.5%, COPD in 17.5%, and a history of ischemic heart disease in 30.6%. Prosthetic valve IE was observed in 43.8% and device-related IE in 16.9% of patients. Staphylococcus (37.5%) was the most frequent pathogen followed by streptococcus (24.4%) and enterococcus (23.1%). Overall, 30-day and 1-year mortality were 19.4% and 37.5%, respectively. The introduction of prospective data collection and IE heart team was associated with a trend towards reduction of adjusted 1-year mortality (26.5% IEHT vs. 41.2% controls, $p = 0.0699$). An IEHT clinical decision-making approach was independently associated with a shorter length of stay ($p = 0.04$).

Conclusions: Use of a prospective registry of IE coupled with a heart team approach was associated with more efficient patient management and a trend towards lower mortality. Prospective data collection and dedicated IEHT have the potential to improve patient care and clinical outcomes.

The Importance of Centralized Quality Control for Multicenter Clinical Trials Using Cardiopulmonary Exercise Testing

Carrie Ferguson, Louis Holdstock, David Yehle, Jason Blonshine, Janos Porszasz

Pulmonary gas exchange variables [e.g. peak oxygen uptake (VO_{2peak}) and the minute ventilation/carbon dioxide output (VE/VCO_2) slope] measured from a maximal-effort ramp-incremental cardiopulmonary exercise test (CPET) are powerful predictors of severity and prognosis in chronic diseases in which exercise limitation is a common symptom. CPET can also effectively assess therapeutic efficacy. In multicenter clinical trials assessing therapeutic efficacy using exercise-based outcomes, rigorous quality control procedures and a standardized analysis process are essential to minimize variability and maximize reliability of end-point measures, particularly with the use of different CPET vendor gas exchange systems across sites. The ADVANCE CAPACITY study (ROR-PH-302) will investigate the effects of ralinepag (a selective, oral non-prostanoid IP receptor agonist) on VO_{2peak} , and other secondary outcome gas exchange variables, in patients with pulmonary arterial hypertension. This study has implemented a comprehensive pre-testing site evaluation and training process, an in-trial regular biologic quality control protocol, and an independent centralized laboratory for standardized analysis of CPET data that generates 155 variables for each ramp-incremental CPET. To date, 28 sites from the US, Canada, South America and Europe have submitted qualifying initial biologic quality control data and are currently submitting regular biologic quality control data as outlined in the study protocol. In this

presentation, the centralized quality control procedures implemented in ADVANCE CAPACITY will be explained, case-examples will be used to demonstrate quality control concerns identified and overcome using initial and regular biologic quality control tests, and the importance of standardizing the CPET data analysis process to minimize variability and maximize reliability of CPET variable endpoints will be highlighted. In demonstrating the importance of these centralized quality control procedures, we will advocate using centralized quality control methods in future multicenter clinical trials using CPET to assess clinical efficacy.

The effects of Bioactive peptides from Spanish dry cured ham on cardiovascular health: From in vivo to in vitro results

Sara Maria Martinez-Sanchez

Cardiovascular disease is the largest cause of morbidity and mortality in Europe. Different cardiovascular risk factors such as hypertension, diabetes, dyslipidemia and obesity have an important influence on the development of these diseases. Among the modifiable risk factors, diet has the greatest influence on the prevention of these diseases. Bioactive peptides (BPs) are small peptide sequences that usually contain between 2 and 20 amino acidic residues. They are released by the hydrolysis of food proteins, either of animal or vegetable origin, through multiple industrial or natural processes: fermentation, heating or enzymatic hydrolysis, among others. The ability of these BPs to interact easily with very distinct proteins/receptors in the body is mainly due to their low molecular weight, high bioavailability, and flexible molecular behavior. Thus, BPs with diverse activities such as antihypertensive, antioxidant, anti-inflammatory, opioid agonist, anti-obesogenic... developing multiple functions at the same time have been described, which has led to the term "multifunctional peptides".

A clinical trial was conducted, healthy mild-hypertensive volunteers (n=38) were recruited into a two-arm randomized controlled crossover trial in which they received 80 g/day of dry-cured pork ham with >11 months of proteolysis or 100 g/day of cooked ham (placebo product) for 4 weeks. After regular consumption of this intervention product rich in characterized BPs, a remarkable variation of platelet activation membrane markers (P-selectin) and monocyte (MCP-1) was observed, as well as a remarkable decrease of biomarkers of inflammatory (IL-6) and thrombotic (soluble P-selectin) status.

By means of a subsequent in vitro test, four peptides (KPVAAP, KAAAATP, KPGRP and AAATP) previously characterized in the cured ham and with previously confirmed ACE inhibitory activity (ACEI) were used. We analyzed the IC₅₀ of these BPs for human ACE and conducted studies in silico to further explain the affinity for this enzyme. It should also be noted that the incubation of human endothelial cells with these BPs significantly prevented the expression of genes related to endothelial dysfunction and inflammation (eNOS, ICAM-1, VCAM-1, IL-6) and reduced the activation of NF- κ B ($p < 0.05$). By in silico couplings it was confirmed that the four BPs could interact with the NEMO regulatory subunit of the NF- κ B transcriptional factor in the same site as other characterized inhibitors (CC2-LZ region) do. This is the first study that put together experimental and computational approaches to demonstrate that NF- κ B is a real target of foodborne BPs.

The results showed that bioactive peptides from dry-cured pork ham demonstrated in vitro and in vivo anti-inflammatory and antiplatelet effects so they might have potential therapeutic use to attenuate the atherosclerotic inflammatory process.

Melatonin as a Potential Tool for Correcting Cardiac Arrhythmicity

Harold Dowse

The hormone Melatonin is a powerful antioxidant commonly used to prevent reperfusion injury to the heart after infarction. We show here it has other more far-reaching effects on cardiac function. Using the *Drosophila* model, we show that injection of melatonin increases the regularity of heartbeat significantly and can rescue rhythmicity in flies bearing mutations that adversely affect cardiac function. Notably, melatonin increases cardiac regularity independent of alteration of heart rate. We provide compelling evidence that melatonin's action as an antioxidant is not the mechanism underlying improved cardiac performance. We have established that melatonin's action on the heart is mediated via a specific G-Protein-coupled receptor encoded by the CG4313 gene that our results implicate as a candidate melatonin receptor. These results open a line of questioning about fundamental aspects of cardiac pacemaking.

Remote Ischemic Preconditioning for Prevention of Contrast-Induced Nephropathy EA Randomized Control Trial

Akshay Bafna and Hetan C. Shah

Background: There is a lack of sufficient data regarding the protective effects of remote ischemic pre-

conditioning (RIPC) in patients at risk of developing contrast-induced nephropathy (CIN). Thus, this study was conducted to determine whether RIPC as an adjunct to standard therapy prevents CIN in high-risk patients undergoing coronary intervention.

Methods: In a single-center, double-blinded, randomized controlled trial, 162 patients who were at risk of CIN received standard hydration combined with RIPC or hydration with sham preconditioning. RIPC was accomplished by four cycles of 5 min ischemia and 5 min reperfusion of the forearm. The primary endpoint was a rise in serum creatinine (>0.5 mg/dL or $>25\%$) from baseline to serum creatinine 48e72 h after contrast administration.

Results: Of the 162 patients, 81 were randomly allocated to receive sham preconditioning and 81 to receive RIPC. Significantly reduced serum creatinine levels were observed in patients with a Mehran moderate risk allocated to sham group compared to the RIPC group (0.070 ± 0.16 mg/dL vs. 0.107 ± 0.13 mg/dL, $p = 0.001$). With regards to the primary endpoint, a significantly higher change in serum creatinine from baseline to 48e72 h was observed in the sham group compared to the RIPC group (0.023 ± 0.2 mmol/L vs -0.064 ± 0.1 mmol/L, $p < 0.001$).

Conclusion: RIPC as an alternative to standard therapy, improved serum creatinine levels after contrast administration in patients at risk of CIN. However, present data indicate that RIPC might have beneficial effects in patients with a moderate or high risk of CIN

A "Swiss Army Knife" Approach to Targeted EFNA1 Therapeutic Proteins

Jitka Virag, Patee Amin, Brittany Jefferson, Robert Hughes

Ephrin is a cell surface bound ligand for the Eph receptor, the largest tyrosine kinase family. They are crucial for controlling cell to cell communication, which in turn regulates cytoskeleton-mediated cell motility and morphology. More specifically, one type of Ephrin, Ephrin A1 (EFNA1), is a cell surface bound ligand for Eph receptors, which has been demonstrated to have positive effects in model organisms, such as acute and chronic mice models of Ischemia and Parkinson's disease. We are working to optimize targeting and bioavailable delivery of a molecularly engineered ephrinA1 construct for therapeutic administration. Specifically, a targeted EFNA1 that can rapidly reach the therapeutic target after injection by IV, catheter, or delivery by surgical implant represent formulation and delivery challenges that need to be addressed to develop strategies for harnessing the currently untapped therapeutic potential of site-specific ephrin signaling. Moreover, a targeted entity would have numerous advantages, including increased longevity, decreased off-target effects, and would offer unlimited 'tunability', as the sequence can be adapted to meet multiple therapeutic targets. Herein, we describe several targeted formulations of the EFNA1 ligand that will promote general (Eph receptor = EphR) and more specific (cardiomyocytes) targeting of EFNA1. These targeted modules also incorporate strategies to promote Eph activity through multimerization. We are working to characterize the expression of these engineered ligands in E. Coli and investigate their ability to induce activation of Eph receptors in cultured cells. Efficacy of these constructs are also being compared to that of EFNA1-Fc will be assessed and validated utilizing an experimental murine model of acute cardiac ischemia/reperfusion injury.

Therapy for the Malnourished Heart

Nchafatso G. Obonyo

Severe, acute malnutrition (SAM) remains a frequent cause of paediatric hospitalization in resource-limited low-and-middle income countries (LMICs), where it is associated with in-hospital mortality rates as high as 20%, co-morbidities and poor long-term outcomes despite adherence to World Health Organization (WHO) treatment guidelines.

Volume resuscitation therapy in severe malnutrition has been hypothesized to be deleterious owing to compromised cardiac function with increased risk of incipient biventricular failure. In the Cardiac Physiology in Malnutrition (CAPMAL) study, we investigated cardiac dysfunction in a cohort of children with severe acute malnutrition, comparing kwashiorkor and marasmus phenotypes. In the Appropriate Fluid Resuscitation In Malnutrition (AFRIM) study, we examined myocardial function and haemodynamic response to fluid resuscitation in severely malnourished children with hypovolaemic shock due to gastroenteritis.

This presentation will provide an overview of cardiac function and fluid resuscitation in critical illness states among severely malnourished children.

Validation of an Electrocardiographic Marker of Low Voltage Areas in the Right Ventricular Outflow Tract In Patients with Idiopathic Ventricular Arrhythmias

Ana Leonor Costa Parreira

Background: Previous studies have reported the presence of subtle abnormalities in the right ventricular outflow tract (RVOT) in patients with apparently normal hearts and ventricular arrhythmias (VAs) from the RVOT, including the presence of low voltage areas (LVAs). These LVAs seem to be associated with the presence of ST-segment elevation in V1 or V2 leads at the level of the 2nd intercostal space (ICS).

Objective: Our aim was to validate an electrocardiographic marker of LVAs in the RVOT in patients with idiopathic outflow tract VAs.

Methods: 120 patients were studied, 84 patients referred for ablation of idiopathic VAs with an inferior axis by the same operator, and a control group of 36 patients without VAs. Structural heart disease including arrhythmogenic right ventricular cardiomyopathy was ruled out in all patients. An ECG was performed with V1-V2 at the 2nd ICS, and ST-segment elevation > 1mm and T-wave inversion beyond V1 were assessed. Bipolar voltage map of the RVOT was performed in sinus rhythm (0.5–1.5 mV color display). Areas with electrograms <1.5 mV were considered LVAs, and their presence was assessed.

We compared three groups, VAs from the RVOT (n=66), VAs from the LVOT (n=18) and Control group (n=36). ST-elevation, T-wave inversion and left vs right side of the VAs were tested as predictors of LVAs, respective ORs (95% CI) and p values, were calculated with univariate logistic regression. Variables with a p value <0.005 were included in the multivariate analysis.

Results: ST-segment elevation, T-wave inversion and LVAs were present in the RVOT group, LVOT group and Control group as follows: (62%, 17% and 6%, p <0.0001), (33%, 29% and 0%, p=0.001) and (62%, 25% and 14%, p<0.0001).

The ST-segment elevation, T-wave inversion and right-sided VAs were all predictors of LVAs, respective unadjusted ORs (95% CI), p values were, 32.31 (11.33-92.13), p<0.0001, 4.137 (1.615-10.60), p=0.003 and 8.200 (3.309-20.32), p<0.0001. After adjustment, the only independent predictor of LVAs was the ST-segment elevation, with an adjusted OR (95% CI) of 20.94 (6.787-64.61), p<0.0001.

Conclusion: LVAs were frequently present in patients with idiopathic VAs. ST-segment elevation was the only independent predictor of their presence.

Endoplasmic Reticulum Stress, Inflammation, Oxidative Stress and Neutrophil Extracellular Traps in Cardiovascular Diseases

Chiara Mozzini MD PhD and Mauro Pagani MD

The talk is intended primarily to summarize the understanding of the interrelated roles of endoplasmic reticulum (ER) stress, oxidative stress and inflammation in cardiovascular diseases. Insults interfering with ER function lead to the accumulation of unfolded and misfolded proteins in the ER. An excess of proteins folding in the ER is known as ER stress. This condition initiates the unfolded protein response (UPR). When the UPR fails to control the level of unfolded and misfolded proteins, ER-initiated apoptotic signalling is induced. Moreover, the role of the protective nuclear erythroid-related factor 2 (Nrf2)/antioxidant-related element (ARE) and the activation of the pro-inflammatory nuclear factor-kappa B (NF- κ B) are analysed. Oxidative stress, inflammation and ER stress are closely entwined phenomena. They are involved in the pathogenesis of different cardiovascular diseases. Current literature data are presented, focusing on three topics of related pathologies: atherosclerotic plaque, coronary artery disease and diabetes. This talk will provide a basic

platform for study and application to several other conditions in which oxidative stress, ER stress and inflammation are key features. Future studies in this area may identify the most promising molecules to be investigated as common targets for cardiovascular diseases.

The potential beneficial effects of hydralazine via xanthine oxidase inhibition

Ting-Ting Chang

Background: Oxidative stress is related to the progression of renal diseases and modulation of oxidative stress can contribute to a reduction in vascular events in patients with chronic renal insufficiency (CRI). Actually, the incidence of peripheral arterial disease (PAD) is usually associated with poor clinical outcomes in patients with chronic renal insufficiency (CRI). Hydralazine is a vasodilator used for clinical blood pressure control. While its pharmacological mechanisms may be complex and obscure, this study aimed to investigate whether hydralazine could improve ischemia-induced neovascuogenesis in CRI animals by reducing reactive oxygen species (ROS) levels.

Methods: Mouse subtotal nephrectomy and hindlimb ischemic models were conducted. Nitrendipine, probenecid, and allopurinol were used to reduce blood pressure, uric acid (UA), and xanthine oxidase (XO) activity levels, respectively, for comparison. In the in vitro part, both endothelial progenitor cells (EPCs) and human aortic endothelial cells (HAECs) were used.

Results: Blood pressure, XO activity and UA levels that were increased after subtotal nephrectomy were reduced by the administration of hydralazine. Allopurinol decreased blood XO activity and UA levels. Nitrendipine decreased blood pressures and probenecid decreased UA levels without improving neovascuogenesis in CRI mice. Only hydralazine and allopurinol increased the number of circulating EPCs and improved neovascuogenesis in CRI mice. Indoxyl sulfate (IS) activated XO mRNA and ROS and inhibited the functions of EPCs and endothelial cells, which could be reversed by hydralazine. However, no additional beneficial effects were observed when XO was inhibited with both hydralazine and siRNA.

Conclusions: Hydralazine, as a potential XO inhibitor, not only reduced blood pressure and UA levels but also increased the number of circulating EPCs and improved neovascuogenesis in CRI animals. Meanwhile, hydralazine reduced IS-induced ROS and XO activation in EPCs and HAECs, and restored their functions in vitro. Further studies should evaluate whether hydralazine could provide additional vascular protection in patients with CRI.

Influence of Chronic Exercise During Pregnancy on resting Maternal Cardiovascular Measures Throughout Pregnancy

Linda E May, Jennifer Knowlton, Jessica Hanson, Richard Suminski, Carol A. Johnston, Cody Strom, Christy Isler, Edward Newton, Samantha Mcdonald, Xiangming Fang

Background: Ten percent of pregnancies are complicated by hypertensive disorders of pregnancy. Previous research has shown that moderate-vigorous intensity exercise can

normalize autonomic control and has a positive effect on maternal resting cardiovascular system. A research gap exists related to how exercise during pregnancy, specifically types of exercise (resistance, aerobic, combined resistance and aerobic), affect the maternal cardiovascular system during pregnancy.

Objective: We tested the hypothesis that exercise throughout pregnancy improves maternal cardiac autonomic control as evidenced by decreased heart rate (HR) and increased heart rate variability (HRV). Additionally,

we examined the effects of exercise types on maternal blood pressure throughout pregnancy.

Methods: For the first study, magnetocardiography (MCG) recorded maternal HR and HRV (time and frequency domains) at 28, 32, and 36 weeks of pregnancy from 30 pregnant exercisers (>90 minutes/week of aerobic activity; E) and 26 healthy pregnant non-exercisers (C; controls). The second study employed a secondary analysis from a randomized controlled prenatal exercise intervention trial. This study utilized 3 exercise intervention groups (aerobic, resistance, combination) in comparison to a non-exercise control group. Participants completed 150 min/week from 16 weeks of gestation until delivery. Maternal systolic (SBP), diastolic (DBP) blood pressure and heart rate were measured every 4 weeks throughout the intervention. Between-group mean differences in maternal measures were assessed by Pearson's Chi-Square tests for continuous (age, pre-pregnancy BMI, heart rate, SBP, DBP, pulse pressure) variables. For gravida, exact Wilcoxon Two-Sample test were performed to determine between-group differences in mean values. Hierarchical linear growth curves were used to estimate maternal trajectories of SBP and DBP from 16 weeks to 36 weeks in each of the four groups (aerobic, combination, control, and resistance).

Results: For the first study, HR is significantly lower in the E group at 28 ($p < 0.01$) weeks compared to C group. The E group had significantly ($p < 0.05$) increased measures of HRV in the time domain at 28 (RMSSD, SDNN), 32 (SDNN), and 36 weeks (SDNN) compared to the C group. There was significantly ($p < 0.05$) increased HRV in the frequency domain (VLF, LF, HF) at 32 weeks in the E group relative to the C group. For the second study, 36 weeks SBP was lower in the resistance group by 12.17 mmHg ($p < 0.001$), and the aerobic group by 7.90 mmHg ($p < 0.001$) relative to controls. Controlling for maternal BMI, a significantly lower SBP curve throughout the pregnancy was noted for women who participated in resistance exercise, then aerobic exercise relative to no exercise throughout pregnancy. Similarly, we demonstrated a significantly lower linear growth curve in DBP that was maintained throughout pregnancy in any exercise type relative to controls. Controlling for maternal BMI, all three exercise types (combination, resistance, and aerobic) significantly predicted a similar decrease in DBP that was maintained throughout pregnancy. At 36 weeks, DBP was lower in the aerobic group by 7.30 mmHg ($p < 0.01$), in combination by 6.43 mmHg ($p < 0.05$), then the resistance group relative to controls.

Conclusion: Exercise throughout pregnancy improves cardiac autonomic control and attenuates the increased sympathetic control naturally associated with pregnancy. All exercise types were beneficial in lowering maternal resting blood pressure throughout pregnancy. Resistance training was noted to be the most beneficial in improving systolic blood pressure, followed by aerobic exercise. All three exercise groups were noted to improve diastolic blood pressure equally. These cardiac adaptations to exercise may reduce adverse outcomes associated with gestational diabetes, hypertension, pre-eclampsia, and excessive weight gain and leads to healthier mother and child. Further research needs to be

done to determine if either resistance or aerobic exercise throughout pregnancy, decreases the risk of hypertensive disorders of pregnancy and the associated morbidity and mortality.

How to best calculate LDL-cholesterol and small dense LDL-cholesterol

Anna Wolska, PhD, MS

Based on decades of both basic science and epidemiologic research, there is overwhelming evidence for the causal relationship between low-density lipoprotein-cholesterol (LDL-C) and atherosclerosis cardiovascular diseases (ASCVD).

Starting in 1972 until very recently, the Friedewald formula was the only available equation for estimating LDL-C from the patients' standard lipid panel. Although widely and commonly used, this formula was found to have several limitations. Therefore, new equations have been developed since then e.g., Martin-Hopkins equation and Sampson-NIH formula. Sampson-NIH equation has been described to be more accurate than both Friedewald and Martin equations, because it is accurate in samples with up to 800 mg/dL of TG and all spectrum of LDL-C levels.

It has been well described that ASCVD risk is even more strongly associated with small dense LDL-C (sdLDL-C) and was added to the list of emerging risk factors for ASCVD by the NCEP. It can be measured by advanced lipoprotein separation methods, but the novel sdLDL-C equation based only on the standard lipid panel was developed by Sampson and Wolska from NIH. In both univariate and multivariate analysis after adjustment for the conventional risk factors, it was found to be superior to LDL-C and other routine lipid measures for predicting ASCVD.

Summarizing, patients' CVD risk evaluation and monitoring the response to lipid-lowering therapies are heavily dependent upon accurate assessment of plasma lipids in a clinical laboratory. Dr. Wolska provides an update on available methods for calculating LDL-C and sdLDL-C and how can they serve as markers of ASCVD risk.

Keywords: atherosclerosis cardiovascular diseases, cholesterol, equations, LDL-C, sd-LDL-C

The use of non-invasive cardiac output monitoring technology in neonatology

Lizelle Van Wyk, PhD,

Neonatal hemodynamic compromise is linked to numerous adverse neonatal outcomes. Objective, comprehensive, continuous hemodynamic monitoring of the systemic circulation is required to timeously intervene and improve outcomes. Various types of TEBT are available – thoracic and whole body bioimpedance as well as thoracic bioreactance. These technologies have been used in numerous neonatal studies – both for accuracy determination as well as for clinical monitoring purposes. The agreement and trending ability of TEBT in neonates is questionable but may be influenced by a variety of clinical and technological factors. This presentation will focus on the types of technology, the accuracy and trending ability of TEBT in neonates and the way forward with this technology

Genetic Variants in Calcium Calmodulin Pathway in Association with Cardiovascular Disease: Focus on the Potential Role of Camkk1 in Heart and Vessels

Sofia Beghi

Cardiovascular disease (CVD) is the leading cause of death all over the world and it affects an increasing number of people annually. Numerous risk factors are involved in the etiology of this complex disease. In addition to an unhealthy lifestyle, environmental factors, and other comorbidities, genetics also plays a role. The study of genetic variants associated with CVD is one of the main areas of interest nowadays. This is because it can aid in the identification of genetic biomarkers for prevention, prediction and treatment of patients affected by CVD.

Regulation of calcium signalling through calmodulin (CaM) is a key pathway involved in the physiology and molecular biology of the heart. CaM binds calcium and regulates calcium, playing a crucial role in several processes, such as cellular excitation-contraction coupling.

Research has shown that genetic variants, such as polymorphisms, can be factors predisposing to complex diseases. Thus, I hypothesized that studying and characterizing polymorphisms in the components of the CaM pathway could unravel how genetic traits influence CVD predispositions. In this thesis I focused on polymorphisms in 3 isoforms of CaM (CaM1, 2, 3) and proteins involved in its signalling, NOS (nitric oxide synthases) and CaMKs (calcium/calmodulin dependent protein kinases), in CVD. The analysis of the polymorphisms was performed on a cohort of 300 cardiopathic patients; a blood sample was collected and spotted on FTA cards. DNA was isolated and RLFP-PCR was performed in order to analyse the single nucleotide polymorphisms (SNP) of interest. The comparison of the genetic and allelic frequencies between the group of interest and the European reference group, used as control, showed interesting results in increasing the risk to develop a specific CVD, specifically for the SNP rs1549758, rs61202009 in NOS3 and mainly for the SNP rs7214723 in CaMKK1. The significant and interesting results of this last SNP in the cardiopathic Italian population, I analysed it also in a dutch cohort population and carried out an in-depth study of the role of CaMKK1 (calcium calmodulin-dependent protein kinase kinase I) in the heart and blood vessels, through in vitro studies on human vascular smooth muscle cells. In this in vitro experiment I found that CaMKK1 is a novel regulator of phenotypic switching of hVSMC towards synthetic VSMCs, thereby providing CaMKK1 as a new therapeutic target to reduce vascular remodeling, as well as a new potential genetic biomarker in the contest of cardiovascular diseases.

The Ancient Heart: What the Heart Meant to Our Ancestors**Vincent Figueredo**

How was the heart viewed by our ancestors from the dawn of human civilization through the Dark Ages? What was the role of the heart for the philosopher, priest, and physician during early human history? This review of the heart's meaning to different ancient cultures explores how beliefs about the purpose of the heart evolved over millennia as humans tried to understand what life forces it contained. Revered by many ancients as the "king" of the organs, surely the heart was the repository of thoughts, consciousness, and the soul.

Calculated effect of fluid retention upon turbulence of blood flow and risk of atherosclerotic cardiovascular disease**Robert Peter Blankfield**

Turbulent blood flow increases endothelial dysfunction. Atherosclerosis occurs primarily at arterial branch points and bifurcations. That is because blood flows turbulently at these

locations. Utilizing a mathematical analysis of the physical properties of the cardiovascular system, it can be shown that fluid retention increases turbulence of blood flow regardless of whether or not the fluid retention raises blood pressure. Numerous prospective studies demonstrate that medications that cause fluid retention (cyclooxygenase-2 inhibitors, estrogens and progestins) increase the risk of heart attacks and strokes. Numerous retrospective studies demonstrate that medications that cause fluid retention (non-steroidal anti-inflammatory drugs, oral contraceptives, androgens, insulin and sulfonylureas) are associated with an increased risk of heart attacks and strokes. Fluid retention due to medications used to achieve intensive glucose lowering explains the cardiovascular outcomes of the ACCORD trial. The cardiovascular risk of many medications that cause fluid retention has not been studied. Agencies that are responsible for regulating medications, the Food and Drug Administration and the European Medicines Agency, should require cardiovascular safety data for drugs that cause fluid retention.

Percutaneous coronary interventions in left main artery lesions: indications and techniques

Homorodean Calin, MD, PhD

The incidence of left main coronary artery stenosis on coronary angiography is between 5-7 %. Untreated left main stenosis carries a mortality risk of 20 to 50% by 3 years of follow-up. In patients with low coronary disease complexity scores, for which complete percutaneous revascularization is achievable, interventional strategy is a suitable alternative to cardiac bypass surgery. In randomised clinical trials, patients with more complex coronary disease continued to derive a benefit from surgery over stenting at long-term follow-up. However, in acute coronary syndromes especially in myocardial infarction, percutaneous revascularization often remains the only treatment option.

The outcomes after left main percutaneous interventions could be improved following stent optimization strategies, using intracoronary imaging guidance through intravascular ultrasound or optical coherence tomography. Intracoronary imaging also quantifies lesion severity, guides lesion preparation and facilitates stent selection and identifies acute complications as dissections, or intramural hematoma.

Currently, the preferred interventional technique at the level of left main bifurcation is provisional stenting. Nevertheless, when complex bifurcation lesions are present a double stent technique is needed. In this clinical situation, the double kissing crush technique has been shown to be associated with improved outcomes when compared to other strategies in clinical trials and meta-analyses. The outcomes after such complex interventions are largely dependent of the experience of the operator with different stenting techniques.

Constrictive pericarditis and single coronary artery: Rare presentation

Zaira Yadira Garcia Lopez

Constrictive pericarditis is an inflammatory process that involves the parietal layer of the pericardium and causes constriction.

Autoimmune diseases are a frequent cause. HLA-DR1 and DR4 genes has been observed in Rheumatoid arthritis.

Congenital coronary anomalies affect 1% of the population. We present a 68-year-old male with 7-months history right heart failure and Rheumatoid arthritis. The diagnostic approach included multimodal imagines.

The findings were a pericardial thickening, calcification and constrictive physiology with a single coronary artery. The treatment was pericardiectomy.

This presentation constrictive pericarditis and single coronary artery hasn't been reported, we don't know if the presentation could be causal.

Therapy for the malnourished heart

Nchafatso G. Obonyo

Severe, acute malnutrition (SAM) remains a frequent cause of paediatric hospitalization in resource-limited low-and-middle income countries (LMICs), where it is associated with in-hospital mortality rates as high as 20%, co-morbidities and poor long-term outcomes despite adherence to World Health Organization (WHO) treatment guidelines.

Volume resuscitation therapy in severe malnutrition has been hypothesized to be deleterious owing to compromised cardiac function with increased risk of incipient biventricular failure. In the Cardiac Physiology in Malnutrition (CAPMAL) study, we investigated cardiac dysfunction in a cohort of children with severe acute malnutrition, comparing kwashiorkor and marasmus phenotypes. In the Appropriate Fluid Resuscitation In Malnutrition (AFRIM) study, we examined myocardial function and haemodynamic response to fluid resuscitation in severely malnourished children with hypovolaemic shock due to gastroenteritis.

Updated and revised reference values of aortic pulse wave velocity in children and adolescents aged 3-18 years

Hidvégi E.V., Jakab A.E., Cziráki A., Illyés M.

Introduction: Measurement of aortic stiffness – expressed as aortic pulse wave velocity (PWV_{ao}) – is an accepted method in the process of detecting organ damages and stratifying individual cardiovascular (CV) risk in adults. Diseases in children and adolescents might influence aortic stiffness. It is necessary to exclude overweight (OW), obese (O) subjects, and individuals with increased systolic (SBP) and/or diastolic blood pressure (DBP) from the population, when creating reference values of PWV_{ao} in paediatric population. Body mass index (BMI), SBP and DBP cut-off values have changed in this population during the last decade.

Aims of our study were to expand the database of our previously published (2012) reference values of PWV_{ao} for children and adolescents; and to revise it by the application of the recently determined BMI and SBP, DBP cut-off values.

Methods: PWV_{ao} was measured by an invasively validated occlusive-oscillometric device in a healthy population aged 3-18 years. To categorize subjects into OW and O subgroups, cut-off values published by *Cole* (2012) were used. Increased SBP, DBP were defined by applying the reference values published by *Schwandt* (2015). Finally, n=4.690 (2.599 boys) participants were recruited.

Results: Mean PWV_{ao} values increased with around 1 m/s between the ages of 3 and 18 years in both sexes, namely, this parameter rose from 5.4±0.6 to 6.4±0.5 m/s (p<0.05) in boys and from 5.5±0.6 to 6.4±0.5 m/s (p<0.05) in girls. Mean PWV_{ao} values were significantly higher in boys according to girls in the age groups of 13-15, and 17 years. After

the comparison of mean PWV_{ao} values measured in 2012 and 2018, significantly lower mean PWV_{ao} values were found in 2018 (in boys in the age group of 7-16 years; in girls in the age group of 10-17 years).

Conclusions: To the best of our knowledge this is the largest database of PWV_{ao} of healthy population aged between 3-18 years published to date. Due to the change of anthropometric and physiological cut-off values during the last decade, the “old” database of PWV_{ao} needed to be revised. As a result of this, reference values of PWV_{ao} decreased significantly in both genders.

Hormones and Thrombosis: Risk Across the Reproductive Years and Beyond

Margaret V Ragni

The hemostatic effects of endogenous and exogenous hormones on coagulation are significant. In some cases, sex hormones which are important to men’s and women’s health, may increase risk for thrombosis. The occurrence of inherited or acquired thrombotic risks may tip the balance toward thrombosis, and thus, careful monitoring of patients at risk of thrombosis is necessary, as well as gaining a better understanding of the mechanism of sex hormones associated thrombosis and approaches to reduce thrombotic risk.

Thromboembolism risk is associated with endogenous hormonal changes in pregnancy and polycystic ovary syndrome and with exogenous hormonal contraception, hormone replacement in menopause, and transgender cross-hormone replacement. The relative risk of hormone associated thrombosis, based on meta-analyses, population-based case-control studies, and randomized trials.

Among exogenous hormones, estrogen-containing oral contraceptives are associated with increased VTE risk, but no increase occurs with progesterone-only pill, progesterone intrauterine device, or transdermal estrogen. Among polycystic ovary patients, VTE risk is attributed to estrogen replacement, free androgen index, and obesity. Among women undergoing assisted reproduction, VTE risk is associated with ovulation induction and is greatest in the first trimester. While testosterone for female-to-male transition is not associated with VTE, estrogen for male-to-female transition is associated with increased VTE risk but risk is lower with transdermal estrogens. In men receiving testosterone replacement therapy for testicular failure, the greatest risk is in the first six months after starting therapy. Similarly, in pre- and post-menopausal women receiving hormone replacement, the greatest risk is in the first six months after starting therapy. In women with breast cancer receiving anti-estrogen therapy, VTE risk may be increased.

Among endogenous hormonal conditions, pregnancy VTE risk is highest in the 6 weeks postpartum. In those with thrombophilia, in particular homozygous factor V Leiden or homozygous prothrombin gene mutation, VTE risk is increased.

To prevent hormone associated VTE, standard VTE risk factors should be addressed, including smoking, obesity, diabetes, hypertension, and personal or family history of VTE. For those receiving hormone therapy, the lowest effective hormone dose should be used. For those with thrombosis, low molecular weight heparin (LMWH) or unfractionated heparin are given acutely, followed by chronic anticoagulation, if indicated, with LMWH or a direct oral anticoagulant (DOAC), per current American Society of Hematology (ASH) Thromboembolism guidelines.

COVID-19**Longitudinal Analysis of Nontraditional Social Support, Core Belief Disruption, and Posttraumatic Growth During COVID-19****Whitney Dominick**

The 2019 Novel Coronavirus (COVID-19) pandemic and corresponding social distancing policies provide an opportunity to examine different ways humans obtain social support during a prolonged period of isolation. Additionally, it provides the opportunity to examine how non-traditional social support, such as support from animals or through social media, impacts core beliefs and Posttraumatic Growth (PTG). PTG is the positive change a person may experience due to struggling with a highly stressful event that shakes a person's assumptive beliefs about the world. Social support in the aftermath helps with processing the event and shaken beliefs, allowing for the rebuilding of core beliefs that may lead to the experience of PTG. The COVID-19 pandemic is an ongoing stressor that has disrupted typical human support networks, providing a unique opportunity to examine how non-traditional sources of social support change over time and impact core belief disruption and PTG.

Data on perceived support from pets and humans, coping through social media, core belief disruptions, PTG, and experiences with COVID-19 were gathered from 201 adults in the United States through an online survey given at four time points from the 31st of March, 2020, until the 31st of March, 2021. Over the first year of the pandemic, core belief disruption and growth in the New Possibilities and Personal Strength domains of PTG increased, but the use of video conferencing, social media, and pets for social support declined. Participants experienced higher core belief disruption the more they were impacted by COVID-19, and higher core belief disruption both corresponded with and predicted higher perceptions of PTG. PTG was also predicted by human support and video conferencing, although pet owners used physical touch with their pets and social media for support more than video conferencing. Overall, while the pandemic caused mental health declines it also allowed for the possibility of growth. Interventions aimed at fostering growth should assist with processing assumptive beliefs about the world and encouraging social support through both traditional and non-traditional avenues.

Facilitating Decontamination of N95 Masks in the COVID-19 Pandemic: Challenges, Lessons Learned, and Safeguarding the Future**Yan Long**

N95 mask shortages have been a persistent and enduring problem in past pandemics. During COVID-19, the demand for N95 masks quickly depleted the supply chain, forcing the public and healthcare workers to reuse their masks. N95 masks need to be decontaminated before emergency reuse, but proper decontamination is challenging in under-resourced healthcare facilities.

Our VeriMask wireless sensor platform facilitates the measurement of moist-heat decontamination. VeriMask is capable of monitoring hundreds of masks simultaneously in commercially available heating systems and provides a novel throughput-maximization functionality to help operators optimize the decontamination settings. VeriMask can serve

as a template for managing the safety of N95 mask decontamination in future emergency shortages.

In this talk, we will discuss the challenges of moist-heat decontamination in under-resourced healthcare facilities with commercial heating devices. Our research explores (1) the problem of non-uniform heat distribution that can cause decontamination failures, (2) the difficulties in detecting heat and humidity leakage that can be easily caused by operational errors, and (3) the challenge of optimizing the throughput of the decontamination process. We will introduce the VeriMask experimental platform and discuss our electronics and software design choices. We will also summarize engineering lessons learned to prepare for future N95 mask shortages.

Displacing Sedentary Behavior with Light Activity as a Method of Improving Health in Older Adults (Implications for COVID-19 Quarantine)

Dale Grant

Rationale: The COVID-19 pandemic is limiting outdoor and community-based activities, especially for older adults owing to the requirement for self-isolation, potentially increasing prolonged sedentary behaviour (SB). Given a poor tolerance for intense exercise, SB displacement with light intensity physical activity (LIPA) is a promising health enhancing alternative. Therefore, the aims of this study were to investigate the effects of two different types of SB displacement on health outcomes in older adults and any differential impact of associated LIPA pattern. Method: 28 older women (age: 73 ± 5 years, height: 1.60 ± 0.07 m, weight: 67 ± 10 kg, and BMI: 26.1 ± 3.6 kg/m²) underwent overnight fasted dual energy x-ray absorptiometry (DEXA) imaging, blood sampling, and functional assessments before being randomly allocated to one of two groups: (1) single continuous bout of 45–50 min LIPA daily ($n = 14$); or (2) SB fragmentation (SBF; ~48 min LIPA daily, 2 min LIPA for every 30 min of SB; $n = 14$). Compliance was systematically monitored using tri-axial accelerometry. All measures were taken at weeks 0 and 8. Results: Physical behaviour significantly altered (decreased SB/increased LIPA; $p < 0.05$) and to a similar extent in both groups. We observed a significant reduction in serum triglycerides [$p = 0.045$, SBF: -0.26 ± 0.77 mmol/L, LIPA: -0.26 ± 0.51 mmol/L], improved 30 s sit-to-stand (STS) count ($p = 0.002$, 2 ± 3 STS) and speed ($p = 0.009$, $-10 \pm 33\%$), as well as increased average handgrip strength ($p = 0.001$, $6 \pm 12\%$), and gait speed ($p = 0.005$, 0.09 ± 0.16 m/s) in both groups. Interestingly, SBF caused a greater increase in peak handgrip strength ($8 \pm 14\%$), compared to LIPA ($2 \pm 10\%$; $p = 0.04$). Conclusion: SB displacement induced significant improvements in fasting triglycerides, gait speed, as-well as STS endurance/speed in older women. Frequent vs. continuous SB displacement also caused greater increases in handgrip strength. While both SB displacement protocols display promise as efficacious home-based interventions for self-isolating older adults, our results would suggest a physical functioning advantage of the SBF protocol for certain outcomes.

The Impact of COVID-19 on Eating Disorders

Christine M. Peat

The COVID-19 global pandemic and restrictive measures aimed at containing it have had a significant negative impact on those with eating disorders. This impact has been reflected in the United States with a doubling of eating disorder hospitalizations (particularly for children and adolescents), a greater number of emergency department visits, and marked increases in utilization of support groups and hotlines for those affected by eating disorders. The pandemic has also affected the way in which treatment is provided to patients with eating disorders and underscores the importance of telehealth as a means of ensuring consistent access to care during public health emergencies. A growing body of global evidence has been published in the wake of the pandemic regarding the impact of COVID-19 on eating disorders, and there are a number of clinical and research implications from this emerging literature. Thus, the goal of this presentation is to provide an overview of recent data regarding COVID-19 and eating disorders as well as a discussion of information pertinent to clinicians and researchers alike.

Resilience in the Storm: Impacts of Changed Daily Lifestyles on Mental Health in Persons with Chronic Illnesses under the COVID-19 Pandemic

Elizabeth Austin

Emergency preparedness exercises help to prepare communities for the collaboration required for successful navigation of disasters. Such exercises also provide an avenue to introduce university and other students to the concepts of disaster and the need to prepare for mass casualty events. Towson University's College of Health Professions sponsored seven mass casualty exercises over a span of eight years. The exercises included students from multiple disciplines in the University, local fire and emergency medical service responders, local hospitals, military units, senior centers. In addition, two local schools participated with eighth graders and students who were deaf. Multiple agencies gained valuable training in the full-scale exercises. Emergency preparedness exercises are complex events that require significant planning, attention to detail, debriefing, funds, and attention to security details that include the ability to respond to actual emergencies that may occur within the exercise.

University-sponsored Pediatric Emergency Preparedness and Response Exercises

The study of some physiological and biochemical indices as predictive markers of an unfavorable outcome of COVID-19 pneumonia

Rogacheva Svetlana

The study is aimed to determine via mathematical methods the significance of some physiological and biochemical indices as predictive markers of an unfavorable outcome of pneumonia caused by the SARS-CoV-2 virus.

For this purpose a retrospective analysis of the clinical data of the COVID hospital patients was carried out. A random cohort of patients with COVID-19 pneumonia numbered 209 people. In total 15 indices were studied: the physiological characteristics of patients described during hospitalization, the indices of blood coagulation, C-reactive protein (CRP) level, urea and creatinine concentration in blood. The analyzed parameters were categorized relative to the reference intervals of physiologically normal values. Correlation

analysis was carried out using categorical data on the disease outcome. The algorithms for calculating statistical characteristics, as well as results visualization, were implemented in the Python language. The significance of differences in signs when comparing patient groups was assessed using the Pearson's χ^2 test with Yates' correction. The reliability of the results was assessed using one-way analysis of variance using Fisher's F-test. The studies were carried out in accordance with international and Russian ethical principles and norms. There were revealed maximal correlation coefficients between the level of blood oxygen saturation (-0.43), as well as the respiratory rate (0.43), and a mortal outcome. For patients over 50 years of age, oxygen saturation below 80% at the time of hospitalization turned out to be a marker of mortality. It was shown that D-dimer blood level above 625 ng/mL and an increase in the concentration of creatinine and urea in the blood by 2.5 times are associated with mortal outcomes of the old patients. No correlation was found between the CRP level and the disease outcome. The effect of corticosteroids on the disease outcome was analyzed in patients with different CRP levels. It was found that while using corticosteroids, the mortality rate in patients with $\text{CRP} \leq 12.5$ mg/L is 2.7 times higher than in those with $\text{CRP} > 12.5$ mg/L ($p < 0.01$). Thus, the use of adequate mathematical methods made it possible to define more precisely some mortality-associated indices in patients with COVID-19 pneumonia.

Post-Covid Variant's Impacts on Service Sector in Indian Market

Dr. Divya Bharathi

The COVID-19 Pandemic, which enrooted in India in 2020, resulted in lockdowns across the country and world where business operations were made mandatory to work with SMS (Social-Distancing, Mask, and Sanitizer) conditions to fight against the pandemic. As we know, the service sector contributes the highest GDP to the economic growth of the country, but due to the emergence of the pandemic, it had a major impact on the service sector both positively and negatively. According to the economic survey report, service sectors like personal care, fitness centers, tourism, hotels, offline education system, media & entertainment, construction, manufacturing, railways, transport, and airlines were drastically impacted with no business. Sectors like e-commerce, online education, IT, food & agriculture, healthcare, information, communication, financial, professional, and business services had less impact as they were non-contact businesses. Now that COVID has moderately reached the stable phase and lockdown has been lifted majorly for every sector across the country and world, there are a lot of positive opportunities found in the future growth of the Indian economy. In order to recover from the losses caused by the pandemic, inflation in society is increasing and the cost of living has flared up, but incomes and deductions for common men and women have come down, which is a worrying factor. On the contrary, the scope for new business operations and jobs is created, which is a positive roadmap for economic development. To name a few optimistic predictions following the pandemic, consider the following: In the IT domain, Indian companies witnessed revenue growth of over 21% in H1, 2021–22. Emerging tech areas like IoT software, big data/analytics, AR/VR, etc. are expected to grow the fastest by 104% between 2018 and 2024. India's healthcare industry, valued at US \$1.9 billion in 2020, is expected to reach US

\$5 billion by 2023, growing at a CAGR of 39%. Overall, the market for online education is projected to reach US \$350 billion by 2025. In India, Worldplay FIS (financial technology product and services provider) predicts that e-commerce will grow by 84% to US \$111 billion by 2024. The services sector's GVA is expected to increase by 8.2 percent in 2021-22. In 2021-22, it is expected that trade, hotels, transportation, communication and broadcasting services, financial, real estate, professional services, public administration, defense, and other services will grow by 11.9 percent, 4 percent, and 10.7 percent, respectively.

Keywords: Pandemic, Lock downs and Services, COVID

Covid-19 Mitigation: What the Evidence Demonstrates is Effective

David J. Weber, MD, MPH, FSHEA, FIDSA, FRSM

SARS-CoV-2 was first reported from Wuhan China in late 2019. SARS-CoV-2 is causative agent of COVID-19, a disease that has resulted in a worldwide pandemic. Worldwide COVID-19 has resulted in over 500 million cases and greater than 6.2 million deaths. The key to preventing or mitigating SARS-CoV-2 is interrupting viral transmission, use of effective and safety vaccines, and uses of pre- and post-exposure medications. SARS-CoV-2 is transmitted by aerosols expelled by infected persons, generally over short distances (i.e., <2 meters). Transmission via hand contamination or via the contaminated environment is felt to play a minor role in transmission. However, transmission from asymptotically infected persons or pre-symptomatic persons has played a major role in transmission.

This presentation will review COVID-19 mitigation strategies with a focus on preventing transmission in healthcare facilities. Effective mitigation strategies will be subdivided into those specifically developed for COVID-19 prevention and strategies generally used to prevent transmission of communicable diseases. Strategies developed specially for COVID-19 mitigation include: universal masking by healthcare providers, patients and visitors; use of N95 respirators and eye protection for all aerosol generating procedures, and care of known and suspected COVID-19 patients; physical distancing when making is not possible (e.g., eating and drinking); personal protection monitors to aid in appropriate donning and doffing; and requiring COVID-19 vaccination as a condition of employment. General infection prevention strategies include hand hygiene, surface disinfection, and wellness checks with evaluation of ill providers by occupational health.

This presentation will also discuss recommended COVID-19 mitigation strategies that lack supportive evidence including improved or enhanced ventilation, Plexiglas barriers, and routine testing of patients prior to aerosol generating procedures.

This presentation will also focus on research published by the presenter on successful strategies for COVID-19 mitigation in K-12 schools, vaccine as a condition of employment in healthcare facilities, and effectiveness of masks for use in both healthcare facilities and communities.

The Financial Impact of Healthcare-Associated Infections from A Hospital Management Perspective

John Shepard

Background: Measuring the financial impact, from the providers perspective, related to healthcare-associated infections (HAIs) is important but complicated. Programs focused on preventing HAIs rely on accurate financial accounting to secure resources needed to prevent HAIs. HAIs contribute to excess length of stay (LOS) and mortality, but the financial burden to the provider is less clear.

Methods: Chart review was performed to identify HAIs using NHSN definitions for patients discharged from Stanford Hospital. Using a two-tail t-test, we tested whether patients with an HAI will have a different daily total hospital cost (DTHC) and a longer LOS than patients without an HAI. We calculated the change in hospital profit related to HAIs by calculating the difference in DTHC and LOS between patients with and without an HAI in the same admit All-Patient Refined Diagnosis Related Group (APR-DRG) and complexity score.

Results: Between October 1, 2015 and September 30, 2018, there were 78,551 inpatient discharges and 1,541 HAIs identified. DTHC and LOS for HAI patients versus patients without an HAI was \$6,433 (\$6,251, \$6,615) versus \$6,604 (\$6,557, \$6,651), ($p=0.073$), and 26.30 days (24.89, 27.71) versus 5.69 (5.64, 5.74) ($p < 0.001$).

Discussion: For each HAI eliminated, data suggests that hospital's total cost, on average, would increase \$25,008 and gross revenue would increase by \$1,518,682 by backfilling hospital beds with new patients at a 4.62:1 ratio (26.30 days/5.69 days). The data suggests a reduction of HAIs is profitable for healthcare facilities.

Conclusion: No matter the cost, patient safety is a top priority. Fortunately, the data suggests hospital cost will increase as HAIs are reduced but hospital profits will also increase.

Heterotopic Ossification post COVID-19

Emad Allam, MD, Rishabh Choudhari, MD, Amany Aziz, MD, Anup Jacob Alexander, MD

Heterotopic ossification has been associated with trauma, surgery, burns, neurologic injury, and infrequently reported with other critical illnesses. More recently, it has been reported in patients following severe COVID-19 infection. Statistically significant risk factors seem to be the length of hospitalization and duration of mechanical ventilation. Such heterotopic ossification may develop around major joints, including the shoulders and hips, and less commonly the elbows and knees. Exacerbation of fibrodysplasia ossificans progressiva has also been reported following COVID-19. The etiology of development of heterotopic ossification following COVID-19 is unclear, with immobilization, prolonged inflammation, and neurogenic causes likely contributing. The rate of heterotopic ossification post COVID-19 has been found to be four times higher than the rate in patients with acute respiratory distress from other causes. Physical examination and radiography are essential to diagnosis. Awareness of this complication and early diagnosis may help minimize functional impairment. Prophylactic measures such as early and frequent mobilization, certain medications, and radiation therapy may be considered in high-risk patients.

Application of Health-Care Networking in COVID-19: A Brief Report

Punidha Kaliaperumal

Healthcare systems all over the world are stretched out and being reconfigured to deal with COVID 19 pandemic. Some countries have flattened the curve, some are still fighting to survive it and others are embracing the second wave. Globally, there is an urgent need to increase the resilience, capacity and capability of healthcare systems to deal with the current crisis and improve upon the future responses. The epidemiological burden of COVID 19 has led to rapid exhaustion of local response resources and massive disruption to the delivery of care in many countries. Healthcare networking and liaison are essential component in disaster management and public health emergencies. It aims to provide logistical support between hospitals; financial support through local or regional governmental & nongovernmental agencies for response; manpower & mechanism for coordination and to implement policies, procedures and technologies in the event of such crisis. This brief report describes how four independent private hospitals in northern India had adopted the principles of healthcare networking, pooled their resources, and scaled up one of the partner hospitals as Dedicated COVID 19 Hospital (DCH) to treat moderate to severe category of COVID 19 patients. It brings out the importance of a unique coalition between private and public healthcare system.

Keywords: COVID 19, healthcare networking, surge capacity, disaster preparedness, pandemic

Deep Learning–Driven Automated Detection of COVID-19 from Radiography Images: A Comparative Analysis

Sejuti Rahman

The COVID-19 pandemic has wreaked havoc on the whole world, taking over half a million lives and capsizing the world economy in unprecedented magnitudes. With the world scampering for a possible vaccine, early detection and containment are the only redress. Existing diagnostic technologies with high accuracy like RT-PCRs are expensive and sophisticated, requiring skilled individuals for specimen collection and screening, resulting in lower outreach. So, methods excluding direct human intervention are much sought after, and artificial intelligence-driven automated diagnosis, especially with radiography images, captured the researchers' interest. This survey marks a detailed inspection of the deep learning–based automated detection of COVID-19 works done to date, a comparison of the available datasets, methodical challenges like imbalanced datasets and others, along with probable solutions with different preprocessing methods, and scopes of future exploration in this arena. We also benchmarked the performance of 315 deep models in diagnosing COVID-19, normal, and pneumonia from X-ray images of a custom dataset created from four others. The dataset is publicly available at <https://github.com /rgbnihal2/COVID-19-X-ray-Dataset>. Our results show that DenseNet201 model with Quadratic SVM classifier performs the best (accuracy: 98.16%, sensitivity: 98.93%, specificity: 98.77%) and maintains high accuracies in other similar architectures as well. This proves that even though radiography images might not be conclusive for radiologists, but it is so for deep learning algorithms for detecting COVID-19. We hope this extensive review will provide a comprehensive guideline for researchers in this field.

Descriptive analysis in the COVID -19 database after one year of the pandemic disease in indigenous patients from the State of Acre**Felipe Lopes and Adolfo Fernandes**

The first cases of coronavirus reported in Acre were confirmed on March 15, 2020, in Rio Branco, and the first contamination case of an indigenous person was confirmed almost two months later, on May 4, 2020. This article aims to follow up on the work Descriptive analysis in the COVID-19 database after one year of the pandemic disease in indigenous patients from the State of Acre, presenting a descriptive analysis of COVID-19 cases in indigenous people after two years of the pandemic in the state. In this paper, new statistical graphs of the total samples and their respective subsamples will be presented when divided by deaths and recovered cases to compare the current situation with the previous one.

COVID-19 convalescent plasma is more than neutralizing antibodies: potential beneficial and detrimental factors**DeLisa Fairweather, PhD**

COVID-19 convalescent plasma (CCP) has been studied for both treatment and post-exposure prophylaxis. The FDA/BARDA funded, Mayo-led Expanded Access Program showed that CCP was safe to administer and decreased mortality at 30 days and that neutralizing antibodies in CCP reduced mortality. Factors that increased mortality included age, ICU admission and gender. Factors that improved the efficacy of CCP included administering CCP early after infection or admission to hospital, using high neutralizing antibody titer CCP, and not using CCP for the treatment of ventilated patients. Aside from neutralizing antibodies, there are a number of other potential additional factors in CCP that can be either beneficial (e.g., AT-III, alpha-1 AT, ACE2+ extracellular vesicles) or detrimental (e.g., anti-ADAMTS13, anti-MDA5 or anti-interferon autoantibodies, procoagulant extracellular vesicles). Variations in these factors in CCP may contribute to varied outcomes in patients with COVID-19 that are undergoing CCP therapy. My lab is examining the role of extracellular vesicles from plasma and CCP for beneficial or detrimental factors. We have found that extracellular vesicles from healthy women can decrease viral myocarditis in male animals, inhibiting many of the proinflammatory pathways that drive COVID. Research into beneficial and detrimental factors may be used to improve the clinical efficacy of CP for COVID and other infections as well as provide insight for the field of regenerative medicine.

The Effects of the COVID-19 Pandemic on Undergraduate Students' Stress and Anxiety in a University in the UAE**Khulood Alfasali, Solomon Arulraj David, Rana M. Tamim**

Education sector faced a significant transition recently, shifting from face-to-face classes to online classes due to the unprecedented COVID-19 pandemic. The pandemic's consequences affected teaching and learning and negatively influenced students' psychological well-being. This study aimed to explore the pandemic's impact on undergraduate students' academic stress, especially as related to their academic performance. Furthermore, the students' coping strategies during the pandemic, if any,

were investigated. The researcher used a mixed-method approach, and surveyed 191 participants from the College of Education (COE) and students from other colleges enrolled in elective courses in the COE in one selected university in the UAE. The qualitative data was collected through a focus group discussion with seven COE undergraduate students doing their internship. The key findings showed that the xenophobia factor (the fear of strangers) causes the highest stress levels, and students reported that workload and time constraint factors were top stressors. Also, A-range students (students with a GPA of 3.7 and above) were significantly less stressed than B-range students (GPA of 2.7–3.3). First-year students were significantly more stressed than second-year, third-year, and fourth-year students. It was found that internship students expressed their stress and anxiety due to the change to online education caused by the pandemic. Single site focus was a key limitation of the study and it was recommended to increase the number of sites and samples. In conclusion, this study helped educational leadership and psychologists to better understand students' needs and create innovative educational platforms.

Keywords: Academic Stress, Academic performance, COVID-19, Leadership, Educational Management, Online Education

COVID-19: The Potential Role of Copper and N-acetylcysteine (NAC) in a Combination of Candidate Antiviral Treatments Against SARS-CoV-2

Andri Andreou, Sofia Trantza, Demetrios Filippou, Nikolaos Sipsas, Sotirios Tsiodras

Background: On March 11, 2020, the World Health Organization (WHO) declared the outbreak of coronavirus disease (COVID-19) a pandemic. Since then, thousands of people have suffered and died, making the need for a treatment of severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) more crucial than ever. Materials and Methods: The authors carried out a search in PubMed, Clinical Trials.gov and New England Journal of Medicine (NEJM) for COVID-19 to provide information on the most promising treatments against SARS-CoV-2. Results: Possible COVID-19 agents with promising efficacy and favorable safety profile were identified. The results support the combination of copper, N-acetylcysteine (NAC), colchicine and nitric oxide (NO) with candidate antiviral agents, remdesivir or EIDD-2801, as a treatment for patients positive for SARS-CoV-2. Conclusion: The authors propose to study the effects of the combination of copper, NAC, colchicine, NO and currently used experimental antiviral agents, remdesivir or EIDD-2801, as a potential treatment scheme for SARSCOV-2.

Efficacy of a Polyphenolic, Standardized Green Tea Extract for the Treatment of COVID-19 Syndrome: A Proof-of-Principle Study

Saverio Bettuzzi, Luigi Gabba, Simona Cataldo and Valeria Naponelli

Introduction: Catechins from green tea are known to be powerful antioxidant, anti-inflammatory and antiviral agents that are safe for human use. The lack of therapies for moderate COVID-19 syndrome prompted us to use a standardized polyphenolic green tea extract rich in catechins during the lockdown due to the pandemic in Italy that occurred in Autumn 2020. To this end, we designed a clinical trial that could leverage an easy-to-perform and low-cost home treatment. Patients were recruited and followed by family doctors at their home.

Methods/Treatment: While awaiting hospitalization, 10 swab-positive patients, all symptomatic for SARS-COV-2, were treated at home for 15 days with a highly purified catechin extract (Theaphenon E, provided by Tea Solutions, Tokyo, Japan) given as two sessions of inhalation plus three capsules per day (total catechins/day: 840 mg; total EGCG: 595 mg). Nasopharyngeal swab and blood laboratory tests were performed at beginning and at the end of treatment.

Results: All patients responded to treatment and recovered fully, showing no symptoms at a median of 9 days, with a range of 7–15 days. Seven switched to a negative SARS-COV-2 nasopharyngeal swab test at a median of 9 days, with a range of 6–13 days. Among the 3 patients still swab-positive, one had a strong decrease of infection down to a “very low” SARS-COV-2 nucleic acid load at 5 days. All patients exited quarantine at the end of therapy because they were free of symptoms. Inflammation markers alpha-1 anti-trypsin, C-reactive protein and eosinophils significantly decreased. IL-6 and erythrocyte sedimentation rate decreased in 7 out of 10 patients. No side effects of any kind were recorded during the study.

Conclusions: To the best of our knowledge, this is the first report of the efficacy of green tea catechins against COVID-19 syndrome. If confirmed by further studies, this proof-of-principle study shows for the first time that a highly purified catechin extract, given both by inhalation and orally, may result in a very cheap and easy to perform therapy that could be done at home, reducing hospital admissions and treatment costs. Considering that COVID-19 vaccines are not widely available, mostly in poor Countries, these results may open new perspectives in the fight against the disease.

Keywords: antioxidant; antiviral; catechin; COVID-19; cytokine storm; EGCG; green tea; IL-6; inflammation; polyphenols; SARS-COV-2; Theaphenon E

The Role of the Thymus in COVID-19 Disease Severity: Implications for Antibody Treatment and Immunization

Ozlem Equils

The thymus is a largely neglected organ but plays a significant role in the regulation of adaptive immune responses. The effect of aging on the thymus and immune senescence is well established, and the resulting inflammaging is found to be implicated in the development of many chronic diseases including atherosclerosis, hypertension and type 2 diabetes. Both aging and diseases of inflammaging are associated with severe COVID-19 disease, and a dysfunctional thymus may be a predisposing factor. In addition, insults on the thymus during childhood may lead to abnormal thymic function and may explain severe COVID-19 disease among younger individuals; therefore, measurement of thymic function may assist COVID-19 care. Those with poor thymic function may be treated prophylactically with convalescent serum or recombinant antibodies, and they may respond better to high-dose or adjuvanted COVID-19 vaccines. Treatments inducing thymic regeneration may improve patients' overall health and may be incorporated in COVID-19 management.

COVID-19 Associated with Pulmonary Thrombosis

Shaghayegh Rahmani

We describe a 33 yrs. Old male patient with COVID-19 who developed pulmonary thrombosis. A young man, with history of trauma, 2 weeks before, was admitted with a 4-day breathlessness and chest pain. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection was revealed by a real-time reverse transcription polymerase chain reaction (rRT -PCR) test. He received enoxaparin for the last 10 days. A lung HRCT and CT pulmonary angiography (CTPA) was performed for him and acute pulmonary thromboembolism (PTE) was confirmed. This case highlights the risk of vascular sequences associated with SARS-CoV-2, and the fact that thrombotic events can occur in these patients' despite of prophylactic dose anticoagulation. We suggest to administer directly therapeutic doses of anticoagulants for a prolonged phase in COVID-19 patients.

Keywords: COVID-19; Embolism and Thrombosis; Computed Tomography Angiography

Telemedicine Application & Innovation in Surgical Outpatient Clinics During & Beyond COVID-19

Thomas McMaster

The COVID-19 pandemic caused a dramatic shift in how medical professionals deliver safe and effective healthcare whilst located remotely from consumers. Telemedicine rapidly became the most feasible solution to address strict social distancing requirements worldwide, as it is the, "use of electronic communications and information technologies to provide clinical services when participants are at different locations"¹. It's universal application across many domains of clinical practice has paved the way for exciting and innovative advancements in healthcare delivery.

Specific to surgical clinics, virtual interactions which may be particularly challenging include consent, breaking bad news and clinical examinations for surgical planning, which need to be met with adaptations to how telemedicine is delivered.

Based on current literature, we will discuss the following innovations: protocol/workflows, software/medical record integration, consent, billing, virtual examinations, and monitoring systems. We also aim to present practical a means to implement an effective telemedicine service as well as provide a glimpse into future developments and ideas shaping healthcare delivery. The universal uptake of telemedicine and high satisfactions suggests longevity in its application to surgical care, as patients and providers become increasingly accustomed to its use.

Building a Life Worth Living During a Pandemic and Beyond - Adaptations of Comprehensive DBT to COVID-19

Virginia O'Hayer

Our team at the Jefferson Center City Clinic for Behavioral Medicine was urgently challenged to find a synthesis between the need to adapt to circumstances associated with the COVID-19 pandemic, while at the same time retaining the spirit and essential components of comprehensive DBT. This fine balance between unwavering centeredness and compassionate flexibility is central to DBT (Linehan, 1993), and has proven essential during these times of uncertainty. Dr. O'Hayer highlights challenges and innovations faced by our DBT Team, Skills Group, individual DBT sessions, phone coaching, and also our

community at large, as we strive to help our patients and team members build a life worth living during and following a pandemic.

Dispositional mindfulness mediates the relationship between conscientiousness and mental health-related issues in Chinese adolescents during the COVID-19 pandemic

Shoukuan Mu, Tiantian Liu, Zhenliang Liu, Lijia Zhang

The COVID-19 pandemic is seriously affecting the mental health of adolescents and triggering a series of mental health-related issues. The present study investigates the relationships between conscientiousness, dispositional mindfulness, and adolescents' mental health-related issues during this time. In this study, 5994 Chinese adolescents completed an anonymous online survey; this survey included the conscientiousness subscale of the Big Five Inventory, the Mindful Attention Awareness Scale, and a series of mental health scales including anxiety, depression, and perceived stress. Conscientiousness was found to be negatively associated with anxiety, depression, and perceived stress. It was found to be positively associated with dispositional mindfulness, which, in turn, negatively predicts anxiety, depression, and perceived stress. Conscientiousness is thus related to mental health-related issues, and this relationship is mediated by dispositional mindfulness. This mediation effect is stronger in females than in males. These findings provide new and strong evidence for the protective role of conscientiousness and dispositional mindfulness in adolescents' mental health-related issues during the COVID-19 pandemic.

Keywords: conscientiousness, mindfulness, anxiety, depression, perceived stress, gender differences

Towards Quantitative and Comparable Serological and Neutralization Assays for COVID-19

Lili Wang

The global response to COVID-19 has spurred innovations in diagnostics, surveillance, and vaccine development at an unprecedented pace. Quantitative and robust serology assays are critical measurements for accessing the complex patient responses to SARS-CoV-2 that causes the disease. Hence, we developed quantitative, multiplexed flow cytometry based serological and neutralization assays. The serology assays test the IgG and IgM against both the full-length spike antigens and the receptor binding domain (RBD) of the spike antigen. Both cell-based pseudovirus and bead-based surrogate neutralization assays were also developed. We further demonstrated good correlation between anti-RBD and anti-spike antibody titers and neutralizing antibody titers. The suite of serology and neutralization assays help to improve measurement confidence and are complementary and foundational for clinical and epidemiologic studies.

Numerous serology assays have been developed for SARS-CoV-2, utilizing a wide range of technologies, antigens, and reagents. However, there are limited direct comparisons of datasets from different serology assay platforms provided by different laboratories and manufacturers in the public domain. We have teamed up with CDC and organized an interlaboratory study for evaluating assay performance and inter-assay correlations using WHO International Standard and an anti-SARS-CoV-2 mAb panel. The primary objective of the study is to determine the suitability of a mAb panel to be used in conjunction with the

WHO IS for enabling more quantitative serology assays. Preliminary results demonstrate the utility of a mAb panel particularly in the absence of matrix-matching reference standard(s).

The Association Between Antibody Response to Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Post–COVID-19 Syndrome in Healthcare Workers

Christopher Pereira

It is currently unknown how post-COVID-19 syndrome (PCS) may affect those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This longitudinal study includes healthcare staff who tested positive for SARS-CoV-2 between March and April 2020, with follow-up of their antibody titers and symptoms. More than half (21 of 38) had PCS after 7-8 months. There was no statistically significant difference between initial reverse-transcription polymerase chain reaction titers or serial antibody levels between those who did and those who did not develop PCS. This study highlights the relative commonality of PCS in healthcare workers and this should be considered in vaccination scheduling and workforce planning to allow adequate frontline staffing numbers.

Mitigating the increase in developmental and mental health presentations in children: Challenges and Opportunities in the Covid and the post-Covid period

Valsamma Eapen

Children with developmental and mental health disabilities are experiencing significant challenges to service access due to suspension of in-person services during the current COVID-19 pandemic. Telehealth is rapidly becoming the new service delivery model, which presents a unique opportunity for innovation in care that could be beneficial in the post-pandemic period. However, there are also significant limitations and challenges due to the surge in need and the limited availability of child mental health workforce capacity. In this regard, our national survey of parents of children with a developmental condition in Australia and Italy has shown the emergence of a 'shadow' mental health pandemic. Our Australian survey also highlighted a gap between the mental health needs of these children and what could be provided via telehealth. An attitudinal survey of child and adolescent psychiatry professionals that we conducted also revealed the need for safeguards to be put in place to address issues of risk and safety while delivering care via telehealth indicating the need for further innovations to close this gap. In addition, our research using data on hospital attendance has indicated that the demand for child and adolescent mental health services has exceeded the existing capacity of the system to meet this demand. It is proposed that a collaborative care model through a consultation and capacity building approach by mental health specialists involving primary and secondary health care professionals as a 'MIND LINK Community of Practice' is the need of the hour. This is expected to empower primary (GPs) and secondary (Paediatricians) care physicians to provide mental health services in the community with options for 'step up' to specialist child and adolescent mental health experts and services. This will need to be coupled with implementing innovative digital 'front door' solutions with a 'triage and review' and a 'tiered' approach to service delivery, further complemented by prevention and wellbeing strategies such as lifestyle programs and parenting supports as key examples. While child

and adolescent psychiatrists will continue to be at the centre of delivering care for children and young people presenting with mental health issues, the rising demand and the limited manpower resources would mean that this challenge cannot be met by mental health specialists alone and therefore there is a convincing argument for enhancing psychiatric education within the medical curriculum and for psychiatry skills building of the medical workforce in general.

ESMED Presentation on Diversity, Migration and COVID-19

Dr. Ulrike Elsdörfer PhD

The presentation centers on mental challenges of migrants and asylum seekers in Europe, fleeing situations of war, persecution and oppression. It refers mainly to refugees from culturally diverse regions, mostly diverse to Western standards.

COVID-19 is topping the existing social insecurity and feelings of adversity and estrangement. A study of refugees and asylum seekers in Nottingham, UK, points out the situation which is worsened by COVID-19.

Transcultural psychiatry and ethnosocial approaches to psychology provide a theoretical framework to point out the needs of Mental Health Care for migrants in Europe – without limits of law and finances. PTSD as diagnosis and different approaches to Trauma Counselling may assist to lower the blood pressure of migrants (Ilkic 2007). DSM-5 presents an Outline for Cultural Formulation (OCF) and Cultural Formulation Interview (CFI). Global Mental Health is rooted in critical self-reflection of Western standards of psychiatry and in growing cultural sensitivity. When promoting Global Mental Health programs, an interdisciplinary discourse is necessary as well as the willingness to step away from ethnocentric based production of generalizable knowledge in psychotherapy.

A Protocol for Carotid Artery Stenting in COVID Times. A Single Canadian Centre Experience

Ruba Kiwan.MD

Objectives: The COVID-19 pandemic has resulted in huge disruption to healthcare delivery worldwide. There is a need to balance the urgent needs of the neurovascular patient population with the desire to preserve critical inpatient hospital capacity

Patients still require semi-urgent carotid revascularisation after ischaemic embolic events. We present a review of a novel protocol for expediting patient flow through the carotid stenting process, in accordance with government directives to minimise non-essential inpatient admissions, ensure its efficacy, & evaluate its safety. We also evaluate the literature regarding complications with attention to the timing of these related to the procedure.

Methods: A retrospective review of 45 consecutive carotid stenting cases performed at London Health Sciences Centre (LHSC) between March 2020 and March 2021 for symptomatic extracranial Internal Carotid Artery (ICA) stenosis utilising a default same day discharge policy was performed. Complications were plotted as a function of time.

Results: 24 patients underwent carotid artery stenting with same day discharge and 21 patients underwent stenting with an overnight inpatient stay. A single stent occlusion occurred 27 hours post stenting.

Conclusion: Simple modification of protocol for symptomatic carotid artery stenting during the COVID-19 outbreak with radial access as first approach appears to provide safe, efficacious care.

Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19

David Altschul

Objective: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is protean in its manifestations, affecting nearly every organ system. However, nervous system involvement and its effect on disease outcome are poorly characterized. The objective of this study was to determine whether neurologic syndromes are associated with increased risk of inpatient mortality.

Methods: A total of 581 hospitalized patients with confirmed SARS-CoV-2 infection, neurologic involvement, and brain imaging were compared to hospitalized non-neurologic patients with coronavirus disease 2019 (COVID-19). Four patterns of neurologic manifestations were identified: acute stroke, new or recrudescing seizures, altered mentation with normal imaging, and neuro-COVID-19 complex. Factors present on admission were analyzed as potential predictors of in-hospital mortality, including sociodemographic variables, preexisting comorbidities, vital signs, laboratory values, and pattern of neurologic manifestations. Significant predictors were incorporated into a disease severity score. Patients with neurologic manifestations were matched with patients of the same age and disease severity to assess the risk of death.

Results: A total of 4,711 patients with confirmed SARS-CoV-2 infection were admitted to one medical system in New York City during a 6-week period. Of these, 581 (12%) had neurologic issues of sufficient concern to warrant neuroimaging. These patients were compared to 1,743 non-neurologic patients with COVID-19 matched for age and disease severity admitted during the same period. Patients with altered mentation ($n = 258, p = 0.04$, odds ratio [OR] 1.39, confidence interval [CI] 1.04-1.86) or radiologically confirmed stroke ($n = 55, p = 0.001$, OR 3.1, CI 1.65-5.92) had a higher risk of mortality than age- and severity-matched controls.

Conclusions: The incidence of altered mentation or stroke on admission predicts a modest but significantly higher risk of in-hospital mortality independent of disease severity. While other biomarker factors also predict mortality, measures to identify and treat such patients may be important in reducing overall mortality of COVID-19.

COVID-19 Remote Consultation Services and Population in Health Inequity-Concentrating Territories: A Scoping Review

Angelica Baptista

Systematic studies on people's opinions most affected by health inequities are limited. We aimed to map initiatives for measuring the satisfaction of vulnerable populations with teleconsultation services offered by public and private health care providers in their territories during the coronavirus disease (COVID-19) pandemic. We included evaluations of

teleconsultation-based services offered globally to socioeconomically disadvantaged and clinically vulnerable populations, focusing on COVID-19 healthcare.

We selected analytical and descriptive observational studies primarily from MEDLINE, EMBASE, SCOPUS, and Web of Science databases, in the first year of the pandemic (2020). The search strategy combined aspects of COVID-19, telemedicine, patient satisfaction, and key concepts of vulnerable populations. We selected 33 studies for full-text reading, and two themes emerged: telehealth evaluation and services during COVID-19 and opinions of vulnerable populations. Television and social networks played a crucial role in providing information. Although teleconsultations are practical and cost-effective for patients, most prefer receiving in-person treatment in primary care clinics.

Vulnerable groups and others living and sleeping in the same rooms or on the streets, deprived of basic needs, such as freshwater, have different problems and require special communication. They need to be treated in a specific way that preserves their rights and allows them to survive during pandemic times. Listening to vulnerable groups' opinions and their caregivers was critical before and during the adoption of COVID-19 control measures. Health managers need to closely monitor the health of and delivery of services to socioeconomically and clinically vulnerable people to improve services and provide care from a human rights perspective. The perception of patients about teleconsultation models should be taken into account because, despite the possible challenge of access to resources, the acceptance of the offered services indicates a great investment opportunity for public digital health policies. The pandemic has created a favourable scenario to conduct gold-standard epidemiological studies combined with telehealth and digital health among various medical specialities.

E-education in crisis situations affects new thinking in higher education

Prof. Nitza Davidovitch, Ariel University

Introduction: The COVID-19 year was a difficult and challenging year in all areas of life. , In a matter of days, the academic world was compelled to shift from face-to-face learning on campus to e-learning from a distance, with no adequate preparation. Equipped with the lessons learned from this experience, the Israeli Council for Higher Education and institutions of higher education are preparing for a new era, where online courses will constitute an integral part of studies.

Research Methods: This study uses a systemic, multi-institutional perspective to examine lecturers' and students' attitudes toward e-teaching, including the benefits and shortcomings of its elements. The study included 2,015 students and 223 lecturers in Israeli universities, academic colleges of education, academic colleges of engineering, and private colleges.

Results: Findings show that only one third of the lecturers expressed a preference for e-learning. With regard to the types of preferred e-lessons: 69% would prefer to teach theoretical classes online, while 42% would prefer to teach tutorials online. A small minority preferred to teach practical classes conduct workshops online. Lecturers were found to have more negative opinions of e-teaching than students: 60% of the lecturers but only 40% were dissatisfied with e-learning's effect on the interpersonal interactions between lecturers

and students About two thirds of lecturers noted the lack of social and emotional personal interaction with students and lecturers as one of the main shortcomings of e-learning. Only one third of the lecturers stated that teaching standards in e-learning were higher than in face-to-face teaching. Only one sixth of the lecturers stated that e-learning is beneficial for students, specifically their ability to master the material.

Discussion and Conclusions: The study indicates the need for lecturers to reexamine the teaching and learning processes and adjust their roles and responsibilities to the new opportunities offered by the new technological tools and learning environments. E-learning success requires new pedagogical educational approaches rather than copying teaching patterns from traditional frontal approaches to online teaching platforms. Despite its challenges, the academic education system has proven that distance learning has many advantages, including the ability to study anytime and anywhere, increased planning efficiency, and increased ability to adapt courses and study methods to the students. Nevertheless, the research findings prove that there is no substitute for personal contact and encounters between s teachers and students and among students. E-learning constitutes a unique, powerful solution, but it is not an exclusive solution, and not necessarily appropriate for all disciplines and teaching and learning goals. Combining e-learning with face-to-face learning can enhance students' learning experience and achievements. To this end, advance preparation, including new campus schedules, might help lecturers to adapt to the challenging tasks of future teaching.

Culture, Political Ideology, and Responses to a Global Pandemic

R. Jeffrey Melton

Over the past two years, COVID-19 has caused millions of deaths, hospitalizations, and cases of severe and long-term illness. However, its impact has, even prior to the introduction of COVID-19 vaccinations, varied widely across different geographical regions. Our research has shown that, although vaccines have been effective in reducing rates of infection and, even more so, severe disease and death, differences in behavior and government policy have had a greater impact than differences in vaccination rates. We found that individualistic cultures (cultures oriented toward self-interest) had substantially higher rates of COVID infections and deaths than collectivist cultures (cultures that are oriented toward group welfare). Moreover, within individualistic cultures, geographical regions (states or provinces) that are more politically conservative had higher infection and death rates than less conservative regions. Furthermore, collectivist countries enacted mask mandates and lockdowns sooner after their first reported case than individualistic countries, and the timing of mask mandate and lockdown enactment was associated with IPM and DPM rates. Anti-mask or anti-lockdown protests were also more common in individualistic countries, and the occurrence of such protests was related to “spikes” in infection rates. Similar differences in government policy (e.g., mandating masks for longer periods of time and being more likely to enact vaccine mandates) and individual conduct (e.g., vaccination rates) were found between more conservative and more liberal U.S. states and Canadian provinces. In addition to presenting the details of these findings, we will discuss implications and directions for future research.

Vulnerability and the Resilience Against Covid-19 in India

Satya Paul

This paper measures vulnerability and discusses resilience to fight against Covid-19 virus in India. The vulnerability indices are constructed for the domains of hospital infrastructure, demography, housing, and health for 36 states and territories of India. An overall vulnerability index is computed as the weighted average of domain-specific indices. The results reveal that vulnerability to corona virus varies significantly across the states. The hospital and health vulnerabilities contribute most to the overall vulnerability in all the states. The coronavirus cases vary across the states and change daily. As on 24 Nov. 2020, the corona cases are the highest in Maharashtra, followed by Karnataka, Andhra Pradesh, and Tamil Nadu. These four states account for around 47% of total corona cases in India. The resilience to fight against the virus is weak in India. Compared to developed nations, the hospital infrastructure facilities are quite poor. India spends incredibly low percentage of GDP on health. The lockdown imposed by government of India to control the spread of virus has severely affected jobs, incomes, and consumer demand. The government should enhance fiscal spending to stimulate consumer demand and strengthen the national resilience to fight against the virus.

Keywords: Covid-19, lockdown, vulnerability indices, testing of virus, resilience, hospital infrastructure, health spending, fiscal spending.

Skin Reactions to Personal Protective Equipment among First-Line COVID-19 Healthcare Workers

Marraha Farah

Introduction: Health care workers (HCWs) adopted several protective measures, including hand hygiene and wearing personal protective equipment (PPE) during the COVID-19 outbreak. However, the frequent use of these preventive measures can lead to skin reactions. Our study aimed to determine the frequency of these reactions in Northern Morocco. In addition, we also looked at the risk factors and the consequences of these injuries on work efficiency and performance.

Materials and methods: An anonymous online survey was used to collect data, which was sent to

500 health workers in the study region. It was in the form of a short or multiple-choice response with several photos and illustrations to facilitate the choice of answers. Each part dealt with one type of protective activity or equipment, the frequency of its use, the duration of the symptoms, and the lesions reported after wearing. Descriptive and inferential statistics were used to analyze the data on IBM SPSS software. The results of this work have already been published in an international indexed journal: doi:10.1093/annweh/wxab018.

Results: In total, 273/500 responded to the questionnaire (55%). For the participants' profession, 41% were doctors, 32% were nursing staff, and 26% held other jobs. The general prevalence rate of adverse reactions for all health workers was (80%), including skin problems: after wearing goggles (58%), after wearing surgical masks and respirators (57%),

after handwashing and wearing gloves (45%), after wearing a face shield (23%), and after wearing protective clothing (11%). Bleach immersion was highly significantly associated with hand reaction (OR: 2.9, 95% CI: 1.77–4.90; $P < 0.001$).

Moreover, we found a statistically significant association between hand cream use more than twice

daily and fewer reactions (OR: 1.9, 95% CI: 0.98–3.77; $P = 0.038$). The skin reactions related to goggles use were also significantly associated with use duration (OR: 1.7, 95% CI: 0.988–3.12; $P = 0.05$).

Similarly, wearing masks and N95 respirators and their related adverse reactions were significantly

associated with use duration (OR: 0.5, 95% CI: 0.20–0.7; $P = 0.02$). In addition, adverse reactions of regular use of protective clothing were related to the frequency of its use per shift (OR: 3.5, 95% CI: 1.47–8.54; $P = 0.05$).

Discussion: The COVID-19 pandemic has heightened the use of personal protective equipment and hygiene activities among healthcare workers. We surveyed healthcare workers in Morocco, and found that 80% of respondents reported adverse skin reactions associated with work. Bleach immersion for cleaning and was associated with increased prevalence of skin reactions on the hand, and skin reactions were generally associated with personal protective equipment (other than gloves) when used over longer durations or more days of work per week. Intensive use of personal protective equipment and hygiene may adversely affect skin health.

Talent Management for a Post-COVID-19 Supply Chain—The Critical Role for Managers

Remko Van Hoek

This session considers supply chain risk scenarios during the pandemic and explores how these apply in the pharma and medical industry. A roadmap for navigating the risks and improving supply chain resiliency is offered and a procurement executive perspective is offered.

Work Stress, Dysbiosis, and Immune Dysregulation: The Interconnected Triad in COVID 19 Infection in the Medical Team Staff – A Mini Review

Shimaa Mohammad Yousof, Imrana Tanvir, Eman Kolieb, Rasha Atta

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The COVID 19 pandemic has affected almost every community on the planet. Pandemics have previously been shown to have psychological effects on general populations as well as specific communities such as students and health professionals. A small number of publications have focused on the interaction of complicated elements that contribute to the disease's etiology. The goal of this review was to bring together available information on the various molecular mechanisms that predispose to COVID 19 infection in health care workers. The "stress, microbiota, and immunity" triad was our summary of these factors. We

searched the literature using the PubMed database, Google, and Google Scholar search engines for combinations of these keywords: "pandemics, COVID 19, coronavirus, SARS CoV2;" "work stress, workload, health workers, health professions, and medical team;" "gut microbiota, gut lung axis, dysbiosis, nutrition;" "Immunity, cytokine storm, and viral load," for example. There were no discussions about the medical team individuals that combined the suggested triad. We shed light on the potential pathogenic function of the "stress, microbiota, and immunity triad" in COVID 19 infected health workers for the first time to our knowledge.

Keywords: Coronavirus, COVID 19, cytokine storm, dysbiosis, immunity, microbiota, work stress

Improving Outcomes for Hospitalized Patients: Pre- and Post-COVID-19

Richard Hurtig

Barriers to effective patient-provider communication increase the risk that a patient will experience a hospital acquired condition (HAC) that will negatively impact the patient's health outcomes. This is of critical relevance now, as the COVID-19 pandemic has dramatically increased the number of patients who face communication barriers and the accompanying challenges encountered by their health care providers.

Providing hospitalized patients with communication tools can significantly reduce patient and provider stress as well the risks of patients experiencing HACs.

Effect of covid-19 Pandemic on Sleep Parameters and the Practice of Sleep Medicine in India

Shweta Kanchan

COVID-19 Pandemic which began in the early part of 2020, was marked with sleep disturbances as a result of different psychosocial factors. Sleep disorders during the COVID-19 pandemic were increased however the sleep medicine practice could not keep up with the increased burden of disease owing to a number of factors. The present study was conducted to understand the effect of COVID-19 pandemic on sleep variables and the practice of sleep medicine across India during the pandemic time

The study showed that the subjective sleep quality estimation using Pittsburgh sleep quality index became significantly poor, mean PSQI scale before COVID-19 pandemic was 4.37 and after COVID -19 pandemic it became 5.68. Sleep Latency also showed a significant increase during the COVID-19 pandemic. The prevalence of Insomnia increased by nearly 44.9 %, there was also a significant increase in the circadian rhythm sleep disorders during the pandemic.

The practice of sleep medicine declined during the COVID-19 pandemic. 72% of the sleep laboratories were closed while 24% of the sleep Laboratories had shifted to an exclusive home sleep testing during the pandemic. 61% of sleep physicians started advising mitigation strategies as a temporary measure for their patients of sleep apnea. 58.6 % opined that auto positive airway pressure might be used in patients of uncomplicated obstructive sleep apnea without conventional diagnostic testing. 84% of sleep physicians reported that they continued to give services through telemedicine services.

The above study clearly depicted poor sleep quality and increased burden of sleep disorders during the COVID-19 pandemic. However, sleep medicine practice declined during the covid-19 pandemic and could not keep up with the increased the burden of sleep disorders.

Pulmonary function evaluation after hospital discharge of patients with severe COVID-19

Isac Ribeiro Moulaz

Background and Objectives: Coronavirus disease 2019 (COVID-19) may be associated with prolonged symptoms and post-recovery health impairment. This study aimed to evaluate the persistence of symptoms, lung function, and pulmonary diffusion for carbon monoxide (DLCO) in patients between 15 and 30 days after hospital discharge after admission for severe COVID-19.

Methods: This is a cross-sectional study conducted with patients of both sexes, aged >18 years, hospitalized with a diagnosis of COVID-19 who needed supplemental oxygen or ventilatory support and presented with a severe form of the disease. The evaluation consisted of 1) comparative analysis between the initial symptoms and symptoms still present at the post-discharge evaluation, 2) analysis of the chest images obtained during hospitalization, and 3) conducting spirometry, plethysmography, and DLCO assessment.

Results: Forty-one patients who were hospitalized for 16 ± 8 days with severe COVID-19 were included. Patients were predominantly men (73%) and had a mean age of 51 ± 14 years. The most frequent comorbidities were arterial hypertension (51%) and diabetes mellitus (37%). Pulmonary evaluation was performed a mean of 36 days after the onset of symptoms, with the most frequent persistent symptoms being dyspnea (83%) and coughing (54%). Approximately 93% of patients still had at least one symptom, and 20% had more than five symptoms. Chest imaging revealed a typical pattern of COVID-19 on X-ray (93%) and computer tomography (95%). Lung function test results showed a restrictive pattern with a reduction in forced vital capacity (FVC) in 54% of individuals, with an average FVC of $78\pm 14\%$. A reduction in DLCO was observed in 79% of patients.

Conclusions: Individuals who developed severe COVID-19 had various persistent symptoms after hospital discharge. In these patients, changes detected using spirometry and DLCO were present in approximately 80% of patients, representing possible functional impairment resulting from lung damage. Considering the high number of survivors of COVID-19, it is extremely important to characterize these symptoms' evolution to implement therapeutic interventions aimed at their prevention and/or treatment. Our study indicates an important economic consequence of the disease at an early post-hospital phase, given the persistent pulmonary impairment and functional capacity, limiting patients' return to routine work activities.

A Safer World after Vaccination against COVID-19 a comparison of Government Responses and Health Outcomes in 14 countries

Johnston HC Wong

During the first year of Pandemic attack in 2020, world governments split between the herd immunity strategy and that of strict social distancing. Health outcomes of 14 countries analyzed revealed unexpectedly high levels of deaths due to the disease particularly among those countries which relaxed control as early as April 2020. Public health experts predicted that the Pandemic of COVID-19, though mutated into Delta, would come to an end in mid 2021, when vaccination became available. Unfortunately, the situations were more complicated and disappointing as the corona virus mutated further into another generation. Omicron spread even faster and killed much less than Delta, some early records showed. Some countries, for example United Kingdom and Japan, have declared the dates of returning to normal; other countries like China is still struggling to Zero the Omicron. As Hong Kong has lost 3875 lives in spring of 2022, a similar death rate projected on China will be astronomical. For China the public health crisis prolonged, policies of social distancing were upheld, and international doors cannot be opened. This study reviewed government responses and health performances of 14 countries in 2020, 2021 and early 2022. The 3 periods were characterized by the impact of COVID-19, Delta and Omicron. Major indicators analyzed include data from Government Responses and Stringency Index developed by Oxford Tracker, and health data provided by WHO and John Hopkins University. Effects on economies and health care financing, mostly reported by the Economist Intelligence Unit, would also be discussed.

Keywords: Social Distancing Stringency, COVID-19 mutations, Government Emergency Responses, Public Health Crisis

Clinical spectrum and outcome of patients visiting coronavirus screening centre in North India and clinical predictors for COVID 19

Neeraj Singla

Aim: The aim of the study was to elucidate the demographics, symptoms and outcome of sick persons visiting coronavirus (COVID) screening OPD of a tertiary institute in North India.

Study Design: The descriptive, prospective study was done on 1030 patients and information about presenting symptoms, demographics (age, sex, nationality, residence), contact and travel history, comorbidities etc., were recorded. On the basis of criteria given by Indian Council of Medical Research, patients were divided into suspected (SARS-CoV-2) and non-suspected group. Of the suspected patients, with RT-PCR test positive was classified as confirmed COVID-19 case and negative RT-PCR symptomatic individual was defined as negative COVID-19 case.

Results: Out of the total patients, 65.6% were male and 34.4% were females. The mean age was 37.04 years. Fever 49.3%, cough 57.1% and sore throat 43.5% were the main symptoms. Comorbidities were seen in 8.5% patients with hypertension (3.5%) and diabetes mellitus (3.4%). Forty patients were positive. Highly significant correlation ($P < 0.01$) was found between COVID-19 positive status and in patients without any symptoms, between COVID-19 and cough and sore throat, between COVID-19 and comorbidity (diabetes mellitus), between COVID-19 and high-risk exposures (resident of hot spot and history of contact with confirmed case). Our study also found

COVID-19 positive status, shortness of breath and tachycardia as independent predictors of mortality ($P < 0.05$).

Conclusions: Most of the patients were young adults and males were mainly affected. Main presentation was cough followed by fever. Infectivity was higher in patients who had underlying comorbid diseases, especially diabetes and chronic kidney disease. Critical patients with decreased oxygen saturation, tachypnoea and tachycardia had strong predictability for COVID-19 positivity. COVID-19 positive status, shortness of breath and tachycardia are important predictors of mortality.

Keywords: COVID-19, clinical predictors, cough, critical condition, tachycardia, tachypnoea

Morbidity And Mortality in Patients Undergoing Lower Limb Arthroplasty Surgery During the Initial Surge of the COVID-19 Pandemic in The UK At a Single-Specialty Orthopedic Hospital

A Vasudev, A Sharma, G Cooper, J Stevenson, M Parry, D Dunlop, Y Agrawal

Aims: The COVID-19 pandemic posed significant challenges to healthcare systems across the globe in 2020. There were concerns surrounding early reports of increased mortality among patients undergoing emergency or non-urgent surgery. We report the morbidity and mortality in patients who underwent arthroplasty procedures during the UK first stage of the pandemic.

Methods: Institutional review board approval was obtained for a review of prospectively collected data on consecutive patients who underwent arthroplasty procedures between March and May 2020 at a specialist orthopaedic centre in the UK. Data included diagnoses, comorbidities, BMI, American Society of Anesthesiologists grade, length of stay, and complications. The primary outcome was 30-day mortality and secondary outcomes were prevalence of SARS-CoV-2 infection, medical and surgical complications, and readmission within 30 days of discharge. The data collated were compared with series from the preceding three months.

Results: There were 167 elective procedures performed in the first three weeks of the study period, prior to the first national lockdown, and 57 emergency procedures thereafter. Three patients (1.3%) were readmitted within 30 days of discharge. There was one death (0.45%) due to SARS-CoV-2 infection after an emergency procedure. None of the patients developed complications of SARS-CoV-2 infection after elective arthroplasty. There was no observed spike in complications during in-hospital stay or in the early postoperative period. There was no statistically significant difference in survival between pre-COVID-19 and peri-COVID-19 groups ($p = 0.624$). We observed a higher number of emergency procedures performed during the pandemic within our institute.

Conclusion: An international cohort has reported 30-day mortality as 28.8% following orthopaedic procedures during the pandemic. There are currently no reports on clinical outcomes of patients treated with lower limb reconstructive surgery during the same period. While an effective vaccine is developed and widely accepted, it is very likely that SARS-CoV2 infection remains endemic. We believe that this report will help guide future restoration planning here in the UK and abroad.

Retrospective analysis of COVID-19 patients in the region of Eastern Achaia, Greece, in a Primary and Secondary Health Care Setting

Panagiota Xaplanteri

Background: Since December 2019 mankind is agonized over the deadly coronavirus disease 2019 (COVID-19) which is due to the novel coronavirus (2019-nCoV) or Severe Acute Respiratory Syndrome Coronavirus-2 (Sars-cov-2).

Methods: In this retrospective study, laboratory findings and demographic features from all confirmed COVID-19 patients who attended the Emergency Department of both branches of our hospital during the first semester of 2021 were collected and analyzed. The working hypothesis was that initial laboratory data at the time the patients sought medical assistance for the first time, regardless of comorbidities and day of onset of symptoms, can help predict patients' outcome. Demographic data and laboratory tests were compared between hospitalized and non-hospitalized patients.

Results: Data of 270 patients were collected and analyzed retrospectively. 31 blood measurement parameters performed in both hospital branches were compared between hospitalized and non-hospitalized patients. Of those, WBC count ($p=0.016$), neutrophil percentage ($p<0.001$), lymphocyte percentage ($p<0.001$), platelet count ($p=0.041$), glucose ($p<0.001$), urea ($p<0.001$), creatinine ($p<0.001$), SGOT ($p=0.024$), CK ($p<0.053$), LDH ($p<0.001$), GGT ($p<0.001$), sodium ($p<0.001$), calcium ($p<0.001$), high sensitivity Troponin I ($p<0.001$), and ferritin levels ($p<0.001$), proved statistically significant. Regarding demographic data, age was significantly linked to patients' survival.

Conclusion: Our data suggest that common initial laboratory findings of COVID-19 patients who seek for the first-time medical assistance regardless of comorbidities and time from onset of symptoms can give clues to the patient outcome. Age is also important for patients' survival. Especially in a Primary Health Care Setting, common blood parameters like WBC count, neutrophil and lymphocyte percentage, platelet count, glucose, urea, creatinine, SGOT, CK, LDH, GGT, sodium, calcium, high sensitivity Troponin I, and ferritin levels, could be really helpful to predict disease severity.

Influence of Obesity on Serum Levels of SARS-CoV-2-Specific Antibodies in COVID-19 Patients

Daniela Frasca

Infection with the SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus-2), cause of COVID-19 pandemic, represents a significant risk to people living with pre-existing conditions associated with inflammation and consequent dysfunctional immunity. We have evaluated the effects of obesity, a condition associated with chronic systemic inflammation, on the secretion of SARS-CoV-2-specific IgG antibodies in the blood of COVID-19 patients. Results have shown that SARS-CoV-2 IgG antibodies are negatively associated with Body Mass Index in COVID-19 obese patients, as expected based on the known effects of obesity on humoral immunity. Antibodies in COVID-19 obese patients are also negatively associated with serum levels of pro-inflammatory and metabolic markers of inflammaging

and pulmonary inflammation, such as amyloid A protein, ferritin and CRP (C-reactive protein), but positively associated with nonesterified fatty acids.

We subsequently evaluated the quality of the antibodies secreted, and the presence of neutralizing versus autoimmune antibodies in serum samples of COVID-19 patients with obesity. IgG autoimmune antibodies were specific for malondialdehyde (MDA), a marker of oxidative stress and lipid peroxidation, and for adipocyte-derived protein antigens (AD), markers of virus-induced cell death in the obese adipose tissue. Results have shown that SARS-CoV-2 infection induced neutralizing antibodies in all lean but only in few obese COVID-19 patients. Infection also induced anti-MDA and anti-AD autoimmune antibodies more in lean than in obese patients as compared to uninfected controls. Serum levels of these autoimmune antibodies, however, are always higher in obese versus lean COVID-19 patients. Moreover, because the autoimmune antibodies found in serum samples of COVID-19 patients have been correlated with serum levels of CRP, we also evaluated the association of anti-MDA and anti-AD antibodies with serum CRP and found a positive association between CRP and autoimmune antibodies. Our results highlight the importance of evaluating the quality of the antibody response in COVID-19 patients with obesity, particularly the presence of autoimmune antibodies, and identify biomarkers of self-tolerance breakdown. This is crucial to protect this vulnerable population at higher risk of responding poorly to infection with SARS-CoV-2 than lean controls.

Remote care in PHC – cell phone use experience in a Family Health team in a slum area during the COVID-19 crisis

Luiz Montes do Amaral

The Sars-CoV2 pandemic imposed a need to reorganize the work process of the Family Health teams resulting in challenges to access, management of chronic conditions and monitoring of people infected with the coronavirus. This article describes the uses and challenges of technologies like telephone calls and Whatsapp business in a Family Clinic team in a Rio de Janeiro slum. It's possible to say that this use represents a tool to expand access and strengthen bonds, especially to people living with non-transmissible chronic and mental health conditions in a scenario of restricted access due to the context of the Sars-CoV2 pandemic.

The Development of a Family Liaison Team to Improve Communication Between ICU Patients and Their Families During the COVID-19 Pandemic

Santanu Maity, Susie Gabbie, Kin Man, Gareth Morgan,

Summary: A family liaison team was developed to improve communication between ICU patients and their families during the COVID-19 pandemic.

The Problem: High quality family centred care is an integral part of how sick patients are managed in modern healthcare systems, and remains imperative in times of crisis. However, in the 2020 COVID-19 pandemic the necessity of isolation and social distancing prevented families accessing the support they usually would when a relative is on ICU. During the pandemic, families were not allowed to visit the ICU so they could not speak to doctors and

nurses in the usual way, this exacerbated the family's worries and feelings of fear about their loved one.

The COVID pandemic required major changes to the way ICU was run, to allow a 4-fold capacity. This included the redeployment of staff from other areas and huge clinical pressures on all staff. These teams were not able to prioritise communication with families due to clinical pressures. The ICU had received several complaints in regard to this and were welcoming of help in this area.

Aims: Our project aimed to use a group of Paediatricians with pre-existing transferable skills to develop and embed a communication strategy within ICU for the duration of the COVID-19 surge. Paediatricians communicate with families as a matter of course with the triangle of doctor, patient and family. Paediatricians also work in multidisciplinary teams and are used to communicating with other teams.

In our sector, a centralised children's ward was set up at Great Ormond Street Hospital meaning that local Paediatricians were in a position to help in this role.

As families were not receiving a daily update from ICU, our aim was for all families to be updated at least once daily, and for all families to be offered the option of using video links to speak to their relatives should they chose to do so.

Making a Case for Change: Initially a small team went to speak to the ICU matrons in order to put forward our idea of what we could offer. Once we had their approval and understood the clinical need a larger team of acute and community paediatricians along with CAMHS doctors were coordinated. Support contacts were developed with psychological services to provide help for staff and families, anticipating that the role was likely to be stressful.

The Effects of COVID-19 on Higher Education: Lessons Learned from Three Studies

GholamReza Zakersalehi

During the last two years, the effects of the Covid-19 crisis on higher education institutions have been extensive and multidimensional.

The author and his colleagues have investigated these effects in three independent studies whose articles have been published in scientific journals in Persian.

The first study was realized through a scenario-building method and 80 Iranian higher education experts participated in the scenario validation by completing a questionnaire.

Respondents believe that three major trends most likely to happen respectively: Enhancing e-learning (but not in the form of fundamental transformation and virtualization), changing academic lifestyles, and paying more attention to sustainability. These three trends are among the most preferred scenarios.

By excluding the scenarios whose proponents were less than 50%, the preferred scenarios appeared. Regarding "the social identity and status", most respondents believe that the university will deepen its social identity and will respond to humanity's basic questions. 61 percent of respondents oppose the scenario that the university will be isolated. This finding is contrary to some reports, which hastily claimed at the beginning of the crisis that the university identity is declining and academic values are shifting. This optimism and hope for the preservation of university values and mission is also evident in the World Bank report. Regarding "the sustainability", the role of universities in promoting and implementing sustainability will be highlighted. Universities will recognize the importance of sustainability

and environmental protection. As Giorgio Marinoni et al. (2020) emphasize that sustainability will gain importance during this period. Concerning “the effects of the Covid-19 crisis on student enrollment”, it is predicted that finding a job will become more important than education due to financial issues and other factors. Nathan (2020) calls this a horrifying outlook. Regarding “the university life”, respondents believe that new forms of the ‘teacher-student’ and ‘student-student’ relationships will emerge. In terms of “internationalization”, trends show that new forms of scientific collaborations will appear, and the number of foreign students will be reduced significantly. This scenario is consistent with the findings of World Bank researchers as well as the Nathan’s (2020) report. Regarding “the e-learning”, the most preferred scenario is the continuation of e-learning in its current form and as a complement in emergencies, so that blended learning will be expanded, and virtual research will be prevalent. This development confirms Josha Kim’s (2020) views, World Bank predictions, as well as what has been reported in the UAE, India, and many other countries. Concerning “the management”, due to the lack of funding, the major change will be in financial efficiency and discipline. At the same time, some academic activities will be halted. Hubble& Bolton (2020), Josha Kim (2020) and Montazer et al. (2016) have pointed out this financial crisis. To overcome these management and governance challenges, Fernand Washaw’s (2020) suggestion is inspiring and helpful. He suggests that a flexible and service-oriented leadership brings all stakeholders together in a network. This means establishing a kind of intelligent governance in the university.

The second study was conducted in 2020 by adopting a qualitative approach. Participants in this study were 18 experts and administrators from several universities in Tehran. Data were collected through semi-structured interviews and a thematic analysis method was used to analyze the interviews.

From the analysis of the interviews, 18 sub-themes were extracted. At the end, four main themes were structured: educational dimensions and activities, research dimensions and activities, social services, and university governance and management.

This study indicated that the outbreak of Covid-19 have affected different aspects of internationalization, globalization, localization, digital transformation, inequality in access to higher education, educational quality, the prevalence of virtual research, science and technology parks, research quality, research budget, university-industry relationship, local community networking, social accountability, management and leadership, upstream laws and documents, human resource management, financial resource management, crisis management and change management at universities.

Our third study was the conceptualization of university social responsibility in the Covid 19 crisis. This study was performed by a meta-synthesis method and the dimensions of the extracted conceptual model are identifying changes, increasing social knowledge, establishing crisis management, creating a flexible structure, having an effective communication model, and providing executive solutions.

Application of deep learning technique to manage COVID-19 in routine clinical practice using CT images: Results of 10 convolutional neural networks

Nazanin Khadem, Ali Abbasian Ardakani, Alireza Rajabzadeh Kanafi, Rajendra Acharya, Afshin Mohammadi

Fast diagnostic methods can control and prevent the spread of pandemic diseases like coronavirus disease 2019 (COVID-19) and assist physicians to better manage patients in high workload conditions. Although a laboratory test is the current routine diagnostic tool, it is time-consuming, imposing a high cost and requiring a well-equipped laboratory for analysis. Computed tomography (CT) has thus far become a fast method to diagnose patients with COVID-19. However, the performance of radiologists in diagnosis of COVID-19 was moderate. Accordingly, additional investigations are needed to improve the performance in diagnosing COVID-19. In this study is suggested a rapid and valid method for COVID-19 diagnosis using an artificial intelligence technique based. 1020 CT slices from 108 patients with laboratory proven COVID-19 (the COVID-19 group) and 86 patients with other atypical and viral pneumonia diseases (the non-COVID-19 group) were included. Ten well-known convolutional neural networks were used to distinguish infection of COVID-19 from non-COVID-19 groups: AlexNet, VGG-16, VGG-19, SqueezeNet, GoogleNet, MobileNet-V2, ResNet-18, ResNet-50, ResNet-101, and Xception. Among all networks, the best performance was achieved by ResNet-101 and Xception. ResNet-101 could distinguish COVID-19 from non-COVID-19 cases with an AUC of 0.994 (sensitivity, 100%; specificity, 99.02%; accuracy, 99.51%). Xception achieved an AUC of 0.994 (sensitivity, 98.04%; specificity, 100%; accuracy, 99.02%). However, the performance of the radiologist was moderate with an AUC of 0.873 (sensitivity, 89.21%; specificity, 83.33%; accuracy, 86.27%). ResNet-101 can be considered as a high sensitivity model to characterize and diagnose COVID-19 infections, and can be used as an adjuvant tool in radiology departments.

Keywords: Computed tomography; Coronavirus infections; COVID-19; Deep learning; lung diseases; Pneumonia; Machine learning.

External Quality System Growth- HCAC in 4 years

Thaira Madi

Health Care Accreditation Council (HCAC) is an accredited organization by the International Society for Quality in Health Care (ISQua) External Evaluation Association and a leading quality and patient safety organization in Jordan and the Eastern Mediterranean region, which provides consultation, capacity building and accreditation for healthcare organizations.

HCAC has grown to reach the number of 231 accredited organization, including: 104 Primary healthcare centers, 57 Medical Laboratories, 39 Hospitals, 30 Breast imaging units and 1 Ambulatory care center. The number of Accreditation / Certification books reached to 12, till this day we have 140 surveyors to cover the previous mentioned healthcare organizations and after 10 years of experience, HCAC evaluated its accreditation system, to be in line with developing its strategic plan (2018-2020) and founded a mixed design evaluation methodology that was utilized and reviewed by the international expert Ms. Triona Fortune.

Improvement measures were taken by implementing the Automated Accreditation System as well as focusing on Standards Interpretation. Standards Interpretation was conducted by a systematic approach, where guidance notes were added to new and debatable standards. Meanwhile, the improvement measures reached to cover surveyors by training them virtually and strengthening the scoring system for their evaluation.

Even though postponement rate in 2020 reached 72% and the challenge continued in 1st and 2nd quarters of 2021, the total number of accredited organizations increased in (2020-2021). COVID-19 continues to be used as a growth driving force for HCAC, despite all challenges that were caused by lockdowns such as: Postponed surveys, Surveyor's cancelations and survey team changes.

HCAC continues to support healthcare institutions, staff members, and the society by providing interactive policy and practitioner webinars, online educational sessions, awareness campaigns, preparedness toolkit and COVID-19 readiness packages.

Since healthcare quality has always been the target, the Quality Competition took place officially between

(March 1st - October 15th)-2021. The competition aims to support accredited organization efforts to ensure quality and safety of care provided showing their response to the pandemic. The main theme of the competition was maintaining health care quality and patient safety considering the COVID-19.

As a part of HCAC's preparedness to ensure continuity of accreditation services throughout all emergencies, HCAC successfully piloted the virtual model for conducting surveys that was used after evaluating its pros and cons.

HCAC continues its excellency journey and maintains to develop standards that ensures the quality of healthcare in provided in different health delivering organizations, and as previously mentioned, tough times requires flexible actions, the pandemic was an eye-opening trigger to reviewing and updating the accreditation policies, postponing accreditations and adjusting survey days.

Lastly, the future vision is designated to focus on technology by the application of the Virtual Accreditation model and employing digital scope in working progress.

The Clinical Importance of Genetic Variants in Breast Cancer Patients: The Impact of Dna Repair Genes

Susana Nunes Silva and José Rueff

The advent of personalized medicine has opened the path to routine large-scale sequencing and increased the importance of genetic counselling for hereditary cancers, in particular hereditary breast cancer. Breast cancer is the second leading cause of cancer among women worldwide but could have a better prognosis if diagnosed early. Several high penetrance genes for breast cancer (e.g. BRCA1/2, ATM) belong to DNA repair pathways. Thus, genetic testing for susceptibility genes through Next Generation Sequencing (NGS) has become a standard, and a number of genetic variants have been identified in these genes, several of which are variants of unknown significance (VUS). These

VUS can either be pathogenic or benign, but since their biological effect is unclear, functional assays need to be carried out to classify their mutational nature. The involvement of DNA repair genes in breast cancer development has the advantage of allowing us to assess the impact of genotoxic agents through various assays. Accordingly, a functional approach was performed in peripheral lymphocytes of 2 women with a VUS in the BRCA1 gene (NM_007294.3:c.1067A>G) and compared to results of 2 non-carriers. Several assays (chromosomal aberrations, cytokinesis-blocked micronucleus assay, comet assay, γ H2AX, caspases and TUNEL assay) were conducted after a genotoxic challenge by ionizing radiation or doxorubicin in order to evaluate the functional role of the identified BRCA1 VUS. Our results revealed a higher DNA induced damage in the non-carrier group compared with VUS carriers using as end-points the micronucleus (MN) and the TUNEL assays. These results suggest that this BRCA1 VUS is probably benign, since the VUS carriers were even apparently protected from deleterious chromosomal rearrangements, reducing genomic instability and consequently the activation of programmed cell death. Genome sequencing has revolutionized the diagnosis of genetic diseases, requiring a close collaborations between basic scientists and clinical geneticists to associate genetic variants with disease causation. We believe that the strategy followed here could be successfully applied to study other variants, helping in clinical counselling.

Detection of anti-heparin-PF4 complex antibodies in COVID-19 patients on heparin therapy

Daniela Dragonetti

Background: Patients with COVID-19 infection have, as known, amplified reaction of the mechanisms of inflammation and coagulation with multi-distinct thrombosis¹ and frequently thrombocytopenia², which is more pronounced in the severe forms. Heparin is widely used both in prophylaxis and in therapy, regardless of the hypothesis of its direct antiviral role. We know that its administration can produce anti PF4-Heparin complex antibodies.

Many of these patients have thrombocytopenia^{4,5}, we wondered if this could be linked not only to the general clinical picture and the therapies used, but also to the formation of anti-heparin antibodies.

We studied six patients in Intensive Care treated with Unfractionated Heparin and ten patients in Infectious Diseases or Pneumology with LMWH therapy.

Methods: For the research of antibodies, we used a latex immunological automated test which detects all immunoglobulins against the PF4-heparin complex.

Results: Heparin antibodies were present in three of the six patients on Unfractionated Heparin therapy and absent in all treated with LMWH. In positive patients' heparin was replaced with Fondaparinux at a dose of 7.5 mg, with progressive increase in platelets number.

Conclusions: Although the small number of patients, the incidence of the presence of anti PF4-Heparin complex antibodies seems to be higher than we are used to see in our clinical practice. We thought appropriate to make a report, to remember this eventuality in patients with SARS-CoV-2 and take into account if: - the particular condition of SARS-CoV-2 patients make the formation of anti-heparin antibodies more likely and this fact may have a

significant impact on the clinical course; Considering the last two years since the beginning of the pandemic, the cases of suspected HIT have returned to the normal frequency described in the literature, this change is probably related to the continuous evolution of the virus in new variants, but the possibility that a patient affected by Covid-19, treated with heparin, develops a HIT still remains a real risk and a hypothesis to be considered in Covid patients treated with heparin who develop thrombocytopenia.

Stress, Psychological and Physical Health Conditions among University Students During COVID-19 Pandemic: Implications for Clinical Interventions in the Healthcare Sector

Maria Clelia Zurlo, Maria Francesca Cattaneo Della Volta, Federica Vallone

The COVID-19 pandemic and containment measures adopted globally have entailed extensive changes to university students' customary life, and they exhibit stress-related responses not only to fear of contagion but also to limitations of personal and relational life. This has resulted in widespread psychological symptoms reported by students worldwide, mainly in terms of anxiety and depression.

Responding to the need to achieve a greater understanding of the impact of the COVID-19 pandemic among university students, the present study has a two-fold objective: 1. Describing a brief, valid and reliable tool, namely the COVID-19 Student Stress Questionnaire (CSSQ), which measures specific sources of stress featuring the COVID-19 pandemic lockdown experiences among university students

(Stress related to changes in Relationships and Academic Life; Stress related to Isolation; Stress related to Fear of Contagion); 2. Providing examples of research applications of the COVID-19 Student

Stress Questionnaire to understand the impact of specific COVID-19-related sources of stress on students' psychological and physical health conditions. Research is discussed with the aim of providing tailored evidence-based clinical interventions to prevent mental disease escalation and to promote psychological adjustment during and after this exceptional global crisis. Implications for the healthcare sector and for healthcare professionals are discussed.

Keywords: COVID-19, Psychological Health, Physical Health, Pandemic, Lockdown, University Students

Allain Bueno

Malnutrition and Nutrition-Related Disorders in Liver Steatosis as Risk Factors for Severe SARS-Cov-2 Complications

Hepatic steatosis (HS) is mainly characterised by excessive accumulation of fat in the liver parenchyma, with additional findings of mild chronic inflammation. If left untreated, HS can progress to chronic liver disease (CLD), worsened insulin resistance and Type 2 diabetes. CLD is strongly associated with poor diets, and CLD patients often present decreased bowel motility, gut dysbiosis (GD), bacterial overgrowth and increased intestinal permeability. GD further exacerbates HS and CLD due to the ability of pathogenic bacteria

to adhere to the intestinal epithelium, produce endotoxin, disrupt bile acid metabolism, activate the immune system and trigger inflammation, in a vicious cycle.

Metabolic disease is a strong predictor for negative outcomes in SARS-CoV2. COVID-associated liver injury may occur as SARS-CoV2 progresses in patients with or without pre-existing liver disease, and CLD patients may be particularly vulnerable if suffering with cirrhosis-associated immune dysfunction.

In this study, we present findings of the associations between HS and CLD with SARS-CoV2 outcomes. The presence of metabolic and liver disease, inflammation and elevated oxidative stress are all associated with a rapid clinical deterioration in SARS-CoV2. Additional liver parenchyma damage, observed in SARSCoV-2 patients, can be caused directly by infection of liver cells, once the ACE2 protein is expressed in hepatocytes. We also revisit in this study mechanisms associated with GD and intestinal hyperpermeability in advanced CLD and SARS-CoV-2. We discuss the effectiveness of specific nutritional strategies for the management of CLD and SARS-CoV-2 in inpatients and outpatients.

WALANT, a Potion & Solution to a Global Halt of Cases Requiring General Anaesthesia During Covid-19 Pandemic: Surgeon's Dilemma Resolved

Mohamad Hafiz bin Mohamad Hassim

INTRODUCTION: Covid-19 pandemic results in mass reduction in elective and semi elective orthopaedic surgeries worldwide. Globally, the rate of cancellation of cases is reported as high as 70-90% and in Malaysia, the cancellation rate is reported at 90.1%. We utilised wide-awake local anaesthesia no tourniquet (WALANT) as an alternative for selected general orthopaedic and advanced reconstructive procedures where operating theatre slot is limited in the era of Covid-19 pandemic.

METHOD: Orthopaedic procedures are divided into 2 categories into general orthopaedic procedures and advanced orthopaedic procedures. WALANT is used amidst the pandemic using combination of 1% lidocaine, 1:100,000 epinephrine, and 10:1 8.4% sodium bicarbonate. The solution was infiltrated at area of interest to a maximum of 40ml dilution (maximum safe dose). Skin infiltration of 5mm to 10mm from the desired surgical site is given until periosteal surrounding is infiltrated.

Procedures of interests are then carried out which includes plating, tension bend wiring, screw fixation for general orthopaedic trauma as well as corticotomy, chipping osteotomy and invaginated skin release for advance orthopaedic trauma procedures.

Throughout the procedure, potential adverse reactions, bleeding and pain score were monitored in regular interval and recorded post operative as well.

RESULTS & DISCUSSION: A total of 318 cases were done in 3 years duration from 2019-2021. 240 cases of upper limb surgeries and 78 cases of lower limb surgeries of various procedures were recorded.

The recently explored areas utilising WALANT in advance reconstructive procedures were successful in which it comprises 8 cases out of total numbers of cases.

WALANT can achieve equal and adequate anaesthetic effect as regional anaesthesia for both soft tissue and bony procedures. It eliminates risks associated with general anaesthesia as well as local anaesthesia as maximum tolerated dose is strictly monitored plus reduction

in blood loss through the effect of epinephrine. In general, these procedures can be done as daycare surgery, without requiring full anaesthesia team therefore resulting in reduction of hospital stay.

CONCLUSION: WALANT is a viable option for soft tissue release and bony procedures as it achieved both adequate surgical as well as patient tolerance with the additional advantage of reduce hospital stay. WALANT can overcome the obstacles during Covid-19 pandemic and it is to be practiced beyond the era of crisis.

The Importance of In-Person Learning During The COVID-19 Pandemic And Adaptations In Education

Rodger D. MacArthur, Amanda Delgado, Joseph Elangickal

From the beginning of the COVID-19 pandemic, institutions were challenged to deliver content to their learners. As schools closed their doors to in-person learning to mitigate the spread of the virus, online platforms provided an alternative method of teaching. Despite the novel methods that were implemented to account for the shift to online learning, the decision to deliver education virtually was not without consequences.

Learners receiving their primary and secondary education (Kindergarteners - high schoolers) faced developmental and educational setbacks during the pandemic. Virtual learning negatively impacted the physical development of these students by decreasing physical activity and promoting a more sedentary lifestyle. Emotional development also suffered with the introduction of widespread virtual learning as younger students became more emotionally labile and older students reported weaker relationships with their peers and instructors. Of note, high schoolers specifically reported negative educational outcomes with the transition to virtual learning, stating that they put forth less effort in school and engaged less with the online material.

Undergraduate and graduate students were equally impacted. Medical students faced a unique set of challenges due to invaluable in-person experiences, ranging from anatomy lab to clinical rotations. Additionally, as hospitals faced staffing shortages due to the pandemic, institutions were forced to balance learner involvement with safety. These challenges led to student reports of increased stress and burnout.

The detrimental effects the pandemic had on education across all levels supported a swift return to in-person learning. Reopening approaches differed by country and included COVID-19 mitigation strategies such as physical distancing, hygiene, health screening, PPE, and changes to school scheduling. Safety thresholds for reclosure also differ across educational institutions throughout the world and potentially reflect cultural concern over COVID-19.

Our presentation will describe how learners at all educational levels were affected by virtual learning and stress the importance of in-person education. Our presentation features unique virtual and volunteer initiatives designed at our home institution, the Medical College of Georgia, to keep students engaged during the pandemic. Moreover, we will elaborate on the variety of adaptations used internationally to facilitate virtual learning and safely return to in-person education. We will finally detail the lessons the pandemic has left us with to improve education delivery during future public health crises.

IoT Technologies and Covid-19: How wearable and distributed IoT technologies help out with discovering, diagnostics, treatment and further tracking of cases in Covid-19 and similar pandemics situations?

Mohsen Dorodchi, Ph.D.

In this presentation we particularly discuss the contributions of the smart IoT devices in assisting with diagnosis, throughout the quarantine phase, and during vaccination or post-recovery phases as briefly discussed below.

Assisting in diagnosis: IoT devices can speed up the detection process by capturing information from the patients. This can be implemented by capturing body temperatures using different devices, taking samples from suspicious cases, and so on.

Assistance during the quarantine time: when a patient is diagnosed with COVID-19, then isolation is necessary for some time. IoT devices are able to monitor patients remotely with respect to their treatments and stay at home orders by the authorities, and also cleaning areas without human interactions such as the implementation of tracking wearable bands, disinfecting devices, etc.

Assistance for vaccination and post recovery phases: periodic tracking the status of the vaccinated or recovered person can be easily done through IoT devices. Moreover, reminders can be sent regarding vaccination, social distancing, etc. when necessary.

Dynamics of the COVID-19: Comparison between the theoretical predictions and real data, and Relations to be satisfied for returning to normal life

Giorgio Sonnino

We propose a realistic model for the evolution of the COVID-19. We propose a set of differential equations governing the evolution of the COVID-19 pandemic subject to the lockdown and quarantine measures, which takes into account the time-delay for recovery or death processes. The dynamic equations for the entire process are derived by adopting a "kinetic-type reactions" approach. More specifically, the lockdown and the quarantine measures are modelled by some kind of inhibitor reactions where susceptible and infected individuals can be trapped into inactive states. The dynamics for the recovered people is obtained by accounting people who are only traced back to hospitalised infected people. To get the evolution equation we take inspiration from the Michaelis-Menten's enzyme-substrate reaction model (the so-called "MM reaction") where the enzyme is associated to the available hospital beds, the "substrate" to the infected people, and the "product" to the recovered people, respectively. In other words, everything happens as if the hospital beds act as a catalyzer in the hospital recovery process. Of course, in our case the reverse MM reactions has no sense in our case and, consequently, the kinetic constant is equal to zero. Finally, the O.D.E.s for people tested positive to COVID-19 is simply modelled by the following kinetic scheme $S+I \Rightarrow 2I$ with $I \Rightarrow R$ or $I \Rightarrow D$, with S, I, R, and D denoting the compartments Susceptible, Infected, Recovered, and Deceased people, respectively. The resulting "kinetic-type equations" provide the O.D.E.s, for elementary "reaction steps", describing the number of the infected people, the total number of the recovered people previously hospitalised, subject to the lockdown and the quarantine measure, and the total number of deaths. The model foresees also the second wave of Infection by Coronavirus. The tests carried out on real data for USA, Germany, France, Italy, Belgium, and

Luxembourg confirmed the correctness of our model. The theoretical mathematical relations about the descending phase provide valuable information about the duration of the COVID-19 in a given Country, especially when, and if, it will be possible to return to normal life.

Cytokine Storm Induced New Onset Depression in Patients with COVID-19. A New Look into the Association between Depression and Cytokines -Two Case Reports

Orna Alpert

Background: Depression appears to be a common complication in patients during and post-COVID-19 infection. Understanding the mechanism of action of cytokines such as interleukin-6, interleukin-10 and others in depression and in cytokine storm syndrome, the core component of COVID-19, could shine a new light on future treatment options for both disorders. **Objective:** This review demonstrates the role of interleukins in COVID-19 pathogenesis and their role in depression. **Results:** We described cases we have treated as an example for the dual role interleukins have in COVID-19 infection and depression and reviewed approximately 70 articles focusing on the role of interleukins in cytokine storm syndrome and depression. **Conclusion:** This review highlights the key features of cytokines in both diseases. As the scientific community has more time to recover and process the effect of the current pandemic, we believe that additional research will pave the way to diverse pathways to treat depression in these patients and others.

A Systematic Review of Cybersecurity Risk Management Frameworks in the UAE's Oil and Gas Sector

Huma Imran, Dr Mohamed Salama, Dr Colin Turner, Dr Sherif Fattah

Throughout the past decades, academics and industry practitioners have been working together and independently to digitize the oil and gas industry and make it more cost effective and resilient. Hence, cyberspace has become a part of everyday activities in the critical infrastructure and government agencies. The intense market pressure in the COVID 19 pandemic has continued to drive digital revolution in the petroleum sector. This means more reliance of industrial processes on networked and digitally controlled equipment. The increased network interdependence in all aspects of petroleum industry and broad spectrum of cyber threat landscape due to pandemic indicates the need for a holistic approach and combined synergized efforts of all the stakeholders involved, to manage the cyber security of these critical asset and ensure sustainability. To effectively and efficiently manage the cyber risk, oil and gas sector has adopted different cybersecurity frameworks based on various technical and non-technical models. Therefore, the aim of this paper is to develop a holistic framework by adopting a rigorous and methodical approach to conduct systematic reviews of technical and non-technical cyber risk management models and frequently used cybersecurity frameworks in the oil and gas sector. A thorough research was performed in the four major databases, that is AAPG, Web of Science, SCOPUS, and Proquest and the studied articles were shortlisted as per the inclusion and exclusion criteria and further analyzed using the qualitative document analysis driven by thematic analysis. It tries to identify the critical success factors, shared concepts and varied perspectives on the

shortlisted cybersecurity models and frameworks. It also conducts comparative analysis of existing frameworks to identify the gaps in existing risk management approaches. The models and frameworks studied in the paper will help in the development of a more holistic and sustainable framework. It was found that to ensure sustainability, the existing frameworks require further updating and validation due to rise of new and unique challenges in the post COVID-19 world (ranging from sophisticated attacks, COVID-19 restrictions, remote work to limited human and financial resources).

Keywords: Cybersecurity framework; cyber risk management; cybersecurity strategy; digitization; framework life cycle; and oil and gas.

Effect of Ambient Temperature on COVID-19 Infection Rate

Anant Gupta

Previous research has indicated that Covid-19 is less infectious in warmer temperatures under quarantine conditions. The evidence came from highly significant results from Chinese provincial data from February 1st to February 12th, 2021; however, doubts persist about the results due to the authenticity concerns of Chinese data, the wide scope of Chinese provinces, and the unidirectional epidemic during that time. In order to add further evidence, we analyzed California counties from March 22nd to the 5th of April. Taking a 7-day time lag (two more than the Chinese analysis to account for differences in healthcare); we find that ambient temperature again is a significant explanatory variable as to why cases spread faster in certain counties. On average each additional centigrade is associated with a 1.6 percentage point decrease in the percent of new infections from a base of infectious individuals. Considering the mean percentage increase is around 17%, this means that an increase of 1 degree is associated with an 8.2% reduction in infectiousness. These results corroborate prior evidence and indicate that ambient temperature has an effect on areas that enforce social distancing and lock-down measures.

Role of meteorological variables in COVID-19 in Iraq, 2020.

Marha L. Kammona, Ibrahim M. Al-Sudani, Amani I. Altimim and Riyadh S. Al-Rudaini

Background: The "2019-nCoV" is the newest identified member in corona virus family; discovered in Wuhan city, China. On the day 24 of February 2020, the Ministry of Health and Environment announces the first confirm case of novel coronavirus "COVID-19" in Najaf city in Iraq.

Methodology: Cross Sectional Analytic study conducted in five Iraqi cities (Sulaymaniyah, Diyala, Baghdad, Najaf and Basrah) for characteristics of COVID-19 cases both epidemiological (infection, recovery, death) and meteorological variables (mean temperature MT, relative humidity RH and daily temperature range DTR). The published official data has been collected for the period from 23/2/2020 to 2/8/2020, week no.8 to week no.31 directly from governmental web sites. To calculate the association between incidence rates and metrological variables we considered one-week lag phase. in order to estimating correlation coefficient between parameters we use (spearman correlation, coefficient correlation and P. value); considering the confidence interval 95%, if the P. value is equal or less than 0.05. Data analysis was done by MS. Excel 2019, SPSS programs.

Result: Our result show significant correlation of COVID-19 incidence; cure rate% and CFR% with meteorological variables (MT, DTR and RH). The type and strength of the relation were

varied temporally and spatially, which may due to the differences in the climate pattern of Iraqi cities.

Conclusion: The meteorological variables are important factors for in COVID-19 infection in Iraq. The Iraqi government should take this in the account in emergencies and respond plan setting. Another studies direction is to be covering (air pollution, patient health history and age groups) to achieve a better insight for the fighting model against COVID-19.

Key word: COVID-19, Iraq, Epidemiology, Meteorological variables.

Assessment of Frailty during the COVID-19 Pandemic

Tomoyuki Shinohara

As a countermeasure to prevent the spread of the coronavirus infectious disease 2019 (COVID-19), many activities, including social activities to prevent frailty, have been suspended. Regular exercise settings and socialization were restricted, and most individuals stayed at home. The more widespread the infection, the stronger the phenomenon becomes. There is limited doubt that the frailty risk might increase by the continuation of policy measures. Therefore, we are concerned about “corona-frailty” as a secondary effect of COVID-19 for community-dwelling older adults (BMJ 2020, 369, m1543). We believe that additional measures to support the health of older adults are crucial.

Our studies demonstrate that lifestyle has changed due to the COVID-19 countermeasures among older adults. The frailer the older adults, the more obvious the change in their lives that is associated with preventing or improving frailty (GGI 2021,21). A 6-month cohort study showed the transition rate from non-frail to frail was 9.9% among the non-frail older adults (EGEM 2021,12). We propose a simple screening method (AGG 2022,98) and validate a new measurement tool using a questionnaire to assess frailty (GGI 2021,21). In Japan, the questionnaire for medical checkup of old-old was developed by the Japanese ministry of health, labor, and welfare to comprehensively evaluate the health conditions and lifestyles, especially frailty.

The risk factors associated with the worsening frailty status should be properly assessed in social care services by the community-dwelling older adults themselves, supporters, experts, and administrators to prevent vulnerable conditions for infection pandemics.

Wellbeing and Burnout in Diagnostic Radiology in the pre and post COVID pandemic era

Catherine Giess

Burnout is a persistent challenge among physicians, including diagnostic radiologists. Increasing work volumes and reduced time for non-clinical professional pursuits in teaching and research have provided challenges to wellness and work-life balance. For radiologists, the COVID pandemic has resulted in more remote and offsite interpretations, continued high workloads, and new challenges in team building and professional satisfaction. This talk will review challenges and the impact of various initiatives in addressing radiologist wellbeing.

Impact Of Covid 19 Mitigation & Containment Strategies on the Rights of Older Persons in Africa: Survey Based Evidence with Focus on Disruption of NCD Care Services

Osi-Ogbu O., Ayuk C., Amaike B., Somers S.,

Introduction: Older persons are the fastest growing demographics in Africa. The population of older persons (aged 60yrs and over) estimated at 4.9% of the total population in 2015 is projected to reach 7.6% by 2050, which is more than triple in absolute numbers from 69 million in 2017 to 226 million in 2050. COVID-19 was declared a global pandemic on March 11, 2020 by the World Health Organization (WHO). Africa recorded her first case in Egypt on February 14, 2020, since then, a total of fifty-four (54) African countries have been severely and progressively affected, with older persons bearing the higher rates in mortality across all 18 countries surveyed. In response to the COVID-19 global health emergency, African governments adopted extraordinary measures to contain and mitigate the pandemic, in order to save lives. As part of SGA- Africa's contributions to the development and enhancement of older persons' human rights and overall wellbeing in Africa during COVID-19 pandemic, this survey was carried out.

Methodology: This is a longitudinal survey design. The survey was conducted in 2020. Data were collected using survey monkey tool. Both Primary and Secondary data were utilized. Data collected were analyzed using descriptive tools such as frequency distributions, percentages, and charts which allow for comparative analysis. Ethics of social research was duly observed, with due consideration for anonymity and confidentiality of the respondents.

Results: Responses received from 43 SGA Africa member groups across 18 African countries with representation as follows, 33%, 28%, 22%, 11% and 6% for Eastern; Southern, Central, and Northern Africa regions. 56% responded yes to preexisting medical emergencies such as: Lassa fever; Malaria, HIV/AIDS; Tuberculosis; and Ebola. Non communicable diseases (NCD) services were reported as disrupted as follows: 53% for hypertension, 49% for diabetes and diabetes-related complications; 42% for cancer treatment, and 31% for cardiovascular emergencies. Rehabilitation services had been disrupted in 63% of countries. 72% of respondents responded positively to the provision of community support for older adults. The types of support were varied with the following being the top 4: material support, social protection, psychosocial support, sensitization and awareness creation.

Discussion: COVID-19 Pandemic has threatened the lives of older persons and deepened ageism, discrimination and inequality. The absence as reported in most countries, of government social protection infrastructure for older persons, leads to income challenges, especially, with the exclusion of most of the older persons as recipients of palliatives. The other major impact on older adults is the lack of access to needed health care from the disruption of NCD and rehabilitation services. This disruption, leading to suboptimal control of these conditions that have effect on functional capacity and quality of life. In most countries, older persons were not consulted during containment preparatory stages and, their concerns were not considered. Other noticeable effects included increased incidences of elder abuse.

Keywords: Africa, older persons, COVID-19, human rights, Stakeholder Group on Ageing, Non communicable diseases

Computer-Modulated Hemodialysis Filter Rotator for Anticoagulation-Free Hemodialysis: A Brand- New Innovative Paradigm of Care to Enhance Increased Home Hemodialysis Services in the Post- COVID-19 Era.

Onuigbo M, Bowman N, Cobb N, George A, O'Driscoll S, Thomas K, Locke A, Dubief Y.

Introduction - The Problem

The maintenance of the fluidity of blood in the extracorporeal circuit during the hemodialysis procedure usually requires the use of systemic anticoagulants, to prevent the blood from clotting within the tubing and filter or dialyzer of the hemodialysis system. While effective, these medications put the patient at risk of bleeding complications especially in critically ill patients and in patients who are undergoing surgical procedures. Furthermore, there are other adverse effects associated with the different anticoagulants. Moreover, these anticoagulants could be expensive, too. To achieve anticoagulation- free hemodialysis, recently, the use of rotational motion has been studied as a method of mechanical anticoagulation. In 2021, the first author and his group described the "Locke-Onuigbo" maneuver as an innovative novel approach to mechanically prevent the coagulation of the blood of patients undergoing hemodialysis treatment (Figure 1).¹

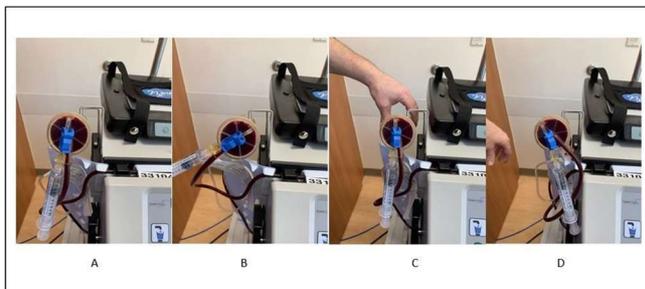


Figure1: Locke-Onuigbo Maneuver (Locke et al. Mayo Clin Proc Innov Qual Outcomes, 2021)¹

Prototype Completion/Conclusion

In collaboration with the University of Vermont Center for Biomedical Innovation (UVM CBI), five Senior Engineering students from the UVM, under the supervision of Yves Dubief PhD, Associate Professor of Mechanical Engineering, UVM, the first author and his Home Dialysis Program at the University of Vermont Medical Center, has successfully prototyped an artificial intelligence-modulated hemodialysis filter rotator that would enable anticoagulation-free hemodialysis (Figure 2).



Figure 2: The completed Hemodialysis Filter Rotator Prototype running test on the HD machine

This Hemodialysis Filter Rotator will enhance the capabilities of enabling more sustainable Home Hemodialysis options for patients with end stage renal disease (ESRD) all over the world. This will represent a most welcome option for the teeming ESRD patients around the world as we continue to adapt to the reality of a “post-COVID” existence. The ability to successfully carry out home hemodialysis while staying away from the in-center hemodialysis unit, will provide a convenient, safe and effective alternative to thousands of patients who would prefer this choice of treatment.

Investors and sponsors for further development are welcome.

Big Events and Drug Overdose Mortality: How Major Pandemics, Economic Changes, and Political Transitions Affect Overdose Epidemics.

Friedman, Samuel R.; Cerda, Magda; Walters, Suzan; Vasylyeva, Tetyana; Adhikari, Samrachana; Mateu-Gelabert, Pedro

Since Fall 2019, the world has experienced a major pandemic, severe economic instability, a wave of sociopolitical movements with varying politics, continuing and worsening climate instability, and consequent changes to everyday life and to hopes for the future. In the United States and some Canadian provinces, these concatenating crises have been accompanied by major increases in deaths due to opioid and polydrug-related overdose and in alcohol-related deaths. There is some evidence that changes in drug markets during the pandemic, and in particular increases in fentanyl use, contributed to this rise in overdose mortality. Evidence suggests the crises have led to increased rates of social and psychological difficulties. Using the Big Events framework developed in studying HIV/AIDS outbreaks in some countries following regime change, economic crises and other Big Events, this paper will discuss both pathways through which these crises have led to increases in overdose mortality and also some potential pathways by which the current global concatenation of crises may lead over time to large increases in the number of people who use drugs and thus to more overdose mortality, and other sequelae of drug use.

An Optimization Framework to Study the Balance Between Expected Fatalities Due to COVID-19 and the Reopening of U.S. Communities

Victoria C. P. Chen, Yuan Zhou, Jay M. Rosenberger, Alireza Fallahi, Amith Viswanatha, Jingmei Yang, Yasaman Ghasemi, Nilabh S. Ohol, Ashkan A. Farahani, Jeffrey B. Guild.

As communities considered reopening during the COVID-19 pandemic, they faced two conflicting objectives. The first is to minimize cases of severe illness leading to hospitalizations and potential fatalities. The second is to revive the U.S. economy, K-12

education, and the livelihoods of millions of Americans. Lockdowns address the first but are detrimental to the second. Phased reopening pursues the second, but once communities reopened, control over transmission was lost. How could we prioritize interventions to simultaneously minimize cases of severe illness and fatalities while reopening? A team of researchers anchored by the Center on Stochastic Modeling, Optimization, & Statistics (COSMOS) at the University of Texas at Arlington has formulated a computationally-efficient optimization framework, referred to as COSMOS COVID-19 Linear Programming (CC19LP), to study the delicate balance between the expected fatality rate due to cases of severe illness and the level of normalcy in the community. Given the disproportionate fatality characteristics of COVID-19 among those in different age groups or with an underlying medical condition or those living in crowding, the key is a framework focused on "COVID-19 key contacts" to protect individuals at higher risk from the rest of the population. CC19LP solutions uncover prioritization guidance on social distancing, personal protective equipment, COVID-19 testing, and vaccination. An online version debuted in July 2020 and was awarded a 3rd place prize in The C3.ai COVID-19 Grand Challenge. This work was published in the journal *IEEE Transactions on Automation Science and Engineering*.

Spatial Spread of COVID-19 for Different Waves

V.V. Aristov, A.D. Yastrebov, A.V. Stroganov

We study the modern scenario of a rapid spread of a pandemic in space (traditional methods are as a rule based on diffusion-type equations used for a relatively slow spatial spread of epidemics associated with contacts). We study the movement of infected people by transport. It leads to a repetition of the pattern of propagation of pandemic waves because the average speed of propagation does not depend on the intensity of infection with viruses, but only on the average speed of the vehicle. The corresponding kinetic-advection equations with suitable initial and boundary conditions for the problems are used. The model has two parameters, which are calculated by comparing with real data. Namely, the mentioned average speed and the frequency of the decrease in the number of infected when moving around the country, associated with the arrival of passengers at their destination. The main assumption is related to the original sources of the first wave pandemic for specific countries: Lombardy for Italy, Moscow for Russia and Santiago for Chile. So, it is possible to determine the delay in the development of the disease both in individual regions and in the country as a whole. It is assumed that recovery is "symmetrical" and can be determined by the maximum number of infections per day. A calculation was obtained according to which the difference between this maximum for Moscow and Russia is about 3 weeks. For the next waves, specific forecasts were made with the calculation of this time shift and these forecasts were confirmed. In the second wave for Moscow, the recovery corresponded to the beginning of December 2020, and for Russia - the end of December 2020. For the third wave these data were the last decade of June 2021 and the mid-July 2021 respectively. For the fourth wave the maximums of infections occurred in the middle of the last decade of October 2021 for Moscow and mid-November 2021 for Russia as a whole. This allows us to predict the analogous character of events for the next waves as well. For the last (fifth) wave the maximums of infections occurred in the

end of January 2022 for Moscow and mid-February 2022 for Russia as a whole. At present, the model has been generalized for two-dimensional geometry.

Standard Racism: Trying to Use “Crisis Standards of Care” in the COVID-19 Pandemic in the US

George J. Annas

Lowering the standard of care to a “crisis standard” during the COVID-19 pandemic in the US was one strategy designed to make hospital-based rationing of medical equipment (such as ventilators), and space (such as ICU beds) fair and equitable. Instead, it threatened to exacerbate inequities and increased racial and income-based discrimination. The reasons are both theoretical and practical.

The theoretical argument against lowering the standard of care in a crisis is that it is unnecessary and confusing because the standard of care already takes into account available medical resources and equipment. Specifically, the standard of care requires a healthcare provider to act in the same or similar way that a “reasonably prudent” healthcare provider would act given the resources available. Healthcare providers are never obligated to provide that which does not exist, and do not need any blanket grant of immunity for practicing medicine during a crisis.

The reason is practical: lowering the standard of care in a crisis will predictably widen the unequal treatment of minorities and low-income patients. For example, since shortages (of virtually everything) are much more likely to affect safety net hospitals that serve poor and minority communities, lowered standards of care are most likely to be applied to these hospitals, while resisted in richer hospitals. In this way, lowering standards of care in a pandemic can dramatically expose structural racism in the US. Nor is there anyway minority communities would agree to such blatant discrimination, so applying the crisis standards of care model requires that their rights to informed choice of treatment be curtailed as well.

Thankfully the National Academy of Medicine (NAM) issued two news reports (in late 2020 and early 2021) that recognized and tried to address the shortcomings of crisis standards of care, seeking to return informed consent to its central place in the doctor-patient relationship, to eliminate the use of SOFA scores for allocating ventilators, and discontinue using “triage teams” for treatment decision-making. The most important overall point the NAM made is that a crisis does not change constitutional or human rights law that protects all patients and does not legally empower physicians and nurses to take harmful actions against the will of their patients regardless of the patient’s race, religion, disability, sexual orientation, or any other categorical characteristic. In NAM’s words, resource allocation decisions should, even in a crisis, be “based on individualized assessment of each patient.”

As we plan for our next crisis we should plan to treat each patient as an individual person, and thereby earn the public trust that the healthcare system needs to effectively respond to a crisis that requires at least some fair, nondiscriminatory, rationing of medical equipment and space.

COVID-19: How Public Health Measures are Changing Health Service Utilisation in the Paediatric Population.

Eilish McAuliffe, Professor of Health Systems, UCD IRIS Centre, University College Dublin

Despite public health appeals to reassure the public that it was safe to access health services during COVID-19 waves, significant reduction in emergency department (ED) utilization patterns have been observed in several countries. The reduction is evident in the proportion of patients presenting at ED across all acuity presentations. Factors contributing to lower utilization of health services include public health messaging and government-imposed population restrictive measures (e.g. restrictions on travel, sports and socialisation and closed schools/childcare facilities). Shifts in health-seeking behaviours due to unwillingness to access healthcare because of concerns about contagion in hospital settings are also a factor. Evidence from SARS and MERS epidemics have shown that risk mitigation behaviours, such as hospital avoidance, were widely practised, with fear of infection associated with avoidance of healthcare facilities. The immediate and long-term effects of this reticence in care-seeking is likely to have negative health consequences for all age cohorts, but especially so for the paediatric population. This presentation will focus on Ireland as a case study to examine the impact of COVID-19 on paediatric emergency department utilisation and assess how this changes in relation to the public health response strategy and public health messaging in the first waves of the COVID-19 pandemic. The decline in paediatric ED attendance is clear and the restrictions on movements and social gatherings, coupled with normal seasonal patterns of attendance, explains much of this variance.

Boosting effect of Intravenous infusion Therapy of a combination of Magnesium-Vitamins-Amino-acids or oral nutrients in the treatment of Post Covid fatigue and Chronic fatigue Syndrome

Jan Pen, F Comhaire, J.P. Deslypere

Background: Systemic and neurological signs and symptoms of patients suffering from chronic fatigue syndrome (CFS) and the Post Covid Syndrome (Long Covid) are remarkable similar, with the exclusion of impaired cardio-respiratory function related to the past viral infection. Pathogenic mechanisms common to these diseases include persistent immune and inflammatory processes inducing dysfunction of cellular / mitochondrial energy production and glucose metabolism. Systemic immune and neuro-endocrine disorders maintain inflammation, oxidative stress and metabolic deregulation.

Material and Methods: In the present real-life systematic registration, we have compared the effectiveness of two therapeutic approaches that aim at improving general well-being, fatigue in particular. Intravenous infusion therapy of a combination of Magnesium, Polyvitamins, Amino-acids and Minerals was given to 21 patients, and was compared with oral therapy using a specific nutraceutical complement of Sodium-Dichloroacetate and

Meldonium, given to 84 patients. After 1 month, the effect of treatment on fatigue was measured using the Fatigue Severity Score (FSS).

Results: In a preliminary analysis both treatment approaches showed similar effectiveness with two thirds of patients reporting a variable degree of improvement, and no differences between CFS cases and the Post Covid patients.

Conclusion: Two thirds of patients suffering from Post Covid syndrome or CFS experienced a variable degree of reduction of fatigue, thanks to treatment with infusion therapy, or with the oral nutraceutical therapy. These preliminary results must be further controlled in a larger number of patients and a longer follow-up.

20-Week Study of Clinical Outcome of Over-the-Counter COVID-19 Prophylaxis and Treatment

Leon Margolin, Daniel Margolin, Michelle Margolin, Sanford Lefkowitz

As the lethal COVID-19 pandemic enters its second year, the need for effective modalities of alleviation remains urgent. This includes modalities that can readily be used by the public to reduce disease spread and severity. Such preventive measures and early-stage treatments may temper the immediacy of demand for advanced anti-COVID measures (drugs, antibodies, vaccines) and help relieve strain also on other health system resources.

We present results of a clinical study with a multi-component OTC "core formulation" regimen used in a multiply exposed adult population. Analysis of clinical outcome data from our sample of over 100 subjects – comprised of roughly equal sized regimen-compliant (test) and non-compliant (control) groups meeting equivalent inclusion criteria – demonstrates a strong statistical significance in favor of use of the core formulations.

While both groups were moderate in size, the difference between them in outcomes over the 20-week study period was large and stark: Just under 4% of the compliant test group presented flu-like symptoms, but none of the test group was COVID-positive; whereas 20% of the non-compliant control group presented flu-like symptoms, three-quarters of whom (15% overall of the control group) were COVID-positive.

Offering a low cost, readily implemented anti-viral approach, the study regimen may serve, at the least, as a stopgap modality and, perhaps, as a useful tool in combating the pandemic.

Mental health and the perceived usability of digital mental health tools among essential workers and people unemployed due to covid-19: Cross-sectional survey study

Felicia Mata-Greve

The COVID-19 pandemic has elicited ongoing mental health consequences for many, including essential workers or individuals who have become unemployed due to COVID-19. Much of the U.S. owns smartphones and many digital mental health tools (DMHTs) are free to download. As a result, the study sought to document DMHT use by essential workers and the unemployed due to COVID-19. Specifically, we explored desirable DMHT features, ratings of app usability, and user burden of DMHTs.

We recruited 2000 individuals remotely from Prolific to complete a cross-sectional survey on mental health symptoms and DMHT features during fall 2020.

Our sample included 1,987 U.S. adults. While three-quarters (1479/1987) of the sample reported notable mental health distress, only 14% of the sample used a DMHT during COVID-19 (277/1957) with meditation apps being the most commonly used feature. Usability ratings were within normal benchmarks; however, individuals that were unemployed or indicated more mental health symptoms rated DMHTs as more burdensome. The sample nominated the top three desired DMHT features to be mindfulness/meditation (1271/1987, 64.0%), information or education (1254/1987, 63.1%), and distraction tools (1170/1987, 58.9%).

Despite high mental health needs, DMHT use remains low and comparable to pre-pandemic use. The study provides insight into what features are desirable for coping with COVID-19 stress. Future directions of the potential of DMHTs to decrease mental health distress in this population will also be discussed.

Combining Normative Safety and Adaptive Safety to Build Quality in a Physiotherapy School and Protect Students and Staff.

William Suarez

Introduction: Over the past two years, our environment has become hostile. Work and life have been strongly impacted by the pandemic and this is not over and no way out is visible. This paper will discuss how we have organised teaching and work in a physiotherapy school since the summer of 2020.

Context: Safety and quality are a construction combining normative and adaptive. It is in this context that this intervention was built, which was strongly intended to be participatory and constructive with the school's teachers and staff initially, and then with the students as soon as they returned to school.

The challenges of the intervention are mixed: To ensure the safety of teachers and administrative staff and students. To ensure an optimal quality of teaching in a constrained context: physiotherapy is a manual discipline; it is thus not possible to propose practical teaching without inter-individual contacts which would be exclusively given at distance.

Methodology: Ergonomics intervention models are based on activity analysis, including observation and interviews. As the period was not a teaching period, the activity could not be observed as there were no courses. The uncertainties associated with the emergence of SARS-CoV 2 were not conducive to traditional methods. It was therefore necessary to deal with these constraints by developing perceptual simulation of activity during the non-activity period.

Results: Three axes of intervention were implemented: (1) Securing the administrative part of the school. (2) Securing the teaching, with a particular focus on maintaining a high quality of teaching, in particular by keeping the practical work in the classroom as much as possible. (3) A relationship of trust has been established with the students.

Discussion-Conclusion: Crisis intervention is complex. One of the factors of success is the collaboration established with the main idea "what happens outside the school can have an

impact on the inside". This intervention has shown once again that the combination of normative and adaptative safety in a new context such as the pandemic makes it possible to build an environment that links quality and safety in work and teaching.

Keywords: Covid 19, ergonomics, normative safety, adaptative safety.

COVID-19 infection in patients receiving hemodialysis in Athens: Findings, experience, and outcome from a single Dialysis Unit

Ioannis Griveas

Objective: Our Nephrology Department during the spring period on the first wave of COVID-19 was the referral Dialysis Unit for Covid-19 positive HD patients in the district area of Athens, Greece. This study aims to report the characteristics, rates, and outcomes of all patients affected by infection with SARS-CoV-2 undergoing HD and treated under our care. 22 Covid-19 positive HD patients were treated under the care of our facility during the period 8 April 2020-17 June 2020. 16 patients were symptomatic at admission and 13 patients were admitted with or developed during their stay pleural effusions. 12 patients (8 male) of our group died during their hospitalization. The mean age of our patients was 74.5 years. It has to be pointed out that 13 patients were over 75 years old. Mean age was higher in those who died compared with those who were discharged with double negative Covid-19 tests (79 vs 74,5 years old respectively). It seems that despite the fact that the immune response of this population has not been clearly clarified, age comorbidities and above all end-stage renal disease by its self is a significant and unpredictable risk factor for clinical outcome of HD patients with COVID-19 infection. Keywords: Haemodialysis, COVID-19, nephrology, outcome, SARS-CoV-2

Waiting for Godot: A cross sectional survey-based analysis of the hydroxychloroquine prophylaxis strategy against COVID-19 in India

Dipu T.S

Background: India currently has the second largest burden of infections due to COVID-19. Health Care Worker (HCW) shortages are endemic to Indian healthcare. It should therefore be a huge priority to protect this precious resource as a critical component of the systemic response to this pandemic. Advisories from the Indian Council of Medical Research (ICMR) have focused on using hydroxychloroquine prophylaxis against COVID-19 in at risk HCW. This prophylaxis strategy has no evidence. In further jeopardy there appear to insubstantial attempts to build this evidence as well. In this connection, we commissioned a survey within our Institution to estimate the penetration of hydroxychloroquine (HCQ) use and use this to statistically model the impact of current ongoing studies in India. We also briefly review the literature on HCQ prophylaxis for COVID-19.

Design and Methods: A structured survey designed using Redcap application was disseminated among healthcare professionals employed at an academic referral tertiary care center via online social media platforms. The survey was kept open for the entire

month of June 2020. The survey was additionally used to statistically model the size of studies required to comprehensively address the efficacy of HCQ in this setting.

Results: A total of 522 responses were received, of which 4 were incomplete. The ICMR strategy of 4 or more doses of HCQ was complete only in 15% of HCW in our survey. The majority of respondents were doctors (238, 46%). Amongst all category of responders, only 12% (n=63) received the full course. A majority of those who initiated the chemoprophylaxis with HCQ turned out to be medical professionals (59/63) with neither nurse nor other categories of healthcare workers accessing the medication. The respondents of our institutional survey did not report any life-threatening side effects. Presuming efficacy as per ICMR modelling for new registry trial on the lines of the published case control study, equal allocation between cases and controls and assuming a RR of 1.3.6, the power of such a study would be very low for n=2000 for event rates from 2.5-12.5%.

Conclusion: We report the low penetration of HCQ chemoprophylaxis among the healthcare workers of our institution. We highlight the inherent drawbacks in the study design of current national COVID related trial based on the statistical modelling of our survey results and published literature, and thereby emphasis the need of evidence-based strategies contributing to research policy at the national level.

Effect of Climate on COVID-19 incidence: a Cross-sectional Study in Japan

Yasuharu Tokuda, MD MPH

Rapid testing, tracing, and isolation among symptomatic patients are the standard for controlling the COVID-19. However, during spring 2020, Japan employed a RT-PCR test restriction policy. The government implemented a guideline for the public to be able to visit hospitals or clinics only when they had symptoms for 4 days or longer (“4-day rule”). It has been unknown of patients’ experience of healthcare use and testing during the period under the guideline. Thus, we investigated the healthcare visiting and testing among patients who developed cold-like symptoms during the period. Our survey was conducted online in September 2020 to a nationally representative sample of adults throughout Japan. We investigated the public's understanding of the guideline. In addition, we asked their experience with healthcare use and testing if they had noticed new-onset cold-like symptoms. Of 2,137 people surveyed, 1,698 (79.5%) recognized the guidelines, but 422 people (19.7%) misunderstood. There were 144 (6.7% of 2,137 people) who developed cold-like symptoms, and many of them experienced difficulties in getting through telephone calls to a public health center, and 25 (17% of 144 people) visited healthcare institutions. Of these 25 symptomatic patients, 15 (60%) could not receive testing because of decisions by physicians (14 patients) or a local public health center (1 patient). Government experts might have tried to restrict public RT-PCR testing only for their public health research institutions to protect their interests. In conclusion, there was a low use of healthcare and testing among symptomatic patients during the first wave of the pandemic in Japan. Testing capacity should be increased to provide effective care for patients with suspected COVID-19 in Japan. Policy should be based on scientific evidence.

The First Case of COVID-19 in Bhutan

Shankar Le Vine

A country's initial response to the index cases of the novel coronavirus disease-19 (COVID-19) can have a major impact in setting the tone given the impact on healthcare providers, the country's preparedness response, and the initial molding of the public perception toward this pandemic. In this presentation we will discuss the index case of COVID 19 in Bhutan from March of 2020. The index case was a 76-year-old immunocompromised man who had traveled from the United States and entered Bhutan as a tourist. He initially presented with primarily gastrointestinal symptoms which were considered quite atypical at that time and led to an initial delay in diagnosis.

Once the patient was diagnosed, he was isolated in a separate hospital with a dedicated medical care team. All contacts were traced and quarantined. The patient's respiratory status deteriorated despite broad-spectrum antivirals, antibiotics, and intensive supportive care. He required intubation and was given a trial of intravenous immunoglobulin to modulate his aberrant immune response. Subsequently, the patient's clinical status improved, and after 8 days of hospitalization, he was transferred out of the country in a medical evacuation flight, ultimately making an excellent recovery. This index case contributed towards a sense of caution and fear towards COVID 19 and simultaneously national pride helping to build the foundation of a highly successful public health campaign in Bhutan.

Pathophysiology of exercise intolerance in ME/CFS provides new insights into long-COVID.

Arabella Warren

Over 100 million confirmed cases of COVID-19 caused by SARS-CoV-2 infection have been reported globally. Persistent physical symptoms experienced by patients after acute COVID-19 are common and include fatigue, dyspnea, chest pain, orthostatic intolerance, heart rate abnormalities, neurocognitive symptoms, and autonomic involvement. Long-COVID symptoms affect a variety of systems that have been described previously in Myalgic Encephalomyelitis/Chronic fatigue Syndrome (ME/CFS), a condition that develops after acute infection in 30-50% of patients. Invasive cardiopulmonary exercise testing (iCPET), which simultaneously measures ventilation, pulmonary and systemic gas exchange and hemodynamics, has been used to investigate the relationship between Small Fibre Neuropathy (SFN) and exertional intolerance in ME/CFS. SFN is a disorder caused by excess firing or axonal degeneration in thinly myelinated peripheral neurons, confirmed using an epidermal skin biopsy. Out of 160 ME/CFS subjects who underwent an iCPET, one third had objective evidence of SFN. This demonstrates significant overlap with postural orthostatic tachycardia syndrome (POTS) and Fibromyalgia, where SFN is reported in approximately 50% of cases. Subject's with SFN and ME/CFS who also underwent an iCPET showed neurovascular dysregulation as a likely cause of exertional intolerance. It has since

been hypothesised that neuropathic dysregulation causing microvascular dysregulation limits exertion by shunting oxygenated blood from capillary beds and reducing cardiac return, deemed left to right shunting and 'preload failure', respectively. The iCPET has also been used to investigate exertional intolerance in long-COVID in a collaborative study between BWH and Yale New Haven Hospital. In this study, 10 patients who had recovered from acute COVID-19 and 10 control subjects underwent an iCPET. Similar to ME/CFS, long-Covid patients demonstrated preload failure, peripheral shunting; impaired systemic oxygen extraction and an exaggerated hyperventilatory response during exercise. As case reports of SFN have been described in long-Covid, we hypothesise neurovascular dysregulation is a likely cause of exertional intolerance in these patients. Furthermore, emerging data showing similar exercise pathophysiology in patients with ME/CFS and long-COVID could aid in the development of a diagnostic method, profile and future treatment for COVID long haulers.

How are you? A sociological perspective of COVID-19 pandemic from women in Italy

Nicolò Marchesini, Sveva Avveduto, Giuliana Rubbia

The COVID-19 pandemic has changed our lives. The first and unexpected lockdown happened in Italy over Spring 2020 and has seriously upset people's daily routine, working organisation, socialisation, and interactions with colleagues and relatives. To overcome people's physical isolation and collect impressions, the "How are you?" online questionnaire was designed as a potential conversation among friends. Such written conversations took place from mid-March to the end of May 2020, i.e. during a period in which Italy was the first country in Europe to confine people home for all but essential reasons. What impact had this situation on people?

This study aims to investigate some of the social and relational consequences that the first lockdown in Italy had on a group of women, in terms of changes and limitations on work routines and social isolation, focusing in particular on the emotions felt at that time.

Text mining techniques have been applied to almost one hundred women's replies, to highlight similarities and differences in their experiences during the lockdown, changes in daily actions, thoughts, and reflections.

Our findings show that during the Spring 2020 lockdown a moment of physical and relational confinement was bear, causing feelings such as fear, sadness, and restlessness concerning the near future. However, many respondents accepted this lockdown as an opportunity to reorder their own lives, in terms of physical activities such as daily habits, and personal relationships and priorities. The fresco on which the paper is based is unique in terms of time, space, gender, and professions.

Regarding changes in daily habits, almost 83% of respondents showed a feeling of acceptance towards the lockdown and, at the same time, 80% of respondents showed a feeling of restlessness. Along with acceptance, negative feelings such as unease, fear, sadness prevailed. However, such emotion analysis produces different results on a specific subset of respondents. Focusing on women professionals in science only, such as academics or managers having an intellectual profession, a more positive attitude towards

lockdown has shown despite the strong limitations in place when compared with the whole set. In particular, two main feelings seem to spring: an optimistic view associated to hope and desire for improvement of the situation, and the acceptance of practical and social constraints correlated to the ability to understand the situation seriousness as well as the ability to rediscover the pleasantness of the own home.

The lockdown experience brought along a new awareness, spread across the group of respondents. On the one hand, the freedoms taken for granted but at that time considerably reduces, and now been made central and indispensable - such as travelling, going out, and moving around regularly for social relations and physical reasons. On the other hand, the limits of our society, in terms of defending and respecting the environment and the importance of research and healthcare accessible to all.

Keywords: COVID-19, emotion analysis, women in science, text-mining techniques

Rapid adoption of resilience strategies during the COVID-19 pandemic

Florence LeCraw

Healthcare professional (HCP) burnout and mental health issues were a public health challenge before the pandemic. The pandemic has worsened the situation. Physicians experiencing burnout are more likely to generate unsolicited patient complaints that may be associated with avoidable medical and surgical errors and excess malpractice claims experience. Surveys have found an association between symptoms of burnout and physician perceptions of increased medical error, as well as increased physician intent to reduce clinical hours or leave clinical practice. Many experts believe that the greatest share of HCP burnout is related to healthcare organization's operations and its culture. The American Medical Association has made recommendations that a medical facility can use to improve the health and well-being of the HCP. These recommendations include frequent data collection of the HCP during the pandemic, establishment of a 5-member multidisciplinary committee to assess the data and make decisions based on the data, a mechanism to communicate the committee's decisions to senior leadership and HCP, and HCP feedback of the committee's decisions to assess the need for any revisions. Physicians can help their institution implement these recommendations. Easier said than done, but not impossible! Gerald Hickson, MD and Florence LeCraw, MD will share their experiences and observations on successes and obstacles encountered in initiatives to support professionals to improve their well-being and their professionalism in pursuit of safety and high reliability. Gerald Hickson, MD serves as the ViceChair on the board of the Institute of Healthcare Improvement and past chair of the National Patient Safety Foundation. He has led teams that successfully implemented elements of the AMA's recommendation at over 220 Hospitals in the U.S. A research focus of Florence LeCraw, MD has been patient safety and HCP burnout. She is a member of teams that successfully helped healthcare organizations implement a program that improved the well-being of HCP and patients when an unexpected adverse outcome occurred to their patient. They will describe the AMA's recommendations that a medical facility can use to identify professionals who may be struggling and how they can improve the resilience of the HCP and what you can do to help your institution affect change.

What has Covid-19 Pandemic brought about on the well-being of the elderly – a tentative observation from the viewpoint of social capital and AI in Japan

Yoji Inaba

Corona pandemic has a devastating impact for social capital (SC) of the elderly, preventing them from interacting with the outside world, interfering with people's physical connections. Since SC is strongly associated with quality of life (QOL) (Inaba 2016), the deterioration of SC could bring about decline in their wellbeing both physically and mentally. On the other hand, the pandemic has promoted the penetration of ICT and AI which have helped the elderly in mitigating the negative impact of the pandemic by enabling them to access to various sites through the internet. That is the negative impact of the pandemic could be offset by ICT and AI.

The effect of the measures taken by the different countries due to COVID-19 on the habits and amount of physical activity of the population

Arkaitz Castaneda Babarro

As is well known, on 11 March 2020 the World Health Organization declared a global pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-COVID) which has become a public health emergency of international concern. In order to stop the spread, countries enacted various restrictive measures on the population. These measures have had a negative effect on the amount of physical activity and sedentary habits of the world's population, both healthy and with previous pathologies. This lack of activity is directly related

to an increase in other illnesses such as depression, fatigue, stress, metabolic syndrome... and even to a higher probability of severe symptoms in case of infection by the virus or a higher probability of being hospitalised. An individualised activity is recommended, including: resistance, endurance, mobility and balance training, and if it is possible outdoors. It is important that the authorities take into account the consequences of these measures, in order to promote actions aimed at maintaining a minimum amount of physical activity in the population.

Alternating Quarantine for Sustainable Epidemic Mitigation

Baruch Barzel

Battling the spread of SARS-CoV-2, most countries have resorted to social distancing policies, imposing restrictions, from complete lockdowns to severe mobility constraints, gravely impacting socioeconomic stability and growth. Current observations indicate that such policies must be put in place for extended periods (typically months) to avoid the reemergence of the epidemic once lifted. This, however, may be unsustainable, as individual social and economic needs will, at some point surpass the perceived risk of the pandemic.

To bypass this gridlock, with future potential outbreaks in mind, we present the alternating quarantine (AQ) strategy: first, households are partitioned into two cohorts, then these cohorts undergo weekly successions of quarantine and routine activity. Hence, while Cohort

1 remains active, Cohort 2 stays at home and vice versa, ensuring little interaction between the cohorts. This provides highly efficient mitigation, alongside continuous socioeconomic productivity, in which half of the workforce remains active at each point in time.

The AQ strategy limits social mixing while providing an outlet for people to sustain their economic and social routines. Its efficiency is rooted in two independent mitigating effects: Dual-partition of population and time. Splitting the population into two isolated cohorts reduces the number of infectious encounters, as, indeed, classrooms, offices, and public places operate at half their usual density. On top of that, each cohort is only active for half of the time, one week out of two - further attenuating infections within each cohort by, roughly, an additional factor of one-half.

Synchronization with the disease cycle. AQ treats one of the main obstacles for COVID-19 mitigation – the ~1 week incubation period of SARS-CoV-2. During this incubation, exposed individuals behave as invisible spreaders, unaware of their potential infectiousness. To illustrate AQ's remedy, consider an individual in Cohort 1 who was active during week 1, and therefore might have been infected. This individual will soon enter their presymptomatic stage, precisely the stage in which they are invisible, and hence contribute most to the spread. However, according to the AQ routine, they will be confined to their homes during week 2, and consequently, they will be isolated precisely during their suspected invisible spreading phase. Hence, the weekly succession is in resonance with the natural SARS-CoV-2 disease cycle, and in practice, leads to isolation of the majority of invisible spreaders.

The Root Cause of the Failure of American COVID-19 Governance Based on the Criticism of Liberal Democracy From Error-Tolerant Democracy

ZHOU Zhifa*, QU Pan

Liberal democracy cannot help America govern COVID-19 effectively for liberalism's misunderstanding of the concept of liberty. Error-tolerantism divides liberty into the right to liberty in innovative fields, the right to be wrong as an original right, and the right to be right in non-innovative ones as sub-rights; rights come from mutual empowerment among people. The major defects of liberal democracy from the perspective of error-tolerant democracy constructed on error-tolerantism are as follows: The essence of election is to transfer people's right to be wrong and corresponding right to be right to politicians, but the separation and balance of powers does not evaluate whether presidents, states, mayors, et al., have exercised the power to be wrong reasonably, so that they could even abuse it in the COVID-19 governance, and did great harm to people's human rights without any accountability or impeachment. Democratic governor' power to be wrong authorized by election was deprived by President Trump through issuing false information in the COVID-19 governance and encouraging people to protest against the anti-pandemic laws, which made liberal democracy in the United States threatened and COVID-19 out of control.

Impact of Covid-19 on psychosocial issues faced by cancer patients in India

Nirjari Dalal

Cancer or Covid-19, Who is the bigger Killer? This question is one which took root in 2020 and is still prevailing. More than 2.25 million people in India were suffering with cancer in 2018. Cancer is a disease which does not just affect the patients, but also devastates the family. The psychosocial issues faced due to cancer are immense. With Covid-19, the vulnerability of cancer patients increased and their immune system is further compromised due to the double attack on their bodies. When the pandemic brought India to a standstill, the plight of cancer patients, especially those in the low-income group increased manifold. Here we look at the psychosocial issues faced from financial crunch, infrastructure collapse, logistical issues, scheduling appointments for treatment, accommodation, emotional trauma, mental health, distress and many more. The burden of this is mostly on the health-care systems. In these uncertain times, nonprofit organizations like Gunvati Jagan Nath Kapoor Foundation and various others played a vital role in keeping the connection between the patients and health care system alive. Various digital models and other strategies proved a boon and in working in concert with hospitals patients were helped in the best possible way. A serious discussion needs to be in the works where all stakeholders work in concert to create a roadmap for such pandemics/adversaries ahead and develop and ready a risk management strategic plan in place so cancer care or any other devastating disease treatment does not come to a standstill.

Mental health of nurses involved with COVID-19 patients in Japan, intention to resign, and influencing factors

Takashi Ohue

The purpose of this study was to investigate the association between mental health (posttraumatic stress disorder, depression, anxiety disorder, and burnout) and intention to resign, and influencing factors regarding nurses involved with COVID-19 patients in A Prefecture as subjects.

Methods were conducted between August 4 and October 26, 2020. Basic attributes (gender, age, years of experience, etc.) were examined. Patient Health Questionnaire-9 and the Generalized Anxiety Disorder-7, Impact of Event Scale-Revised, Maslach Burnout Inventory, "intent to resign," were used to collect data from nurses working at hospitals treating patients with COVID-19 in Japan.

Result: between 20% and 30% of nurses involved with patients with COVID-19 are in a state of high mental distress. Regarding the associations between psychiatric symptoms and intention to resign, "I want to quit being a nurse" was affected by "cynicism" and "professional efficacy"; "I want to change hospitals/wards" was affected by "cynicism"; and "subthreshold depression," "anxiety disorder," and "burnout" affected "I want to continue working as a nurse." The increase in the number of patients with COVID-19 was a factor affecting mental health and intention to resign. When the number of patients increased, anxiety disorders and intention to resign also increased. Damage from harmful rumors increased the severity of every psychiatric symptom. To prepare for a pandemic such as COVID-19, it is necessary in normal times to construct psychological support systems and community systems to prevent damage from harmful rumors. "The amount of food has

increased," "the food is no longer delicious," "constipation has occurred," "I have become isolated," "I can no longer sleep," "the rough hands have become worse," and "the rough skin has become worse due to masks, etc." It was suggested that "decreased family income," "trouble with family," and "cannot do household chores" may be related to mental health problems.

Discussion: The mental health of nurses involved in COVID-19 infectious disease patients was associated with psychosocial factors. At the same time as it is necessary to reduce psychosocial factors, it is necessary to build a mental health support system for nurses.

Progression of COVID-19 under the Highly Restrictive Measures Imposed in Argentina

Jose-Luis Sagripanti

The variety and extent of non-pharmaceutical measures implemented by the government to control COVID-19 in Argentina were exceptional, making this country the best example to analyze the evolution of COVID-19 under the most stringent and longer-lasting restrictive policies- which included 119 days of strict nation-wide lock-down, 304 days of less restrictive lock-downs, and 35 days of curfews. Two of the three peaks of infection correlated with the germicidal solar flux received in Argentina, suggesting a seasonal component and a role for the virus persisting in the environment. A massive public gathering crowding the presidential square in Buenos Aires, during which nearly half of those present were without face masks, did not alter the infection curve in that city. Comparative epidemiological data (standardized per million inhabitants) shows that COVID-19 in Uruguay, a neighboring country whose capital is at a similar latitude than Buenos Aires and who did not mandate lock-downs or curfews, progressed much slower (until vaccination started) than in Argentina. The number of yearly deaths caused by respiratory diseases and influenza in Argentina before the pandemic was similar to the total number of deaths attributed to COVID-19 cumulated on April 25, 2021, more than a year after the pandemic started. The failure to detect any benefit on ameliorating COVID-19 by the long and strict nation-wide lock-downs in Argentina should raise world-wide concerns about mandating costly and ineffective restrictive measures during ongoing or future pandemics.

Socio-economic Changes of Cities during Covid-19, Case study: Dortmund City Centre

Ahmad Sahraei Juybari

During the COVID-19 pandemic, people's daily lives and patterns of behaviour, movement and communication have changed. Several lockdowns, regulations for protecting people, and social distancing have changed people's daily trip patterns especially in the big cities. According to the results, these fast radical changes faced cities also Dortmund city with social-economic tragedies. The pandemic has threatened people's mental health, closed most of big and small businesses particularly in the city centre and faced them with financial crisis, declined job opportunities, increased the unemployment rate, and health issues. Regarding the SWOT model results, the sum of the rate of the internal factor is currently higher than that of the external factor. That means we need to implement some strategies that can help to grow and build. Also, unfortunately, looking at the results of the matrices,

the weakness rate is higher than the opportunity or strength rate. So, for developing and recovering Dortmund city during and after this pandemic we have to consider short-, medium, and long terms strategies at the same time, as listed in the matrices. Although the effects of the short-term strategies are temporal, but can be very effective to help the city to get back on its feet. The short-term strategies are very important and must be implemented, but are not enough for come back to the situation bevor the pandemic. Therefore, the medium- and long-term strategies are designed to support the city for long-term recovery steps.

Keywords: COVID-19 pandemic, Big cities, Social-economic issues, Dortmund city, Changing commuting patterns

Ayaz Ahmed Abbasi

Our Experience of COVID-19 at a Large District General Hospital in the North West of England

Ayaz Ahmed Abbasi

The aim of this retrospective cohort epidemiological study is to review our patients who were presenting with COVID 19 from March 17, 2020 to May 20, 2020 to determine the outcomes in terms of mortality, discharge rate and current admissions, comorbidities and to further investigate the high mortality rate observed at our hospital. From March 17, 2020 to May 20, 2020 a total of 514 patients were admitted with a positive COVID-19 swab. Out of the 514 patients, 284 (55%) were male while 230 (45%) were female (Figure 1). Among the 514 patients admitted, 236 (45.9%) died, 263 (51.2%) were discharged, 1 (0.2%) was discharged and then readmitted, 1 (0.2%) was transferred while 13 (2.5%) are still admitted at the hospital. Out of the 236 patients who died, 144 (61%) were male and 92 (39%) were female. 130 (49%) of the 263 patients discharged were male and 133 (51%) were female. One female patient was discharged but then readmitted and one male patient was transferred. Out of the 13 patients still admitted at the hospital 9 (69%) are male and 4 (31%) are female (Fig 2). Upon review of the pre-existing comorbid conditions of the patients, it was noted that 101 (20%) patients had no comorbid conditions, 59 (11%) had one comorbid condition, 93 (18%) had two comorbid conditions, 106 (21%) had three and 155 (30%) had four or more comorbid conditions.

Pain and Function Deteriorates for Patients Awaiting Total Joint Arthroplasty that has been Postponed due to COVID-19 Pandemic

Zia Maharaj, Jurek Pietrzak, Magdalena Erasmus, Nkhodiseni Sikhauli, Josip Nenad Cacic, Lipalo Mokete

Background: Elective Total Joint Arthroplasty (TJA) procedures were postponed as part of the COVID-19 response to avert healthcare system collapse. Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) procedures comprise the highest volume of elective procedures performed at health care facilities, worldwide. Literature has demonstrated

significantly worse outcomes in patients awaiting TJA for longer than 3 months as evidenced by decreased functional outcomes at 12- and 24-month follow-up.

Aim: To determine the impact of surgery postponement on physical and mental health of patients awaiting. Secondly we aim to assess the impact of surgery postponement on waiting times for elective TJA in South Africa.

Methods: We conducted a prospective cross-sectional telephonic interview-based study on patients awaiting THA and TKA at an academic institution in South Africa. The study was conducted from 20 June until 10 July 2020 subsequent to the initiation of Level 1 Lockdown in South Africa in response to the COVID-19 pandemic. We recorded baseline demographic data and medical co-morbidities and the current length of time spent awaiting TJA. The questionnaire assessed the patients' current physical and mental health, respectively, as per a 5-point Likert Scale. Physical health was assessed with a focus on current pain and function as a consequence of the deferred surgical intervention. Mental health symptoms screened for symptoms of depression and anxiety.

Results: We included 185 patients (65.95% female; mean age 50.28 years) awaiting TJA for a mean of 26.42 ± 30.1 months. The mean length of time for patients awaiting THA was 28.29 mo (SD: 34.87; range: 3-264 mo) and TKA was 25.03 mo (SD: 26.07; range: 4-200 mo), respectively. There was increased joint pain experienced by 101 patients (55.49%) since the postponement of their TJA. The mean NRS pain score overall was 7.37 (SD: 2.24; range: 0-10). There were 123 patients (67.21%) who felt their functionality due to joint pain had decreased since the postponement of surgery. There were 73 (78.5%) patients between the age of 45 to 60 years who had decreased functionality since the postponement of surgery compared to 25 (46.3%) and 24 (68.6%) patients under 45 years and over 60 years of age, respectively ($P = 0.015$). There were 113 patients (61.75%), who experienced increased anxiety about getting infected with COVID-19 should they get their elective TJA during this time.

Conclusion: We found that the impact of elective surgery postponement due to the COVID-19 pandemic has had negative implications on patients' health and waiting times to surgery in our study. There is deterioration in physical function and pain for patients that have had elective TJA procedures postponed during the COVID-19 pandemic. Waiting time for patients in South Africa are already long and continue to grow with increasing concerns for post-operative outcomes in patients awaiting TJA. Initiatives have been taken in countries such as Denmark, Hungary and Poland to account for this unprecedented shutdown of elective surgery. This is important to consider in resource constrained countries where access to healthcare services is more limited.

Mental Health Impact Of COVID-19: Experiences from Healthcare Workers, Caregivers And Inpatients.

Carla Gramaglia, Patrizia Zeppego.

The Coronavirus disease 2019 (COVID-19) pandemic has violently impacted the Italian population and health care system, with relevant consequences on physical as well as on

mental health. Overall, higher awareness is warranted about the mental health impact of COVID-19 at different levels, starting from the general population. The international literature has paid particular attention to some vulnerable populations, including healthcare workers and patients with previous COVID-19 infection; on the other hand, the population of COVID-infected inpatients' informal caregivers has been quite neglected, despite preliminary reports suggesting that anxiety may be a concern in this group of individuals.

In the context of the ongoing pandemic, support may be needed by healthcare workers, who are facing an unprecedented and challenging situation. In a previous study, performed after the first wave of the pandemic, we observed higher levels of burnout (especially in the Depersonalization and Personal Accomplishment dimensions), in the following groups of healthcare workers: females, those aged <30 years, those exposed to changes in their daily and family habits, those who had to change their duties at work, residents in training. A careful assessment of the possible risk and protective factors both in the work environment and in the extra-work one might be helpful to offer targeted support.

The mental health consequences of Long COVID in survivors should be assessed in the context of a multi-disciplinary approach, as it emerges that anxiety, depression, sleep disorders and post-traumatic symptoms correlate with the persistence of somatic symptoms as respiratory ones, fatigue, reduced tolerance to physical efforts, rather than with the severity of the acute infection.

New ways to support the specific problems and needs of the relatives of COVID-19 inpatients should be found, also in the light of the changing feelings of this population as the pandemic continues. While the daily phone call during the first wave of the pandemic was a valuable opportunity to offer both clinical information about the patient and empathic listening and support to patients' relatives, for whom it was at that time difficult to ask for help in another context, now feelings of distrust, exhaustion, tiredness, anger and frustration may be a more relevant priority to address.

Short-Term Research Projects in Cognitive Neuroscience for Undergraduate Students: A Contingency Plan to Maintain Quality Teaching During COVID-19 Pandemic

Shapour Jaberzadeh, Farshad Alizadeh Mansouri

In response to the Corona Virus Disease 19 (COVID-19) pandemic, academic institutions have been severely restricted in their ability to conduct research and teach practical courses.

By implementing online teaching and learning, universities have been able to keep educational activities and maintain learning objectives for undergraduates and postgraduates.

This approach has enabled universities to deliver theoretical content during the pandemic, but practical activities with actual research experiments and teaching hands-on skills have been hampered due to potential violations of safety guidelines.

In this paper, we present an adaptive approach, developed and implemented at Monash University, for running online cognitive neuroscience courses and achieving learning objectives normally delivered through face-to-face classes.

This paper introduces two short-term research projects and describes how different aspects of each project, including tutorials, experiments, and assessments, were modified to comply with social distancing.

Both laboratory-based and home-based cognitive tests yielded similar results, indicating that students followed the required testing procedures and guidelines for a reliable data collection.

Students' performances and feedback indicate that we have met the majority of our educational goals while also meeting all safety guidelines and distancing requirements.

The Impact of Socioeconomic and Demographic Factors on COVID-19 in Virginia

Wanli Tan

Background: Despite the availability of COVID-19 vaccination since December 2020, infection and death counts remained high in America. It is arguable that other than biological risk factors, socioeconomic and demographic factors may have also played important roles in the spread of the pandemic in America.

Data and Methods: In this cross-sectional study, data for 60 potential socioeconomic and demographic risk factors of the 133 cities and counties in Virginia were obtained from the Centers for Disease Control and Prevention and the U.S. Census Bureau based on the American Community Survey conducted prior to the pandemic. COVID-19 data were retrieved from Johns Hopkins University's Center for Systems Science and Engineering. COVID-19 infection cases, deaths, and incidence rates as of December 31st, 2020 and September 30th, 2021 in Virginia were compared using the Wilcoxon Signed Rank Test. Multiple linear regression analysis was applied to investigate the association between social determinants and COVID-19 infection cases, deaths, and incidence rates in Virginia.

Results: The COVID-19 infection cases, deaths, and incidence rates in Virginia from January to September 2021 were statistically higher than those from March to December 2020. Of the 60 potential socioeconomic and demographic risk factors, 38, 31, and 20 were found to be highly associated with confirmed COVID-19 infection cases, deaths, and incidence rates in Virginia, respectively. The results of the stepwise multiple linear regression analysis indicated that sociodemographic determinants contributed to more than 75% of the variation in the infections, deaths, and incidence rates of COVID-19 in Virginia.

Conclusions: Socioeconomic and demographic factors were highly associated with the infections, deaths, and incidence rates of COVID-19 in Virginia. The developed multiple linear regression models could be used to predict the impact of socioeconomic and demographic factors on COVID-19 in Virginia.

Estimation of the probability of daily fluctuations of incidence of COVID-19 according to official data

Andrey Gerasimov

When analyzing the dynamics of morbidity and mortality, they are usually limited to analyzing the average level and trend. However, other characteristics are also of interest, including such as the level of differences in indicators over adjacent time intervals. If individual cases of illness or death do not depend on each other, then the number of cases obeys the Poisson distribution. By comparing the differences in the number of cases or deaths over adjacent time intervals, it is possible to test the hypothesis of whether pairs of observations are values of the same Poisson distribution.

The increased differences in indicators compared to the expected one can be explained in two ways:

- Availability of dynamics. For example, for COVID-19 in many countries, the number of deaths and cases vary significantly depending on the day of the week. In addition, the morbidity and mortality of COVID-19 changed significantly over fairly short time intervals.
- Grouping of cases, for example, family "clusters".

However, all the expected differences in the probability distributions of morbidity and mortality from the Poisson distribution are accompanied by an increase in differences compared to the expected one. But when analyzing the actual data, deviations of fluctuations in morbidity and mortality were found downwards. Such artifacts can be explained by the lack of health data collection and diagnosis (for example, a shortage of test systems that limit the number of detected cases), as well as the "unwillingness to cause public disturbance".

In particular, the regions of Russia are characterized by periods of sudden "stabilization" of morbidity and mortality. In Japan, there is a smoothing of the dynamics of morbidity. For Poland, artifacts are identified when there is not a single person who has died from COVID-19 for several days with sufficiently high average mortality, which is most likely due to the specifics of determining the cause of death and collecting medical statistics. Brazil is also taken as an example, where the number of cases strongly depends on the day of the week, but no reduction in the level of fluctuations in morbidity and mortality has been found.

Influence of Epidemic COVID–19 on Business Strategy, Information Technology and Supply Chain Agility to Firm Performance in Medical Device Industry

Siti Maemunah

This research paper aims to study how COVID-19 can affect the economy of all countries, including Indonesia. The Indonesian government imposes strict regulations on social and economic activities, such as regional traffic lockdowns, and travel restrictions. The impact of the COVID-19 pandemic is on business strategy, information technology, and supply chain agility on company performance in the medical device industry in Indonesia. The analysis used is the Structural Equation Model (SEM) with the AMOS program. This study has 171 respondents. The findings in this study are business strategy, information technology, and supply chain agility have a positive and significant impact on company performance during the COVID-19 pandemic. The practical implication is that business strategies and

information technology save companies and society by involving supply chain agility in securing the supply of medical devices in Indonesia.

Keywords---business strategy, firm performance, information technology, supply chain agility.

Teachers' Perception about Flipped Classroom in Era of COVID-19 Pandemic

Anuradha Yadav

COVID-19 has affected classroom teaching in medical education by flipping to online mode. This posed several challenges, particularly in developing countries, such as internet connectivity, technological concerns, and assessment methods. In this scenario, it was important to analyze the perspective of teachers and challenges related to the e-learning system to ensure effective teaching-learning in medical education. For this purpose, a cross-sectional observational study was conducted on teachers (30 replied) of phase-I MBBS, using a survey questionnaire. The responses were analyzed by using the chi-square test for qualitative data, with a significance level of 0.05. With an 81% response rate, the majority of teachers (70%) were female and from Generation X (60 %). Amongst responses, 53% of teachers had a positive impression of online teaching but preferred face-to-face instructions (67%). The majority of the teaching faculty, with a non-significant difference ($p=0.255$), faced sometimes network and technical issues but were overall satisfied with the online teaching and assessments. Since student participation and feedback were missed by the teachers, conventional classroom learning and assessment were preferred. During COVID-19, teaching faculty acknowledged online mode as an alternative, however, some suggested previous e-teaching training and platform privacy. Altogether, the teachers were enthusiastic about online education but missed face-to-face engagement with students. Many times, it was challenging for them to provide high-quality teaching due to a lack of Internet connectivity and certain technological challenges.

Falling Flat? The impact of state legitimacy, capacity, and political trust on flattening the curve of COVID-19

Kirstie Lynn Dobbs

As countries worldwide struggled to contain the COVID-19 pandemic in March and April of 2020, observers often remarked that countries with higher levels of regime legitimacy, state capacity, and political trust were more likely to curtail the spread of the virus. Remarkably, using quantitative data from 10 different sources, this article finds that this generalizable theory runs counter to expectations. Countries with higher levels of political legitimacy, trust, and capacity experienced greater increases in COVID cases during the onset of the pandemic, albeit the strength of these relationships is modest. To develop generalizable theories predicting virus containment, researchers should turn their attention to unique factors characterizing industrialized democracies that make a virus much harder to contain

and expand their scope by using transdisciplinary approaches to understanding the pandemic.

Phenotypes of post-COVID-19 interstitial lung disease.

Sara Tomassetti, Leonardo Gori, Claudia Ravaglia, Valentina Luzzi, Luca Ciani, Leonardo Giuntoli, Martina Marinato, Alessandra Dubini, Venerino Poletti, Alberto Cavazza, Diletta Cozzi, Camilla Comin, Valeria Pasini, Michele Spinicci, Alessandro Bartoloni, Anna Peired, Elisabetta Rosi, Federico Lavorini, Cosimo Nardi, Venerino Poletti

Background/Introduction: Pulmonary sequelae after Sars-Cov-2 infection, range from limited abnormalities to major interstitial lung diseases (ILD). Bronchoalveolar lavage (BAL) and cryobiopsy findings, integrated with the clinical-radiological scenario, may help both clinicians to correctly manage patients, and researchers to better understand the features and pathogenic mechanisms of post-COVID fibrosis.

Objectives: Describe different phenotypes and management of post COVID ILD.

Methods: We conducted a prospective multicenter national (Italian) study: PCOILS study – Post-Covid-Interstitial Lung Syndrome). In two centres, Florence and Forlì, subsequent patients seen at 4-18 months after the acute infection underwent transbronchial lung cryobiopsy and BAL if they showed a significant ILD on follow-up HRCT (progressive and/or symptomatic and/or with pulmonary function impairment).

Results: 19 patients were biopsied. Patients' characteristics : median age of patients is 66, 18 men and 1 woman; eleven cases (58%) are former smokers, 8 out of 19 (42%) patients have occupational exposure that may result in ILD. All patients underwent pulmonary function test before cryobiopsy with median FVC values 89 % and median DLCO values of 66%. The 6-minute walking test was performed in 9 patients, the patients walked a median of 450 meters As shown in Figure 1 we identified three post-COVID phenotypes: 1) prominent vascular changes; 2) post-COVID fibrosis; 3) persistent Sars-CoV-2 infection. Phenotype 1 (vascular) was detected in two cases that were biopsied early after acute COVID-19 (4 and 5 months respectively). Their HRCT showed pure Ground glass opacities (GGO), the histology showed emangiomas-like features (Figure 1). The patients were followed up without treatment. Phenotype 2 (post-COVID fibrosis) was detected in 7 patients, all with HRCT NSIP/OP features. Histology showed fibrotic or mixed NSIP, fibrotic OP, fibrotic DAD, and bronchiolar damage possibly correlated with ventilation injury in one case (Figure 1). Patients were variably treated with steroids depending on disease extent and symptoms. In the case with post ventilation injury, that didn't show inflammation on biopsy, corticosteroid was stopped. Phenotype 3 (persistent COVID). The patient was immunosuppressed (Rituximab for Non Hodgkin Lymphoma) and HRCT showed GGO that worsened between month 6-12. COVID-19 was detected by BAL (Sars-CoV-2 positivity and CD8+ lymphocytosis - 53% total lymph, CD4/CD8 0.1) and biopsy showed cellular NSIP. He was treated with Casirivimab e Imdevimab with complete resolution. The remaining 9 patients were reclassified as known ILDs and treated according to current guidelines.

Conclusions: We identified three distinct phenotypes of chronic post covid damage leading to different management choices.

Physical Activity Supporting Connection to Nature, and Helping to Maintain Wellbeing during the Covid-19 Restrictions in England

Liz O'Brien

The Covid-19 pandemic and the varying restrictions put in place to prevent or reduce the spread of the disease led to anxiety, concern and stress for many people. In England in 2020 restrictions varied at different times of the year, and throughout this time there was a lot of attention focused on the importance of exercise and on engaging with nature to maintain people's overall wellbeing. We undertook an online survey that ran for six weeks in June/July 2020 and gained a response from 2115 people, of which 25% were male and 74% female, with 35% aged 16–44 and 65% aged 45+. We also carried out 25 interviews with a small sample of those who completed the survey to understanding more about how and why the Covid-19 pandemic was enabling people to engage with nature more or less. The survey and interviews we undertook focused on people who were already interested or engaged with nature as it was publicised through Forestry England's website and newsletter, the organisation manages public forests in England. We explored whether being physically active changed or not, if being active impacted people's wellbeing and whether those who were active benefited from connecting to nature. We found that those meeting the government recommended levels of physical activity in the previous week, of 150 min, were more likely to maintain their overall wellbeing through feeling that the things they did in their life were worthwhile ($p < 0.0001$) and reported an increase in feelings of connection to nature ($p < 0.0001$). While those who did less than 30 min of physical activity in the previous week were less happy ($p < 0.0001$) and more anxious than usual ($p < 0.0001$). The qualitative data highlighted how all interviewees were noticing nature much more and were often discovering new paths and places to visit locally that they were unfamiliar with or had not accessed previously. The research highlights the importance of physical activity and contact with nature and how these can play important roles in maintaining people's everyday wellbeing under extremely difficult national circumstances.

The impact of the COVID-19 2020 outbreak on hospital length of stay following fragility hip fracture surgery

Alex Bebin

Introduction: Hip fractures in elderly patients are a major cause of morbidity and mortality. Great variability in length of hospital stay (LOS) is evident in this population. The Coronavirus 2019 (COVID-19) outbreak led to prompt discharge of effected patients in order to reduce contagion risk. The influence of the pandemic on LOS and discharge destination in COVID-19 negative patients has not been studied. The aim of this study was to evaluate the LOS and discharge destination during the COVID-19 outbreak and compare it with similar patients' cohort in preceding years.

Patients and methods: A retrospective study comparing a total of 182 consecutive fragility hip fracture patients operated upon during the first COVID-19 outbreak to patients

operated upon in two preceding years was conducted. Data regarding demographic, comorbidities, surgical management, hospitalization, as well as surgical and medical complications was retrieved from electronic charts.

Results: 67 fragility hip fracture patients were admitted during the COVID-19 outbreak (i.e. COVID group), 55 and 60 patients were admitted during the same time periods in 2017 and 2018, respectively (i.e. Control groups). Both groups were of similar age, gender and age adjusted Charlson's Comorbidity Index. Patients in COVID group had significantly shorter LOS (7.2 ± 3.3 vs. 8.9 ± 4.9 days, $p=0.008$), waiting time for a rehabilitation facility (7.2 ± 3.1 vs. 9.3 ± 4.9 days, $p=0.003$), and greater prevalence of delirium (17.9% vs. 7% of patients, $p=0.028$). In hospital mortality did not differ between groups.

Conclusions: LOS and time to rehabilitations were significantly shorter in the COVID group. Delirium was more common in the COVID group, possibly due to the negative effects of social distancing.

Sources of Healthcare Workers, COVID-19 Infections and Related Safety Guidelines

Lotta Oksanen

COVID-19 pandemic has changed our view of the previous and current safety guidelines in the healthcare regarding SARS-CoV-2, and other respiratory infections. During the pandemic the understanding of the airborne transmission route has increased remarkably, and it seems that the airborne transmission is important, even predominant transmission route for SARS-CoV-2 in both short and long distances. However, the safety guidelines regarding personal protective equipment (PPE) in many hospitals are still based on the droplet precautions and aerosol precautions are mainly used when performing aerosol generating procedures (AGPs).

In this session we combine findings from multiple studies. The methods include 259 air and 252 surface samples from the surroundings of hospitalized and home-treated COVID-19 patients as well as a measured particle generation during different expected AGPs in real operational room environment, and a wide questionnaire for 1072 healthcare workers regarding COVID-19 infections, potential COVID-19 exposures, ability to follow safety guidelines and used PPE. All potential infections were ensured with COVID-19 PCR-samples.

This session presents our main findings regarding work-related exposure to SARS-CoV-2, the role of aerosol generating procedures as an infection risk compared to the exposure faced from normal respiratory activities during patient contacts and the sources of COVID-19 infections among healthcare workers. The role of different mask and respirators is discussed regarding the findings. The presented data is collected at the Helsinki University Hospital, Finland, during the COVID-19 pandemic.

Pixel precise unsupervised detection of viral particle proliferation in cellular imaging data

Birgitta Dresch-Langley, John Wandeto

Cellular and molecular imaging techniques and models have been developed to characterize single stages of viral proliferation after focal infection of cells in vitro. The fast

and automatic classification of cell imaging data may prove helpful prior to any further comparison of representative experimental data to mathematical models of viral propagation in host cells. Here, we used computer generated images drawn from a reproduction of an imaging model from a previously published study of experimentally obtained cell imaging data representing progressive viral particle proliferation in host cell monolayers. Inspired by experimental time-based imaging data, here in this study viral particle increase in time is simulated by a one-by-one increase, across images, in black or gray single pixels representing dead or partially infected cells, and hypothetical remission by a one-by-one increase in white pixels coding for living cells in the original image model. The image simulations are submitted to unsupervised learning by a Self-Organizing Map (SOM) and the Quantization Error in the SOM output (SOM-QE) is used for automatic classification of the image simulations as a function of the represented extent of viral particle proliferation or cell recovery. Unsupervised classification by SOM-QE of 160 model images, each with more than three million pixels, is shown to provide a statistically reliable, pixel precise, and fast classification model that outperforms human computer-assisted image classification by RGB image mean computation. The automatic classification procedure proposed here provides a powerful approach to understand finely tuned mechanisms in the infection and proliferation of virus in cell lines in vitro or other cells.

Mass testing after a single suspected or confirmed case of COVID-19 in London care homes, April–May 2020: implications for policy and practice

Marina Sanchez Perez

Introduction: Previous investigations have identified high rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among residents and staff in care homes reporting an outbreak of coronavirus disease 2019 (COVID-19). We investigated care homes reporting a single suspected or confirmed case to assess whether early mass testing might reduce risk of transmission during the peak of the pandemic in London.

Methods: Between 18 and 27 April 2020, residents and staff in care homes reporting a single case of COVID-19 to Public Health England had a nasal swab to test for SARS-CoV-2 infection by reverse transcription polymerase chain reaction and subsequent whole-genome sequencing. Residents and staff in two care homes were re-tested 8 days later.

Results: Four care homes were investigated. SARS-CoV-2 positivity was 20% (65/333) overall, ranging between 3 and 59%. Among residents, positivity ranged between 3 and 76% compared with 3 and 40% in staff. Half of the SARS-CoV-2-positive residents (23/46, 50%) and 63% of staff (12/19) reported symptoms within 14 days before or after testing. Repeat testing 8 days later in two care homes with the highest infection rates identified only two new cases. Genomic analysis demonstrated a small number of introduction of the virus into care homes, and distinct clusters within three of the care homes.

Conclusions: We found extensive but variable rates of SARS-CoV-2 infection among residents and staff in care homes reporting a single case of COVID-19. Although routine whole-home testing has now been adopted into practice, care homes must remain vigilant

and should be encouraged to report a single suspected case, which should trigger appropriate outbreak control measures.

Keywords: COVID-19; SARS-CoV-2; care home; long-term care facility; mass testing; older people.

That you can also find here: <https://pubmed.ncbi.nlm.nih.gov/33620453/>

The Law, Economics and Governance of Generation COVID-19 Long-Haul

Julia Puaschunder, Martin Gelter

Abstract: The novel coronavirus SARS-CoV-2 is an external shock to all world societies with lasting impact that changes individual, political, and corporate decisions profoundly. More and more evidence reveals that an estimated 10-50% of those previously infected with COVID-19 face a longer-term or long-term health impact and/or chronic debilitation that in many cases comes and goes in waves. This phenomenon has already been referred to as a pandemic within the pandemic. The broad-based and long-term impact COVID Long Haulers have also holds the potential to change our world and modern society lastingly through the following three outlined speculative trends: (1) The Coronavirus crisis has widened novel and already existing inequalities, of which the rather surprising finance performance versus real economy liquidity constraint gap led to unequal emotional and socio-psychological crisis fallout propensities. Corporate governance and political economy power dynamics may shift in the eye of Long Haulers' relation to work and a healthy productive environment. Employers will likely face pressure to create a safe and secure working environment but also have rising tort liability risks that may be mitigated by hiring health consulting agents. Pro-active care for maintaining a healthy workforce and the overall long-term well-being of employees including preventive care in teams will become an essential corporate feature to attract qualified labor, whose bargaining power increased in the eye of labor shortages in human-contact-facing industries and positions. (2) Long Haulers may initiate an Artificial Intelligence revolution of self-monitoring and constant health status tracking, but also democratization of healthcare information. Artificial Intelligence, robotics and big data offer essential complements to fill in for long-haul attention and productivity deficits gaps that may occur in waves. Long Haulers have already found themselves in online self-help groups - such as Survivor Corps - for quick and unbureaucratic information exchange about an emerging group phenomenon. Social online media platforms serve as easy remedies during a time when COVID hospitalization was precluded by a surge of severe COVID cases. Nowadays COVID long-haul patients have become - more than ever before - citizen scientists that bundle decentralized information on their health status and potential remedies in order to inform the medical profession about newly emerging trends. The rise in medical self-help and mutual support will have profound implications for the regulation of the medical profession and will likely stretch the medical remedy spectrum and boost alternative medicine. In the online exchange of sensitive information about one's health status, citizen scientists are also in particular vulnerable in terms of their privacy, potentially even more susceptible to online marketing campaigns under medically impaired conditions, but also because of their sensitive

information having been publicly disclosed online over time. (3) As historical precedents show, Generation COVID Long-Haul partially being recognized as disabled may result in increased pressures to reform social, healthcare and retirement systems. Given waves of debilitation, the analysis of macroeconomic aggregates will have to change in order to reflect a more diversified and temporal view of social preferences. Future economic policy research may take inspiration from the legal concept of disparate impact. Behavioral insights on how to navigate the world with attention deficits and under uncertainty may pay attention to developing an idea of the economic benefits of rest by incorporating preferences for minimalism in a turbulent world longing for recovery.

Immunothrombosis in COVID-19: Implications of Neutrophil Extracellular Traps

Rebeca Campi Caballero

Coronavirus disease 2019 (COVID-19) is an emerging condition caused by the SARS-CoV-2 virus, and since December 2019, it has represented a serious public health problem that has compromised health systems worldwide. Many patients develop mild forms of the illness, but several studies have shown that some patients progress to a severe acute respiratory syndrome, sepsis, coagulopathy, and multiorgan failure—mainly elderly subjects with certain comorbidities such as diabetes mellitus, hypertension, and obesity. Thrombosis has been reported in a great number of patients, representing a significant cause of death in patients with COVID-19. Increased secretion of inflammatory interleukins and chemokines recruits neutrophils to the site of infection, Unable to eliminate the virus by activation of TLR-2, and -4, the neutrophils release their extracellular traps by NETosis, whose function is to limit infection. NETs are rich in histones, free DNA, and MPO acting as DAMPs, amplifying the inflammatory response and leading to endothelial damage. This leads to platelet aggregation, clot formation, and stabilization. Histones H3 and H4 present in NETs activate the intrinsic coagulation pathway through their interaction with FXI and XII, and they downregulate thrombomodulin, inducing a procoagulant state. Endothelial injury leads to the activation of the extrinsic pathway by the expression of TFIII, which binds to FVII, triggering the coagulation cascade. Thrombin, FXa, and the TFIII–FVII complex interact with protease activated receptors (PARs), causing platelet activation and aggregation with the subsequent release of their granular content, such as p-selectin, which favors the activation and migration of additional PMNs that easily bind to the endothelium through adhesion molecules, in the meanwhile, the complement system activates thrombin by binding C3a and C5a, perpetuating thrombus formation.

Research has shown that diverse pathogens including viruses induce NET formation. Though beneficial for the host's defense, the collateral damage from the sustained formation of NETs can trigger a cascade of inflammatory reactions. Such reactions can result in the destruction of surrounding tissues, promote microthrombosis, and cause permanent damage to the organs of the pulmonary and cardiovascular systems, among others. Elevated serum levels of NETs have been reported in hospitalized patients with COVID-19, suggesting that these structures may be key in the pathophysiological process of the disease and have an association with the patients' prognosis. Therefore, it is

important to analyze the role of NETs as a trigger mechanism for thrombotic processes in patients with COVID-19.

Multidimensional Hardships in the U.S. during the COVID-19 Pandemic

Brian Glassman, Shatakshee Dhongde

This paper estimates multidimensional hardships experienced by Americans during the Covid-19 pandemic. We compile monthly data from the Census Bureau's Household Pulse Survey on job insecurity, food insufficiency, housing insecurity, and mental health. Our analysis spans one and a half years of the pandemic, beginning April 2020 and ending March 2022. We find that 16.4 percent of adults experienced two or more hardships during this time. At the peak of the pandemic, approximately 1 in 5 adults experienced multiple hardships. Non-Hispanic Blacks were most likely to experience food insufficiency and housing insecurity, and Hispanics were most likely to experience job insecurity. Multidimensional hardships were more prevalent in the South and the West and less so in the Midwest. Our results underscore the need to take into account the overlap and interactions between multiple dimensions when designing policies aimed at improving well-being. Aid needs to be targeted towards relief in specific hardships and towards minority communities in order to mitigate the impact of the pandemic on public health.

Keywords: Covid-19, food insufficiency, hardship, housing insecurity, job insecurity, mental health, pandemic, poverty, U.S.

JEL codes: I1, I3, O51

*This paper is released to inform interested parties of ongoing research and to encourage discussion of work in progress. Any views expressed are those of the author and not necessarily of the U.S. Census Bureau. The Census Bureau reviewed this data product for unauthorized disclosure of confidential information and has approved the disclosure avoidance practices applied to this release. CDDRB-FY21-POP001-0190.

The Association Between Antibody Response to Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Post-COVID-19 Syndrome in Healthcare Workers

Christopher Pereira

It is currently unknown how post-COVID-19 syndrome (PCS) may affect those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This longitudinal study includes healthcare staff who tested positive for SARS-CoV-2 between March and April 2020, with follow-up of their antibody titers and symptoms. More than half (21 of 38) had PCS after 7-8 months. There was no statistically significant difference between initial reverse-transcription polymerase chain reaction titers or serial antibody levels between those who did and those who did not develop PCS. This study highlights the relative commonality of PCS in healthcare workers and this should be considered in vaccination scheduling and workforce planning to allow adequate frontline staffing numbers

Persistent Symptoms in Hospitalized and Non-hospitalized Patients Recovering From COVID-19 in Denmark

Jane Agergaard

Background: Following COVID-19 long term persistent symptoms (Long COVID) has been described, and debilitating disease is reported. However, investigations are not conclusive on an organ-specific explanation for Long COVID and documentation for effective treatment options are lacking. In large populations higher risk of persistent symptoms were found in individuals with higher age and female sex and current literature document that long COVID may persist for more than a year. However, while Long COVID describes prevalence of one or more symptoms there are no consensus of a definition of Long COVID disease. We aim to characterize Long COVID-19 disease including duration of and risk factors.

Method: We registered baseline and followed up in patients admitted to hospital with COVID-19 as well as patients referred to the Post COVID Clinic at Aarhus University Hospital due to persistent and non-improving Long COVID. Currently more than 300 hospitalized and 500 non-hospitalized patients were included. Following informed consent patients were asked to report severity of symptoms, and disability, fatigue, quality of life, anxiety and depression using validated scores.

Results: Hospitalized patients from the first wave of the epidemic had a high prevalence of persistent symptoms 48 weeks after discharge (87%). Patients referred to the Post COVID Clinic, at a median of 5 months after initial COVID-19 illness, had a median age of 45 years, 10% were hospitalized and patients had few comorbidities and rarely smoked, drank alcohol or were obese. The most prevalent reported symptoms in these patients were headache (72%), difficulties concentrating (82%), dyspnea at physical activity (65%), and physical fatigue (82%) (preliminary data). Older age, or female sex were not associated with severity of symptoms in patients referred to a Post COVID Clinic. Headache, paresthesia, physical fatigue and functional disability were significantly more prevalent in patients who reported long vs short duration of fever in the acute phase of COVID-19 (preliminary data).

Perspectives: We found high prevalence of persistent symptoms in hospitalized patients. We did not confirm previously documented risk factors for Long COVID in patients referred to a Post COVID clinic, and suggest the Post COVID disease must be defined looking at Long COVID patients more than registering symptoms at a population level or following patients who were admitted with severe COVID-19. Further characterization is needed in order to direct research and treatment options.

Isolated systems towards new constellations: Dance/Movement Therapy interventions to cope with Covid-19

Monica Re

In Italy the first Covid-19 lockdown began at the end of February 2020 when schools of all degrees remained closed after Carnival's holidays. In three weeks we experienced the total lockdown. It was difficult to understand what was happening. Working, teaching, learning needed to be reorganized on-line. It was very complex as far as there were many

geographical areas with web connection difficulties. TV information was frightening and spreading a sense of isolation with the images of the global trauma increasing stress conditions. The dance movement therapist involved felt the responsibility to help the community where she lives, a valley in the north-west Italian Alps. She managed a first free pilot program with the local Center of the Social Care System (Con.I.S.A – Susa Valley – Region Piemonte) trying to reduce the sense of disorientation and isolation. The on-line program was offered to the elderly people living in the two public residential care homes and to three classes of a Scholar Institute with a total number of ninety participants. The program focused on facilitating an integrated body/mind moving dimension, sharing emotions and promoting a creative network of relationship to contrast isolation and to reduce distances during the lockdown. Aim of the program was to facilitate an integrated body/mind dimension through the creative process and maintaining the connection with “the outside” during the restrictions. Anchoring the program to the suite The Carnival of Animals it was possible to develop different functions. Firstly it was necessary to facilitate the movement. Animal’s images encouraged to explore body-effort-shape-space according to the Laban Movement principles. Playing as animals helped to overcome the gap between participants and the therapist as they were working on-line. Secondly the program had a social/educational function such as gently introducing the use of masks and preparing for the future “masked” life outside. In the new on-line playground children and elderly people had the chance to cope with the first lockdown maintaining the sense of community. The program responded to concrete needs such as the necessity to feel useful/important while disoriented by the loss of relationship and to establish the sense of community and belongingness through a common goal with new empowering practices such as dancing on- line. The aim of the program was to contrast physical and emotional diseases that commonly increased during the lockdowns similar to the “prisoner’s condition”. Social-Sensory Deprivation Syndrome, Post Incarceration Syndrome and Post Traumatic Stress Disorder were considered to realize the program. Conditions such as isolation, disorientation, fear, solitary confinement, deprivation of any social contact, state of sensory deprivation were the basis to develop the workshop with the aim to cope with the sense of passivity, helplessness and the feeling on the edge. It was necessary to limit the sense of suspended time and space, contrasting the invasive state hypokinesia and the compromise of all senses. An endless “pain chain” needed to be faced. The success of the first pilot program encouraged the local Center of the Social Care System (Con.I.S.A – Susa Valley – Region Piemonte) to promote a second sponsored program Map & Territory. It was meant to involve in presence the residents of two elderly houses, two first classes of a sporting high school, a group of unaccompanied immigrant minors and a group of minors with fragile families for a total of one hundred participants. Aim was to understand if it would have been worth to consolidate the use of technology for providing care not only in emergency cases, but also in primary care case. In fact the program was developed from September 2020 to June 2021 during the second lockdown and the third lockdown and remained almost on-line. It was important to consolidate the on-line working dimension, offering a focus on the limits to work without contact in a long term process. The presentation will offer an overview on the dance movement protocol that has been applied

from the first starting point to its development with elderly, adolescents and children, in a continuous adjustment. It will be observed how fundamental contact is and how the clients started to reflect about this lack during the months. Finally it will be worth to observe the efficacy of such intervention in terms of health promotion and support to the primary care according to the WHO health definition: “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”.

Considering “Health a dynamic process that, at its core, is about having the capacity to self-management”, which could be the opportunity to open to a wider dialogue between medicine and art, in this case Dance/Movement Therapy?

Phenotypic changes of circulating pDCs in individuals with severe/fatal COVID-19

Amal Hasan

Purpose: Coronavirus disease 2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can range in severity from asymptomatic to severe/critical disease. Severe COVID-19 is linked to insufficient control of viral replication and excessive inflammation driven by an unbalanced immune response. Plasmacytoid dendritic cells (pDCs) are specialized in the rapid production of large amounts of interferons in response to viral infections, and thus, are critical in antiviral immunity. Conventional DCs (cDCs) are also critical for the elimination of viral infections, which is largely due to their specialized ability to prime and activate naïve T cells. However, pDCs can also acquire a mature dendritic phenotype, and prime and activate T-cells. We assessed the frequency and phenotype of pDCs and cDCs in patients with different disease severities. **Patients and methods:** Patients with a PCR-confirmed diagnosis of COVID-19 were recruited. Disease severity was judged according to the Clinical Guidance for Management of Patients with Confirmed COVID-19 and ranged from asymptomatic to severe/critical. Peripheral whole blood was obtained during the 2nd week of illness, stained with antibodies specific for lineage markers (CD3, CD14, CD16, CD19, CD20, CD56), human leukocyte antigen-DR isotype (HLA-DR), CD11c, and CD123, and analyzed by flow cytometry.

Results: Critical/fatal disease was associated with lower frequency of pDCs, and lower expression levels of HLA-DR and CD123 by pDCs and cDC2-like cells. **Conclusion:** A lower frequency of pDCs as well as lower expression levels of surface HLA-DR and CD123 may predict disease severity and outcome.

Development of Second-Generation Androgen Receptor Antagonist Proxalutamide For Mild, Moderate and Severe Patients with COVID-19

Liandong Ma

As of April 21, 2022, there were 500 million confirmed active cases of COVID-19 and 6 million deaths, including 41,891 patients in serious condition. However, there are no effective oral drugs for the treatment of severe COVID 19 patients. We here discuss the

mechanism of action for Proxalutamide to treat mild, moderate and severe COVID-19 Patients.

Cellular entry and infection of SARS-CoV-2 virus are mediated by two key proteins in host cells, angiotensin converting enzyme 2 (ACE2), a host transmembrane protein, providing the binding sites for SARS-CoV-2 on the host cell surface, and transmembrane protease serine 2 protein (TMPRSS2), priming the S protein of SARS-Cov-2 to facilitate the viral entry into the host cells. Both ACE2 and TMPRSS2 proteins are regulated by androgen receptor (AR) signaling. Previously, Proxalutamide has been reported to downregulate the expression of ACE2 and TMPRSS2 in cells derived from prostate, lung cancer and normal lung epithelial cells. In this study, we demonstrate that Proxalutamide inhibited the infection of SARS-COV-2 wild type, alpha and delta variants, with IC50s of 69, 48 and 39 nM, respectively. Moreover, Proxalutamide reduced SARS-COV-2 viral load in outpatients with COVID-19 (82% viral RT-PCR negative rate in active group vs. 31% in placebo group after treatment for 7 days (p-value<0.0001).

Severe COVID-19 disease leads to cytokine storm resulting in pulmonary inflammation and extensive damage in lung and other organs. Anti-inflammatory drugs, including Baricitinib and dexamethasone, have shown limited clinical benefit for hospitalized COVID-19 patients. Therefore, more effective drugs are in urgent need for patients suffering from severe COVID-19. Recently, Proxalutamide has been reported to reduce the mortality rate (HR=0.16) and lung injury (by 57%, active drug vs placebo groups) in hospitalized patients with COVID-19 in an IIT phase III study. We presented here the mechanism of action of Proxalutamide for targeting cytokine storm in severe COVID-19 patients. Proxalutamide was demonstrated to activate nuclear factor erythroid 2-related factor 2 (Nrf2) in macrophages, which stimulates the antioxidant response element (ARE) for reducing cytokine storm-induced organ damage in COVID-19. In addition, Proxalutamide inhibited TNF alpha and IL-6 expression and blocked INF gamma signaling by downregulating STAT1 expression in immune cells. Importantly, Proxalutamide reduced inflammatory cells in lungs in a Poly (I:C), pseudoviral induced-lung injury animal models. Further, Proxalutamide decreased C-reactive protein, D-Dimer and improved lymphocyte count, biomarkers for COVID-19 progression.

Finally, proxalutamide reduced the risk of hospitalization or death by 100% compared to the control group (p < 0.02) in covid-19 patients with Rx for more than 7 days in a phase III MRCT study. In consistent, Proxalutamide has been demonstrated clinical benefits in outpatient and inpatients with covid-19 in investigator-sponsored clinical studies in Brazil. Proxalutamide effectively prevented the disease progression of mild to moderate patients with COVID-19. The hospitalization rates (active drug vs placebo) were 0% vs. 27.3 and 2.6% vs. 18.6%, for male and female outpatients respectively. Remarkably, proxalutamide reduced mortality from 39.6% in placebo group to 8.5% in active drug in hospitalized patients with covid-19.

In brief, these results support the clinical development of proxalutamide for the proposed intended use treatment of mild to moderate and severe patients with covid-19 in adults

COVID-19 Vaccine Failure in a Patient with Multiple Sclerosis on Ocrelizumab

Nikhitha Mantri

Vaccines will play a key role in ending the COVID-19 pandemic. Vaccination against infections remains an important part of the management of patients with multiple sclerosis. However, there are limited data about the safety and efficacy of the currently available COVID-19 mRNA vaccines in patients with multiple sclerosis receiving concurrent immunosuppressive therapies. Patients on B cell depleting therapy such as ocrelizumab have an attenuated vaccine response. We report the first case of COVID-19 vaccine failure in a patient with relapsing-remitting multiple sclerosis on B cell depleting therapy, ocrelizumab. We offer suggestions to improve vaccine efficacy in these patients.

Endothelial cell infection and dysfunction, immune activation in severe COVID-19

Jay K Kolls, Mst Shamima Khatun, Xuebin Qin

Rationale: Severe acute respiratory syndrome coronavirus 2 (SARs-CoV2) is a causative agent of coronavirus disease 2019 (COVID-19). Endothelial cell (EC) infection and immune response-mediated EC dysfunction have been suggested to contribute to severe COVID-19. K18-hACE2 transgenic mice have been used to model severe COVID-19 including the development of ARDS-like pathology and microthrombi. This severe COVID-19 is associated with extensive endothelial cell infection and dysfunction. However, the molecular mechanisms underlying this pathology remain to be elucidated. Thus, we performed single cell RNAseq in this model, day 4 post infection and mapped the data to the both murine and SARs-CoV2 genome. Objectives: To develop a single cell RNAseq pipeline to track viral RNA in the lung and to assess cell intrinsic differences in viral RNA positive cells and viral RNA-negative cells. Methods: K18-hACE2 transgenic mice were infected with 2×10^5 TCID50 of Isolate USAWA1/2020. Single-cell RNA-seq analyses on the 10X Genomics platform were used to examine the lung infection of the severe COVID-19 mice. Measurements and Main Results: To investigate the immune response and mechanisms associated with COVID-19, we performed single-cell RNA sequencing on whole lung. Subgenomic RNA (a measure of replicating viral RNA) was only confined to a few cells whereas the viral ORFs: N, S, and ORF10 were expressed in many cell clusters including macrophages, fibroblasts, and endothelial cells. We next gated on Cdh5+ endothelial cells and compared viral RNA+ cells with viral RNA- cells. Viral RNA+ cells expressed increased level of Irf7 and several interferon-inducible transcripts compared to viral RNA- cells. Moreover, viral RNA+ cells had significantly reduced expression of the tight junction gene, Cldn5. Conclusions: These data show that scRNAseq can be used to track viral RNA dissemination and that lung endothelial cells contain viral RNA and have distinct alterations in their transcriptomes that likely contribute to endothelial cell dysfunction leading to COVID-19 pathogenesis.

COVID-19 and Aging in Place, Informal Care and Social Networks in Flanders (Belgium)

Dominique Vanneste (prof.dr.) (presenter), Wesley Gruijthuijsen (drs), Jakob D'Herbe (drs), Hilde Heynen (prof.dr.), Veerle Draulans (prof.dr.)

Western aging policies prioritize aging in place, re-emphasizing informal care and support. However, organizing informal care at home gives rise to complicated and multilayered negotiations between people and their home environments. Organizing these socio-cultural, economic, and spatial factors, impact the so-called landscapes of care while distance, both geographical and emotional, is a key concept. As the COVID-19 pandemic plunged us unprepared into a health crisis, governmental measures had to be implemented quickly; especially older and at-risk persons had to keep a distance from non-household members. These measures expectedly affected the existing landscapes of care, especially caring task divisions. This contribution discusses how landscapes of care were affected and what role the neighborhood played in terms of social networking in Flanders (Dutch speaking region of Belgium) during and shortly after its first lockdown. Qualitative in-depth interviews by phone were conducted as part of an interdisciplinary research project focusing on aging-in-place to explore how social support and informal care networks of older adults had to change during the pandemic.

Thromboinflammation: Lessons from COVID-19 infection.

Abd Al-Roof Higazi

Inflammation and hemostasis or thrombosis are integrated processes, but the pathways that link these processes are incompletely defined. Severe COVID-19 infection that induces an exaggerated inflammation response, a life threatening pro-thrombotic state and D-dimers elevation, provide a paradigm to study the interactions between inflammation and thrombosis.

Previously published studies from our laboratory showed that α -defensins, small cationic and hydrophobic antimicrobial proteins released in abundance from activated human neutrophils accelerate fibrin polymerization, increase fiber density and branching, incorporate into nascent fibrin clots, impede fibrinolysis and inhibit the efficacy of heparin *in vitro* and in transgenic mice expressing human α -defensin-1.

More recently, we performed prospective studies in patients with COVID-19 infection to address the role of α -defensins in host response. We found that plasma levels of α -defensins are elevated in affected patients, track with disease progression/mortality and resolution and show close correlations with plasma levels of IL-6 and D-dimers. Immunohistochemistry revealed intense deposition of α -defensins in lung vasculature and thrombi of patient with fatal infection. We also found that IL-6 stimulated the release of α -defensins from neutrophils, thereby accelerating clot formation in human blood, effects that were inhibited by colchicine, which blocks degranulation of human neutrophils.

In other prospective studies, we found that Tocilizumab (8 mg/kg) administered to patients who had a positive PCR test for COVID-19 paradoxically was associated with a significant increase in plasma IL-6, as well as pro-thrombotic α -defensins and D-dimers. In contrast, COVID-19 patients given colchicine (0.5 mg twice a day) showed reduced α -defensins and D-dimer levels. *In vitro* studies show that IL-6 stimulated the release of α -defensins from human neutrophils but Tocilizumab, in contrast to colchicine, did not inhibit the stimulatory effect of IL-6. This raised the possibility that the unanticipated incomplete benefit of anti-IL6 therapy is due to an unexpected increase in IL-6, which triggers the release of α -defensins that in turn promote pro-thrombotic events reflected in an increase in D-dimer levels.

Together, these studies suggest that α -defensins are an important and tractable link between innate immunity and hemostasis. Furthermore, α -defensins released during inflammation increase the risk of thromboembolism. Interventions that inhibit neutrophil activation may provide a new approach to mitigate this risk in patients with COVID-19 and other inflammatory prothrombotic conditions.

The IL-6 as an early marker of severe COVID-19

Peter Sabaka, Mária Kachlíková

Background: Covid-19 is a disease associated with considerable morbidity and mortality in elderly population, however only a fraction of those infected will require hospitalisation. During the first days of disease, until hypoxemia develops, it is difficult to identify the patients that will progress to severe respiratory failure. Interleukin 6 (IL-6) plays a crucial role in Covid-19 pathogenesis and is a marker of disease severity. We explored the role of IL-6 as an early predictor for severe disease in elderly population.

Methods: We conducted a retrospective data analysis of cases of Covid-19, diagnosed during the outbreak in one long term care facility (LTCF) in Slovakia during the first wave of Covid-19 in April 2020. Within 24 h after the diagnosis of Covid-19 in LTCF residents, clinical and laboratory screening (IL-6, C-reactive protein, blood count, D-dimer) was performed. Patients were monitored daily and those that developed hypoxemia were transferred to the hospital. We analysed the association between the IL-6 and other potential markers obtained during initial assessment and development of hypoxemia during follow up. Consequently, we determined the cut-off of the IL-6 able to predict the development of hypoxemia requiring oxygen therapy.

Results: Fifty-three patients (11 men, 42 women) with diagnosed Covid-19 were included in the analysis. 19 (53%) patients developed hypoxemia during the follow up. Patients who developed hypoxemia had significantly higher concentrations of IL-6, C-reactive protein, procalcitonin, fibrinogen, total bilirubin, aspartate aminotransferase and alanine aminotransferase at initial screening. We identified IL-6 as the most robust predictor of hypoxemia. The concentration of IL-6 > 24 pg/mL predicted the development of hypoxemia with the 100% sensitivity and acceptable specificity.

Conclusions: The concentration of IL-6 > 24 pg/mL measured during the first stage of the disease is a good predictor of the development of hypoxemia requiring hospitalization in elderly population. Further studies are needed to evaluate the potential role of IL-6 as an effective early predictor for hospitalisation in Covid-19 in the general population and for other coronavirus variants.

Keywords: Covid-19; Hypoxemia; Interleukin 6; Long-term care facility.

Non-Markovian epidemic spreading models

Lasko Basnarkov

The mathematical models used for studying epidemic spreading are overwhelmingly based on ordinary differential equations. These are easier to solve numerically, enable nice interpretation of the results and frequently allow for simple theoretical relationships for the key epidemiological quantity - the basic reproduction number. Behind these models lies the Markovian assumption, which states that the probability of transition of one compartment to another, is independent of the past. This implies that the duration of residence in the compartments is exponentially distributed. However, observations show that the infectivity and onset of symptoms in individuals with COVID-19 have a form that is rather different from the exponential. Thus, non-Markovian models which are able to include general form of distributions are needed for such epidemics spreading modeling. Although being known since the earliest days of the mathematical epidemiology, they are not largely disregarded. We will discuss such models and some results related to the COVID-19 pandemic will be presented.

Determining frailty in people with intellectual disabilities during the COVID pandemic

Dederieke AM Maes-Festen, Josje D Schoufour, Thessa IM Hilgenkamp, Alyt Oppewal

Aim: During the COVID-19 pandemic, the Clinical Frailty Scale (CFS) is used in guidelines for triaging in crisis situations. The CFS identifies frail individuals mainly based on performance of daily tasks. Individuals with intellectual disabilities (ID) experience lifelong varying degrees of dependence. Using the CFS for triage could potentially unjustifiably classify them as too frail and exclude them from Intensive Care treatment. We compared the classification of individuals with ID into different frailty categories based on the CFS and the well-investigated ID-Frailty Index, to determine suitability for evaluation during the COVID-19 pandemic.

Method: Participants with ID ($n=982$, ≥ 50 years) from the HA-ID study, were classified into frailty categories according to the CFS and the ID-Frailty Index.

Results: Based on the CFS, 63.7% would be classified as moderately frail, while 92% was not moderately frail according to the ID-Frailty Index. Additionally, 20.3% would be classified as at least severely frail with CFS, while 74.9% was not severely frail according to the ID-Frailty Index. Overall, 730/982 (74.9%) would be incorrectly classified as too frail by the CFS.

Conclusion: The CFS is not suitable to evaluate frailty in individuals with ID, with potential dramatic consequences for triage and decision-making during the COVID-19 pandemic.

Pharmacological Effects of Selected Medicinal Plants, Vegetables and Vitamins Against COVID-19".

Richard A. Aló, Clement G. Yedjou, Jinwei Liu, Yohn Jairo Parra Bautista, Carlos Theran

Our investigations focus on a comprehensive approach to determine the impact that selected medicinal plants, vegetables, and fruits [VF] and social and structural health determinants have on infection and mortality rates as well as related ethnic and racial disparities in the COVID 19 pandemic health care. COVID-19. a new disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic that has claimed the death of over 5.2 million and infected over 257 million [as of

November 2021] human beings worldwide. Concerns have been raised about the various vaccines and their safety, efficacy, and immunity after vaccination. There is not sufficient scientific evidence to know whether vaccinated individuals can still carry the COVID 19 pathogens and pass them along to others. We must gain a better understanding of different ways to prevent the risk of infection, including vegetable and fruits (VF) that may give the human body a defense boost. Identifying novel antiviral agents for COVID-19 is of critical importance, and VF are an excellent source for drug discovery and therapeutic development. We test the hypothesis that a high intake of vegetables and/or fruits prevents COVID-19 incidence and reduces the mortality rate. We collected diet data of COVID-19 from Kaggle Datasets (<https://www.kaggle.com/mariaren/covid19-healthy-diet-dataset>) and used machine learning to examine the effects of different food types on COVID-19 incidences and deaths. Data generated from the study demonstrates that VF intake can help to combat the SARS-CoV-2. Taken together, medicinal plants, VF may be potential chemo- preventative agents for COVID-19 due to their antiviral properties and their ability to boost the human body immune system. Moreover, we take a comprehensive approach to determine how VF along with social and structural health determinants are related to racial and ethnic disparities in infection and mortality rates.

Transitioning ABA Services from in Clinic to Telehealth: Case Study of an Indian Organization, A Response to COVID-19 Lockdown

Smita Awasthi

Tele-health services have been applied in the treatment of a variety of problems across geographies (Tsami et al., 2019). The COVID-19 pandemic provided such an opportunity to scale up the impact of behavior analysis-based services for children with autism when in-clinic services stopped abruptly worldwide. This qualitative and quantitative case study details how Behavior Momentum India (BMI), an organisation with 10 clinics across India transitioned services from in clinic to telehealth. ABA-based interventions such as teaching language, communication, concept development, academics, making choices, reciprocal interaction and many other skills such as yoga were introduced via tele-health. A cohort of 92 students diagnosed with autism participated in this study under a team of 51 therapists, 9 behavior supervisors, and a doctoral-level Board Certified Behavior Analyst. Smartphones were used by 78% (82) students and 82% therapists for direct and parent-mediated sessions. With 10 students, behavior supervisors provided parent training. Results suggest all students continued to acquire targeted skills with curriculum modification, while 52% of the students acquired more skills in certain specific domains in telehealth compared to in clinic. A social validity survey provided high ratings on our organization's initiative. They reported confidence and improved understanding of behavior analysis based interventions and their efficacy in helping children with autism.

Resilience moderates the relationship between the psychological impact of COVID-19 and anxiety

Claudia Traunmüller

The fact that this pandemic had an adverse impact on mental health has been proven by numerous studies. Resilience is considered to constitute an important factor for protecting mental health, especially during times of crises, like the COVID-19 pandemic outbreak. Therefore, the aim of this study was to examine the protective effects of resilience on mental health with two different samples at different measurement times (first and second lockdown). Analysis were based on data collected from in sum 7,111 Austrian residents (4,113 at the first lockdown, 2,998 at the second lockdown), who participated in anonymous online surveys. Both surveys addressed sociodemographic data, the subjective response to COVID-19 (Impact of Event Scale; IES-R), mental health status (Depression Anxiety Stress Scale; DASS-21), and resilience (Resilience-Scale; RS-11). At both measurement times, structural equation modelling showed significant positive associations between the IES-R scores and depressive symptoms, stress and anxiety, respectively. Resilience was in both cases significantly negatively associated with depression, stress, and anxiety. Furthermore, resilience moderated the relation between the impact of COVID-19 and anxiety symptoms. However, in both samples there was no moderating effect of resilience on the relationship between IES-R and both depression and stress. The psychological impact of COVID-19 on anxiety symptoms seems to vary with the level of resilience. This study confirmed the importance of resilience in such a pandemic.

Balancing pressures for SENCos as managers, leaders and advocates in the emerging context of the Covid-19 pandemic

Elizabeth J. Done

Elizabeth J. Done highlights care of the professional self as, paradoxically, a priority under pandemic conditions that becomes ever more difficult to achieve. It is argued that the Covid-19 pandemic has both highlighted and exacerbated existing issues related to, for example, physician burnout and chronic fatigue due to onerous workloads. The social and political narratives through which the responses of medics and health professionals to the most recent health crisis have been variously presented over the course of the current pandemic will be considered, and the implications for medical education explored.

How does the collection and qualification of COVID convalescent plasma affect the outcome of clinical trials?

Dr. Dana Devine, PhD. Chief Scientist, Canadian Blood Services

Numerous clinical trials have been stopped early owing to inability to meet the pre-determined trial criteria. This has been due in part to the great variety in the ways that CCP is qualified. The gold standard is neutralizing antibody titres, but not all jurisdictions can comply with that. In Canada, we tested all plasmas in the CONCOR-1 trial with a neutralizing antibody assay performed by our National Microbiology Laboratory. Similar clinical trials have demonstrated the importance of having high titre neutralizing antibody levels in CCP and treating patients early in the disease course. CCP only seems to make a difference when patients have not yet developed their own antibodies. This presentation

will cover the collection and qualification of CCP for use in clinical trials. It is important that CCP is collected from either recently infected or recently vaccinated donors. Donors who have had a natural infection followed by vaccination make the most appropriate donors. Current clinical trials use high titres of antibodies tested in high through put assays followed by neutralizing antibody titres if the preliminary testing is at a high titre. CCP and their concomitant antibodies prepared in this manner are likely the optimal product to use in patients early in their course of infection or in patients who cannot mount their own immune response.

PROMIS scales for assessment of the impact of post-COVID syndrome

Ravindra Ganesh

While Coronavirus Disease 2019 (COVID-19) has been much publicized for the deaths and hospitalizations it has caused, with over 6 million deaths worldwide among half a billion recorded cases, there is a shadow pandemic of millions who are unable to return to normal life after infection. An estimated 10-30% of patients are estimated to have lingering symptoms 28 days after onset of COVID-19 infection which may be severe enough to preclude their return to work and daily functioning. Fatigue, cognitive dysfunction, palpitations, and orthostatic intolerance have been noted as the most common symptoms. Here we present data on the use of the PROMIS scales to assess severity of impairment in patients with post COVID syndrome, and preliminary data on how these scales track with clinical improvement. We propose that these scales be used as a clinical tool for assessment and monitoring of patients with post COVID syndrome.

Financial Strain and Loneliness among Young Adults during the COVID-19 Pandemic: The Role of Psychosocial Resources

Tehila Refaeli and Netta Achdut

The COVID-19 pandemic, which has been accompanied by an economic crisis and multiple restrictions on our lives, has sparked renewed interest in loneliness and its determinants. The strict policy implemented by the Israeli government at the beginning of the crisis dictated not only the intensity of events in the labor market and the severity of the economic slump, but also immediately transformed many people's social lives. People were suddenly cut off from their workplaces, from routine activities, and from social interactions in informal and formal networks. Young people are one of the groups most affected by the economic crisis. In addition, they are greatly affected by social distancing guidelines and restrictions, and 'stay at home' orders. Although critical for curbing the spread of the virus, these are likely to increase loneliness. Given that in ordinary times young adults are a high-risk group for loneliness they are of particular concern during the current pandemic.

Here we examined (1) the association between financial strain due to the outbreak of the virus, cognitive social capital, psychological resources and loneliness among Israeli young people (aged 20–35); (2) and whether these social and psychological resources were moderators in the financial strain–loneliness link.

A real-time survey based on snowball sampling was conducted during April 2020 (N = 426). Bivariate analysis and hierarchical linear models were employed to explore associations between financial strain, cognitive social capital, psychological resources, and loneliness. More than one-third of the study participants reported emerging financial strain in the wake of the pandemic, and about half reported feeling lonelier than before. Financial strain emerging during the pandemic was associated with greater loneliness. Cognitive social capital and optimism decreased loneliness. Sense of mastery moderated the financial strain–loneliness link.

The study stresses the large and sustained loneliness related to financial strain experienced during the pandemic. Policymakers must develop and extend mental health initiatives aimed at alleviating the psychological consequences of the pandemic and must also combat financial strain via unemployment compensation and social assistance programs. In line with the United Nations sustainable development goals, these tasks should be viewed as an integral part of promoting public health.

Sheltering the Homeless during COVID-19 in San Jose, California

Frances L. Edwards

COVID-19 posed a serious challenge for large, dense cities with a significant homeless population. The City of San Jose and County of Santa Clara in California worked to protect their large (9,800 person) homeless population from becoming a COVID spreader problem. At the start of the lockdown in March 2020, early shelters were established at community centers, while later families were moved to tiny homes owned by the city and to Project Homekey shelters where the county rented empty motel and hotel rooms to house people. There was a moratorium on clearing out homeless encampments, so the city provided sanitation and trash facilities to encampments to prevent disease propagation, but these programs did not change the problem of encampments' impact on the community from a social perspective.

Crisis Management of the COVID-19 pandemic: The Nordic Way and Swedish exceptionalism

Per Læg Reid

This talk will first present criteria for how to assess if the governments crisis management of the COVID-19 pandemic has been well performing or not by distinguishing between governance capacity (analytical, coordination, regulative and delivering) and governance legitimacy (input, throughput and output) and illustrating the use of these criteria on the cases of Norway and Sweden. Second, it will try to answer why two so similar countries have so different crisis management strategies for managing the same pandemic. Finally, it will discuss some lessons learned

Covid-19 Mitigation: What the Evidence Demonstrates is Effective

David J. Weber, MD, MPH, FSHEA, FIDSA, FRSM

SARS-CoV-2 was first reported from Wuhan China in late 2019. SARS-CoV-2 is causative agent of COVID-19, a disease that has resulted in a worldwide pandemic. Worldwide COVID-19 has resulted in over 500 million cases and greater than 6.2 million deaths. The key to preventing or mitigating SARS-CoV-2 is interrupting viral transmission, use of effective and safety vaccines, and uses of pre- and post-exposure medications. SARS-CoV-2 is transmitted by aerosols expelled by infected persons, generally over short distances (i.e., <2 meters). Transmission via hand contamination or via the contaminated environment is felt to play a minor role in transmission. However, transmission from asymptotically infected persons or pre-symptomatic persons has played a major role in transmission.

This presentation will review COVID-19 mitigation strategies with a focus on preventing transmission in healthcare facilities. Effective mitigation strategies will be subdivided into those specifically developed for COVID-19 prevention and strategies generally used to prevent transmission of communicable diseases. Strategies developed specially for COVID-19 mitigation include: universal masking by healthcare providers, patients and visitors; use of N95 respirators and eye protection for all aerosol generating procedures, and care of known and suspected COVID-19 patients; physical distancing when making is not possible (e.g., eating and drinking); personal protection monitors to aid in appropriate donning and doffing; and requiring COVID-19 vaccination as a condition of employment. General infection prevention strategies include hand hygiene, surface disinfection, and wellness checks with evaluation of ill providers by occupational health.

This presentation will also discuss recommended COVID-19 mitigation strategies that lack supportive evidence including improved or enhanced ventilation, Plexiglas barriers, and routine testing of patients prior to aerosol generating procedures.

This presentation will also focus on research published by the presenter on successful strategies for COVID-19 mitigation in K-12 schools, vaccine as a condition of employment in healthcare facilities, and effectiveness of masks for use in both healthcare facilities and communities.

Dynamics of Perceived Positive Changes and Indicators of Well-Being Within Different Phases of the COVID-19 Pandemic

Arndt Büsing

Background: The COVID-19 pandemic has significantly changed the life of our society in the past two years. Apart from lockdown related social restrictions, people nevertheless were also perceiving positive changes of attitudes and behaviors. We therefore analyzed the perception of loneliness / social isolation and wellbeing, and perceived changes in the context of different phases of the pandemic.

Methodology: Cohort study with standardized questionnaires in the different phases of the pandemic (n=4,637; 65% women, 34% men; mean age 46±14 years): 32% June 2020, 18% July-September 2020, 14% October 2020 to January 2021, 5% February 2021, 11% March-May 2021, 2% June-July 2021 and 17% August-September 2021.

Results: Immediately after the 1st lockdown, 14% felt lonely / socially isolated, with a rise to 46% during the 2nd wave of infection, 57% in the 3rd wave, and 34% in the 4th wave. Both

loneliness and low wellbeing (WHO-5) were significantly higher in women, younger people, and singles.

Perceived changes (PCQ) refer to Nature/Silence/Contemplation, Relationships, Reflections on life, and Digital media usage, but not to Spirituality. These changes were significantly stronger among older people and women, and in those with high scores on Awe/Gratitude (GrAw-7). Feelings of loneliness and 'depressed mood' states (WHO-5) followed the dynamics of the infection process and lockdowns, with a breaking point in winter 2020/2021. In line with these dynamics, perceived changes declined too, while Reflections on life slightly raised.

Those who were able to perceive "conscious times of loneliness" and enjoying "times of reflection" were able to positively perceived changes and to reflect on life, while social isolation was negatively related to perceived changes and strongly associated with low wellbeing. Both qualities had opposite associations with well-being and life satisfaction (BMLSS-10).

Conclusions: The perceived changes in the first phases of the pandemic could be seen in the context of 'posttraumatic growth' (as a process of reappraisal coping), while in the later phases the declines could indicate 'defeat stress'. There are different ways to cope with pandemic related loneliness: 1) self-determined times of reflection or 2) endured times of loneliness and social isolation; their consequences for wellbeing are different.

Evaluating associations between area-level Twitter-expressed negative racial sentiment, hate crimes, and residents' racial prejudice in the United States

Thu Thi Xuan Nguyen

Twitter data can be used to measure place-level racial attitudes and racial bias. Using both qualitative analyses and machine learning approaches, big data can be leveraged to understand the impact of the social context on health and health disparities. During the presentation, Dr. Nguyen will also illustrate how measures of racial sentiment and hate speech can be used to track and detect changes in area-level racial attitudes following recent racialized events. Dr. Nguyen will compare area-level measure of racial sentiment derived from Twitter data is associated with state-level hate crimes and existing measures of racial prejudice at the individual-level.

Impact of COVID-19 on persons with neglected tropical diseases (NTDs): Observations from integrated WASH and NTDs projects in India

Shyamala Anand

The COVID-19 pandemic in India has impacted all segments of the population but it has been particularly detrimental to the most vulnerable and marginalized among whom are people affected by the potentially disabling and poverty related neglected tropical diseases (NTDs). Government imposed lockdowns to limit COVID-19 transmission, the health system's focus on COVID-19, and peoples' own fears during the waves of the pandemic

curtailed field-based activities of national NTD programmes and non-governmental organizations among these same populations. The presentation shares field level experiences and lessons learned from our integrated WASH and NTD projects in different states in India that may help inform better service provider responses in the event of similar unforeseen long-term disruptions in the future.

Can the cycle threshold (Ct) value of RT-PCR test for SARS CoV2 predict infectivity among close contacts?

Jesha Mundodan

Background-COVID-19 global pandemic is an unprecedented health emergency. Rapid identification and isolation of infected individuals is crucial. Qatar's National Health Strategic Command Group adopted a cut off 30 for Ct value of RT-PCR result of a positive case to decide on duration of isolation and quarantine period for their close contacts. *Aim*-to test if Ct value cut off 30 reflects on the infectivity potential among close contacts.

Methodology-all positive cases reported during July'2020 whose contacts had been traced and swabbed were extracted from database after removing personal identifiers. Close-contact was defined as anybody who has been within 2 meters distance of a confirmed positive case for 15 minutes or more, without any personal protection equipment. Descriptive analysis was done and test of significance of difference in positivity among the contacts of those with $ct < 30$ and ≥ 30 was done.

Results-2308 COVID-19 positive cases were followed up. More than three-quarters had a Ct value < 30 , with a mean Ct value of $24.05(+6.48)$. On an average 6 contacts were swabbed per case. More than half the positive cases followed up had at least one secondary case, with median positivity rate 12.5%. A significant relation was noted between Ct value cut-off 30 and secondary transmission (1.5 times more risk among those with Ct value < 30). A significant difference was noted in median positivity rate between close contacts of positive cases with Ct value ≥ 30 or < 30 .

Conclusion-Further studies combining PCR assays, culture studies and contact tracing are needed to define which factors can be used to reliably predict the infectious status of patients with COVID-19.

On Predicting Growth Factor of Daily New Cases Data of COVID-19 Epidemic in Spain Using ARIMA-ANN Hybrid Model

Samir K. Safi

The Auto Regressive Integrated Moving Average (ARIMA) model cannot capture the nonlinear patterns exhibited by the 2019 coronavirus (COVID-19) in terms of daily growth factor of daily new cases data in Spain. As a result, Artificial Neural Networks (ANNs) model is commonly used to resolve problems with nonlinear estimation. Different models that include ARIMA, ANNs, seasonal decomposition of time series, and a combination of these three models (hybrid model) were proposed to forecast the Growth Factor of COVID-19. This study provides forecasting insights and criteria to use for similar time series data to

predict growth factor of COVID-19 and selects the most suitable forecasting model for forecasting purpose. The best forecasting model selected was compared using the forecasting assessment criterion known as root mean squared error (RMSE) and mean absolute error (MAE). The results of this study add to the growing body of literature that seeks to accurately forecast the spread of COVID-19 by combining multiple models used by other researchers. The results are useful because it provides an accurate forecast for growth factor for COVID-19 epidemic. The study underscores the importance of appropriate forecasts for policy makers to enhance better decision making. All Governments and institutions involved in public health can benefit from these results for forecasting purposes using more reliable and accurate forecast model for COVID-2019 epidemic. The additional value of results is encouraging as the world struggles to restrain from the spread of COVID-19.

Keywords: COVID-19, Forecasting, Hybrid Model, ANN, ARIMA.

Longitudinal Trajectories of Psychopathology and Resilience Following COVID-19 Lockdowns in China

Pei Sun, Shuquan Chen, Kaiwen Bi, Xuerui Han, Zeyun Yang, Teng Tu, Ning Ni, Ziyi He, Yanling Yue, Wenhui Xue, George Bonanno

During the COVID-19 pandemic, the Chinese government has enforced strict quarantine and lockdown measures. To understand protective and risk factors that predict longitudinal psychopathology and resilience following strict lockdowns, we used unsupervised machine learning to identify half-year longitudinal trajectories of three mental health outcomes (depression, anxiety, and PTSD) among a sample of Hubei residents, assessed a broad range of person- and context-level predictors, and applied LASSO logistic regression, a supervised machine learning approach, to select best predictors for trajectory memberships of resilience and chronic psychopathology. The results showed that the most critical person-level predictors were worry, optimism, fear of COVID, and coping flexibility, whereas important context-level predictors included features of stressful life events, community satisfaction, and family support. These findings have implications for clinical risk identifications and interventions in the context of potential trauma.

Targeting SARS-CoV-2-Platelet Interactions in COVID-19 and Vaccine-Related Thrombosis **Dermot Cox BSc, PhD, Royal College of Surgeons in Ireland**

While primarily recognised for their role in haemostasis, platelets also play a key role in the innate immune response. Sepsis is characterised by platelet activation and consumption leading to severe thrombocytopenia. Furthermore, the extent of the thrombocytopenia predicts outcome in sepsis. In bacterial sepsis, bacteria directly bind to and activate platelets by a well-characterised process. This involves multiple platelet receptors including GPIIb/IIIa and GPIb. Critical to this process is engagement of the IgG receptor Fc γ R1a on the platelet surface.

There is also evidence for a role for platelets in viral sepsis. Thrombocytopenia due to platelet activation is also a feature of viral sepsis although the pathways involved are less

well characterised. While Fc α R11a plays a role with some viruses, it appears that other receptors are involved as well. These include CLEC-2, DC-SIGN and Toll-like receptors (TLR).

Platelets activation is not just associated with sepsis, but also occurs with vaccination. As the IgG receptor on platelets, Fc α R11a mediates the response of platelets to immune complexes. These immune complexes include virus-antibody complexes and can also be formed with vaccines. Thus, thrombocytopenia is sometimes associated with vaccination, especially with Adenovirus-based vaccines.

COVID-19 is associated with a profound thrombocytopenia and the magnitude of the thrombocytopenia predicts outcome. This is likely mediated by a direct interaction between SARS-CoV-2 and platelets. Multiple platelet receptors, including ACE-2, DC-SIGN and Fc α R11a, have been implicated in the interaction with the virus. These receptors likely mediate the thrombocytopenia associated with both COVID-19 and SARS-CoV-2 vaccine associated thrombosis.

The critical role played by the virus-platelet interaction in COVID-19 makes it a suitable target for pharmacological intervention. This can include anti-platelet agents such as aspirin or ideally specific agents that target the virus-platelet interaction.

Automatic Identification of Covid-19 regions on CT-images using Deep Learning

Rajasekaran Subramanian

Covid-19 is a contagious respiratory illness caused by a new corona virus called SARS-COV-2. This new coronavirus is an RNA virus which is like flu and measles are prone to changes and mutations compared to DNA viruses such as herpes, small pox and human papillomavirus (HPV). Since December 2019, Corona Virus has spread throughout the world and around 500 million people were infected and 6.2 million people died. The diagnostic of Covid-19 can be done by broadly two categories either by laboratory base approaches such as nucleic acid testing, antigens test and serology (Antibody) tests or by medical imaging tools such as X-ray and High-Resolution Computed Tomography (HRCT) Chest Scans. Early Identification of Covid-19 helps to isolate people from the infected and to reduce the spread of the disease. Due to the shortage of RT-PCR test kits, CT-Scan can be used as an alternative for screening and diagnosing of covid-19. Covid-19 affects many organs like heart, blood vessels and lungs. CT-scan investigation helps to identify pre dominant patterns of lung abnormalities like unilateral, multifocal and peripherally Ground Glass Opacities (GGO). At the peak time of Covid-19, due to the high bandwidth of CT images, the radiologists are unable read the number of CT images timely and also due to the newly developed virus they require additional training for diagnosis. Otherwise, it affects the accuracy of diagnosis decision. The SARS-CoV-2 pandemic has overwhelmed health care systems. By integrating imaging data, radiology reports and clinical information, AI will be a powerful tool for rapidly cataloguing information to assist radiologists and clinicians to best care for patients. We are proposing an automated Computer Aided Diagnostic System (CAD), which has sequence of three tasks 1. Images Binary Classification of Covid-19 vs non-Covid using VGG16 and Resnet-50 deep learning model 2. CT Lung Segmentation from the classified Covid-19 images using Deep learning model U-Net 3. Covid-19 region segmentation in the segmented CT Lungs using Deep learning model U-net. Our AI diagnostics system for Covid-19 images, facilitate diagnostics for Lungs Fibrosis, Multi-lobe severity and GGO which are the predominant imaging biomarkers for NSCLC

(Non-Small Cell Lung Cancer) and Tuberculosis (TB), Interstitial Lung Disease (% of Fibrosis - Progression / Regression). It is to be noted that Coronavirus outbreaks have been evolving as SARS in 2003, MERS in 2013, Covid-19 in 2020 and likely continue to evolve and therefore, diagnosis, treatment experience from these pandemics may be helpful in containment of probable future corona virus pandemic and the global load of fibrotic pulmonary changes following future SARS-CoV-2 infections.

A new Fractal Model in Epidemiology (FraME) obtains better fitting time-trends of the pandemic due to SARS-CoV-2. A fractal study of the virus (and of its interactions with host) can also improve diagnosis and cure.

Calogero Rinzivillo, Francesco Casciaro, Renato Bernardini, Antonio Cascio, Ferda Kalegasioglu, Ines Paola Monte, Marcello Migliore, Corrado Spatola, Maria Cristina Scuderi, Angela Morello, Giuseppe Liberti, Massimo Caruso, Elio Conte

Not usual linear nor exponential methods but only our new fractal approach allowed us to obtain the best mid-long term trends for CoViD-19 pandemic in 2020-21. Our model (used for Italy and regions Apulia and Sicily) is named "FraME": Fractal Model in Epidemiology, but also FRActal MEDicine, viewed as a part of most recent precision & targeting medicine. Our fractal formula has allowed to our international translational workteam (from Italy, China, Turkey and Swiss) to discover a tendentially fractal nature of spreading curve and to obtain an high precision in forecasts of the pandemic spread: i.e.,

$$n(t) = kt^{\gamma} \exp\left(\frac{t}{t_0}\right) + c(n)$$
 where n is number of predicted daily cases for months and γ is the "fractal exponent" (3.841) of the fractional k.

Consequently, we studied if the virus itself had a specific fractal form and we published the complex biomathematical method to obtain the Hurst generalized index of the surface as a fractional exponent, the degree and the strength of fractality and other parameters suggesting a multifractal structure with high roughness. A study of fractal shape (and then function) of surface and molecular parts of β -2B-Sarbeco-SARS-CoV-2 (e.g., S, M, E and N proteins) and of its interactions with human host (especially with fractally-structured organs like interstitial lung and with cell receptors) can improve epidemiology, diagnosis and (biochemically; perhaps biophysically also) cures, both to fight bio-aggressiveness of viruses/oncocytes and to enhance defenses of human host. Many times "form fits function" in biology: that particular rough and well-ordered Hyperfunctional Fractal Frame (HFF) of the surface of the virus (and of biosimilar human parasites like other viruses but also oncocytes, whose clonal variants can increase the fractal frames and pathogenicity) can play several roles (biochemically and probably biophysically) such as both evasion / protection from the human immune system and a faster/stronger cellular grab and tissue invasion. It can also cause severe multi-organ syndrome and a so strong and fast immune storm thus due not only to the specific late activation of T-B cells but also to the early involvement of the fast innate immune system (similar to allergy/autoimmunity), resulting in a diffuse "FlogoEdemaFibroTrombo-sys" (PEFT). Not casually, recent antiviral drugs in use or in trial are proteases, kinase-blockers, anti-S-protein antibodies, i.e. targeting molecules forming viral fractal frame and vaccines boost immune system against these viral proteins. Such an approach against target-molecules of frame of oncocyte + immune therapy appears so promising in the recent oncotherapy in use or in trial. And inflamed infected or cancer

tissue emits more ultraweak biophotons than normal one, perhaps also due to this special bioframe.

The critical role of complete blood count in the management of patients with COVID-19

Ahnach Maryame

Background: Since December 2019, the world has declared a global health crisis caused by the coronavirus disease (COVID-19) pandemic. The coronavirus can cause various clinical manifestations, but appears to have a direct impact on the hematopoietic system and blood cells. The hematologic analysis of quantitative and qualitative abnormalities plays a key role in the early diagnosis, severity prediction and follow-up of COVID-19 infection. We aimed to assess hematological change in COVID-19 patients admitted to the Cheikh Khalifa International Hospital in Casablanca and its association with the severity of the disease.

Methods: In this single-center, retrospective, observational study, we included all consecutive patients who were admitted in Cheikh Khalifa International University Hospital, Casablanca, Morocco, between February to April 2020, with a confirmed diagnosis of COVID-19 infection using SARS-CoV-2 viral nucleic acid via RT-PCR. All clinical and laboratory data of patients were collected and analyzed. The complete blood count was routinely measured on admission with blood smears control. The classification of the disease severity was in accordance with the clinical classification of the WHO interim guidance, and the management of patients were adapted to the national management guideline. Patients were separated into two groups: non-severe patients were those with mild or moderate forms of COVID-19, and severe patients were those admitted to the intensive care unit (ICU) who had one of the following signs-respiratory rate > 30 breaths/min; oxygen saturation < 93% on room air; acute respiratory distress syndrome (ARDS); or required mechanical ventilation. We used univariable and multivariable logistic regression to explore predictive hematologic factors of severity.

Results: We reported 134 patients with confirmed SARS-CoV-2 infection. The median age was 53 years (interquartile range [IQR], 36-64), and 73 (54.5%) were men. Eighty-nine non-severe patients (66.4%) were admitted to single bedrooms, and 45 (33.6%) were placed in the ICU. Of the 134 patients, 61 (45.5%) had comorbidities, such as hypertension (n = 36; 26.9%), diabetes (n = 19; 14.2%), and coronary heart disease (n = 16; 11.9%). The most frequent symptoms were fever (n = 61; 45.5%), dry cough (n = 59; 44%), and dyspnea (n = 39; 29%). The hematological analysis found a normal median rate of hemoglobin (14g/dl) and platelet (266. 103/mm³). The most common change occurs in leukocyte lineage with increase of neutrophils count, eosinopenia (0.02 10³/mm³) and significant lymphopenia less than 800/mm³ in the severe form (42,5%). The blood smears testing revealed morphological abnormalities in the white blood cells and platelet lines. In univariable and multivariable analysis, older men, comorbidities, higher neutrophile count, lymphopenia lower than 800/mm³, eosinopenia and neutrophils/lymphocytes ratio were significantly associated with severe forms of COVID-19.

Conclusion

The blood cells perturbations are seen as a prognosis factors, careful analysis and interpretation of blood cell count, allows not only to identify hematologic change, but above a clinician to predict severity. Compared to specific inflammatory biomarker tests, the blood count remains a less expensive alternative, especially in countries with limited resources.

Positive behavioral strategies in COVID era.
Amar S Kanekar

COVID 19 pandemic has had devastating effects across the globe. This pandemic and its after effects on humanity and its social structure will be a landmark event in public health history. The purpose of this key note presentation is to take a view of this pandemic as a life-changing stressful event of public health importance and discuss stress reduction and positive behavioral strategies for coping with its effects at the individual and society level. The speaker will particularly distill various evidence-based best practices in coping such as stress reduction theories, positive behavioral strategies (3:1 ratio), along with concepts of sense of purpose and meaning to provide a comprehensive array of tools for clinicians and practitioners work with themselves as well as their colleagues and patients as we forge ahead with this pandemic and prepare ourselves for the unexpected. Additionally, the speaker will also be discussing techniques for building resilience in face of challenges emerging ahead in times to come.

The psychological response of the COVID-19 pandemic in psychiatric patients
Nina Dalkner, Jolana Wagner-Skacel, Frederike Fellendorf, Eva Fleischmann, Susanne Bengesser, Melanie Lenger, Alexander Maget, Elena Schönthaler, Adelina Tmava-Berisha, Martina Platzer, Robert Queissner, Armin Birner, Eva Reininghaus

Background: The coronavirus disease (COVID-19) pandemic is a global health crisis and the socioeconomic restrictions, including lockdown, social distancing, and self-isolation have had a massive impact on people's mental health. A special research focus is the psychological impact of the COVID-19 pandemic and lockdowns on patients with pre-existing psychiatric disorders as a particularly vulnerable group.

Methods: An online survey was conducted in Austria at several points of measurement (T1 April 2020 during the first lockdown vs. T2 May 2020 at post-lockdown, T3 November 2021, T4 July 2021) and individuals with affective disorders vs. healthy controls were surveyed with a self-created questionnaires assessing emotional distress due to social distancing and COVID-19 fears. In addition, a Believing Questionnaire and several standardized questionnaires, i.e., the Brief Symptom Inventory-18 have been included.

Results: The results demonstrated high scores in psychological symptoms (global symptom load, depression, anxiety) in psychiatric patients at T1. Somatization and global symptom load decreased from T1 to T2 in patients, whereas no changes were found in healthy controls. On a linear regression model, which accounted for 24% of the variance ($F(2, 19) = 4.07, p = .036$), COVID-19 fears during lockdown predicted global symptom load, somatization, and anxiety at post-lockdown, only in patients. In addition, individuals with affective disorder showed significantly more negative propositions and negative emotions while believing about the pandemic, and there was evidence of an adverse impact of the pandemic on lifestyle factors in psychiatric patients.

Conclusions: Results indicated higher vulnerability in individuals with pre-existing affective disorder regarding the COVID-19 situation. However, there might be more resilience and adaptation to the pandemic than initially expected. There was a connection between the lockdown measures and psychological symptoms observed in

patients with affective disorder, and different believing processes regarding the pandemic were found that can be considered in therapies.

Fighting the COVID-19 pandemic by providing easy-to-use RNA Extraction Kits and SARS-CoV-2 Detection Kits based on the LAMP method

Saori Nagi

The LAMP (Loop-mediated isothermal AMPlification) method was solely developed by Eiken Chemical Co., Ltd. It has several characteristics as follows:

1. High specificity because of the use of four primers recognizing six distinct regions on the target.
2. Rapid reaction time (fifteen to sixty min.)
3. Inexpensive machine by isothermal reaction
4. Robust to specimen inhibition

The LAMP method has been put it to practical use as a basis of IVD (in vitro diagnostics). The PURE-TB LAMP system, which is for Mycobacterium Tuberculosis detection, is one example of LAMP-based infectious diseases detection system. It contains DNA extraction step using the PURE (Procedure for Ultra Rapid Extraction) method and DNA amplification step based on the LAMP method. The WHO recommends that it may be used as a replacement for microscopy for the diagnosis of pulmonary TB in adults. We also provide several kits for infectious diseases, like Malaria, NTDs, Influenza, and also for a viral RNA extraction kit.

A genome sequence of SARS-CoV-2 was reported in January 2020, two months after the first case of COVID-19 infection was identified. By referring to that, our SARS-CoV-2 detection kit was launched for IVD in April 2020. This reagent was estimated to be used in one-third of the COVID-19 test in Japan between April to July 2020, which is calculated from the total number of PCR tests on the homepage of Ministry of Health, Labour and Welfare of Japan. This data suggests that the kit played an essential role in the beginning of the pandemic in Japan.

In general, a molecular test can be developed rapidly compared with immunological test. It's because immunological tests use antibody which is time consuming for development. Besides that, our rapid development was accomplished by changing primers and positive control of Influenza detection kit for SARS-CoV-2 without changing LAMP reaction mixture. By combining them with the viral RNA extraction kit, our products make it possible to extract RNA, inactivate SARS-CoV-2 and get diagnostic results less than one hour from a sample. These unique characteristics enabled clinical staff who didn't have prior familiarity or experience with molecular tests to perform them at small to medium clinics.

In this presentation, I'll demonstrate about the basis of the LAMP method, a technology to achieve simple extraction first, then results of clinical performance of the detection kit in Japan.

DERMATOLOGY

Developing the UK's First and only Class IIa Certified AI Dermatology Device

Helen Marsden, Skin Analytics Ltd.

Skin Analytics has developed an Artificial Intelligence (AI)-based medical device, called Deep Ensemble for the Recognition of Malignancy (DERM) which is intended for use in the screening, triage and assessment of skin lesions with a suspicion of skin cancer to help

reduce unnecessary referrals and associated costs. DERM analyses a dermoscopic image of a skin lesion and returns a suspected diagnosis. DERM has been trained to identify 11 skin conditions, including melanoma, Squamous Cell Carcinoma (SCC) and Basal Cell Carcinoma (BCC) with a high degree of sensitivity.

Demonstrating the reliability, usability and ongoing validity of an AI medical device requires multiple strands of research. Skin Analytics has conducted bench research, human factor studies, and prospective clinical validation studies in order to achieve regulatory clearance for DERM. Post market health economics studies, further validation studies, and evidence from real-world deployments have further strengthened the evidence base on which DERM is used.

To date, over 21,000 lesions have been assessed through DERM deployments in the UK, where a sensitivity of over 95% of each malignancy type has been maintained across different care settings.

Data from studies and real-world deployments will be presented, alongside learnings on the challenges of demonstrating the clinical utility of a new technology for regulators and clinical users alike.

The Spectrum of Hiv-Associated Infective and Inflammatory Dermatoses in Pigmented Skin **Prof M.H Motswaledi**

Skin diseases are very common in the setting of HIV.

The introduction of antiretrovirals has changed the epidemiology, morbidity and mortality of HIV.

Antiretrovirals have also altered the incidence of infective and inflammatory diseases affecting the skin.

However, cutaneous disorders due to HIV still remain a major problem in HIV-infected patients.

In patients with pigmented skin HIV associated dermatoses result in special challenges like dyspigmentation, atypical presentation and resistance to treatment.

Functional Microstructured Adhesives - On the Path to Clinical Applications

Gabriela Moreira Lana

Self-adhesive micropillar structures, initially developed for robotics, were adapted for adhesion to biological surfaces. Topped by a Soft Skin Adhesive (SSA) terminal layer, the film-terminated microstructure exhibits effective adhesion to surfaces of different roughness, opening a range of application possibilities in biomedicine. The microstructured adhesive poses an alternative for the current treatment of tympanic membrane perforations, a frequent medical condition that dramatically impacts a patients' life. The microstructure was evaluated regarding adhesion against explanted mouse eardrums. The subsurface microstructure was found to also dampen any impact, protecting the sensitive membrane during surgical application. Long-term animal tests confirmed accelerated, high-quality healing of the injured eardrums with reduced scar formation. Using auditory brainstem responses (ABRs) and distortion product otoacoustic emissions (DPOAE), partial recovery of hearing performance immediately after patch application was confirmed. Additionally, the

glue-free biomedical adhesive has great potential for applications involving skin contact in health monitoring and wearable computer interfaces. Unstructured silicone films with an SSA layer provide interesting adhesion to sub-micron rough surfaces, but as the roughness increases, the microstructured samples present advantageous adhesion due to better compliance through the elastic strain energy of the subsurface micropillars. In addition, the spacing in the microstructure allow for the integration of conductive layers using silver nanowires or printed silver circuits, opening a plethora of applications for sensors. Overall, the film-terminated design is a promising novel concept for adhesives in biomedicine, from wound dressings to wearable electronics.

Mechanism action of Thalidomide in Cutaneous Lupus

Cristina Solé Marcé

Background: Cutaneous Lupus Erythematosus (CLE) is common, largely heterogeneous and characterized by a chronic relapsing course. As many as 70 to 80% of patients with SLE will develop skin lesions at some point during the course of their disease, with a significant proportion being disfiguring and debilitating [1]. Conventional therapy consists of topical steroids and antimalarial agents but 40% of patients will be refractory to this regimen [2]. Thalidomide has been the only one that has shown an effectiveness of 90% [3], however, its mechanism of action in the disease is not known at all. In addition, its use is limited due mainly to its side effects such as teratogenicity and the development of peripheral polyneuropathy.

Objective: Identification of the thalidomide mechanism in cutaneous lupus erythematosus.

Methodology: Skin biopsies before and during treatment has been performed on a cohort of CLE patients treated (N=20) and not treated with thalidomide (N=5). We conducted an RNA-sequencing study using CLE skin biopsies performing a Therapeutic Performance Mapping System (TMPS) analysis to propose a plausible mechanism of thalidomide action. Flow cytometry in blood from patients before and after treatment was also analysed. *In vitro* experiments using isolated lupus cutaneous lymphocyte and primary keratinocytes has been performed to see the specific biological effect of thalidomide.

Results: Immune cell subset analysis in thalidomide's CLE responder patients showed a reduction of circulating and tissue cytotoxic T-cells with an increase of iNKT cells and a shift towards a Th2 response. Integrating RNA-seq data, public databases, and literature, TMPS analysis generated mathematical models which predicted that thalidomide acts via two CRBN-CRL4A- (CRL4CRBN) dependent pathways: IRF4/NF- κ B and AMPK1/mTOR. Skin biopsies showed a significant reduction of IRF4 and mTOR in post-treatment samples by immunofluorescence. *In vitro* experiments confirmed the effect of thalidomide downregulating IRF4 in PBMCs and mTOR in keratinocytes, which converged in an NF- κ B reduction that led to a resolution of the inflammatory lesion.

Conclusion: Taken together, we show that mechanism of thalidomide in CLE is dual. It might inhibited IRF4/NF- κ B in lymphocyte but, in the same time, might inhibited AMPK1/mTOR pathway in keratinocytes. These results emphasize the anti-inflammatory role of thalidomide in CLE treatment, providing novel molecular targets for the development of new therapies that could avoid thalidomide's side effects while maintaining its efficacy.

Exposure to Isocyanates Predicts Atopic Dermatitis Prevalence and Disrupts Therapeutic Pathways in Commensal Bacteria

Ian A Myles, Jordan Zeldin, Prem Prashant Chaudhary, Jacquelyn Spathies, Manoj Yadav, Brandon N D'Souza, Mohammadali E Alishahedani, Portia Gough, Jobel Matriz, Andrew J Ghio, Yue Li, Ashleigh A Sun, Larry F Eichenfeild, Eric L Simpson

Atopic dermatitis (AD) is a chronic inflammatory skin condition that has been increasing in industrial nations at a pace unexplainable by genetic predispositions. Mounting evidence indicates that the dysbiosis associated with AD is a targetable contributor to pathology. Given that humans and their microbiota share exposures, we propose that metabolic differences between health- and AD-associated microbes may represent adaptations to the polluted environment that have come at the expense of symbiotic pathways. This work expands on our prior report identifying health associated isolates of *Roseomonas mucosa* as beneficial organisms to show that they that fix nitrogen in the production of protective glycerolipids and their ceramide byproducts. To assess exposures that may disrupt these pathways, we screened environmental pollutant releases versus the rate of clinical visits for AD by US zip codes. Diisocyanates were the strongest predictor of AD rates and were found to disrupt production of beneficial lipids in, and therapeutic modeling for, commensal isolates of *R. mucosa* and coagulase-negative *Staphylococcus*. Exposure of health associated isolates of *R. mucosa* to the most commonly encountered isocyanates, toluene diisocyanate and hydrogen isocyanate, reproduced the metabolic dysfunction seen in AD-associated organisms. Finally, in a placebo-controlled clinical trial of topical *R. mucosa*, significant and sustained improvement in disease scores were seen; post-hoc analysis revealed that the results were influenced by the reported diisocyanate pollution at the participating study sites. Overall, these findings endorse future prospective studies to evaluate the role of isocyanate and diisocyanates in promoting the dysbiosis associated with AD.

Skin Signs and Skin Disorders Associated with Systemic Cancer

W. Clark Lambert, MD, PhD

Skin signs and skin disorders are associated with systemic cancer in several ways: 1. There a number of cutaneous inflammatory disorders that sometimes, often, or even characteristically are associated with internal cancer. Examples include Erythema Gyrate Repens, Erythema Annulare Centrifugum, Acquired Perforating Dermatitis, and Kyrle Disease. 2. Skin cancer may be directly due to internal cancer, including Carcinoma Cutis, or to an internal inflammatory disorder, such as inflammatory bowel disease that may give rise to Basal Cell or Squamous Cell Carcinoma of the perineum. 3. Genetic diseases, such as the Muir-Torre syndrome, the Birt-Hogg Dubé syndrome, Xeroderma Pigmentosum, and Gorlin syndrome (the basal cell nevus syndrome) may be associated with skin and/or internal cancer. 4. Therapeutic intervention may predispose to cancer, such as skin cancers in organ transplantation recipients and melanomas in sildenafil (Viagra®) users. Examples will be presented with significant new information regarding etiopathogenesis.

Zinc (II) complexes with amino acids as new active ingredients of anti-acne preparations

Urszula Kalinowska-Lis

Since zinc compounds have a number of beneficial properties for the skin, including accelerating wound healing, antimicrobial, sebostatic and demulcent activities, we decided to test a new group of zinc compounds as potential candidates for anti-acne applications. Our research focuses on zinc (II) complexes of the general formula $[Zn(AA)_2]$, where AA represents an amino acid (L-Glu, Gly, L-His, L-Pro, L-Met, and L-Trp). Firstly, we designed and performed complexes' syntheses; we confirmed compounds' chemical structure and composition by 1H NMR spectroscopy, elemental analysis, and by single-crystal X-ray diffraction. In the next stage of the research the antibacterial properties of the zinc complexes were determined against the anaerobic strain of *Cutibacterium acnes*, three Gram-positive strains, viz. *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, and *S. pyogenes* ATCC 19615, and two Gram-negative bacteria, viz. *E. coli* ATCC 25992 and *P. aeruginosa* ATCC 2785. Then, the cytotoxicity of the zinc complexes was evaluated against human skin fibroblasts (1BR.3.N cell line) and human epidermal keratinocyte cell lines. Based on the satisfactory results of these studies, two compounds, i.e., zinc complexes of glycine and histidine, were selected to create original gel formulations with a potential anti-acne effect. Physicochemical stability, microbiological purity (referring to PN-EN ISO standards) and efficacy of the preservative system (according to Ph. Eur. 10 methodology) for the prepared formulations were evaluated. Skin tolerance was determined in a group of 25 healthy volunteers by the patch test.

To sum up, the preparations containing zinc(II) complexes with glycine and histidine as active substances can be topically used in the treatment of acne skin due to their high antibacterial activity against *C. acnes* and low cytotoxicity for the skin cells. In the future, we plan to confirm our assumptions by testing the zinc-amino acids preparations on a group of volunteers with acne symptoms.

Elimination Measures and Skin Care as Important Stages in Prevention of Exacerbations of Atopic Dermatitis in Children

Pavel Gushchin

According to recent data, the pathogenetically significant condition for the onset of atopic dermatitis is increasing epidermal permeability barrier and, therefore, a primary step in the treatment and prevention of atopic dermatitis should be control over the skin condition. Effective use of modern methods of prevention of exacerbations helps to reduce the frequency of relapses, lengthen the periods of remissions and, in general, improve the quality of life of sick children.

Characterization of circular RNA transcriptomes in psoriasis and atopic dermatitis reveals disease-specific expression profiles

Lasse Sommer Kristensen

Psoriasis and atopic dermatitis are two common chronic inflammatory skin diseases accompanied by heterogeneous clinical and histological features, including a characteristic keratinocyte hyperproliferation and dermal immunogenic profiles. Circular RNA (circRNA) constitutes a novel major class of non-coding RNAs that have been implicated in many human diseases, although their potential involvement in inflammatory skin diseases remains elusive. Interestingly, we have found a profound downregulation of most of these molecules

in psoriasis and to a lesser extent in atopic dermatitis using RNA sequencing of lesional and non-lesional skin biopsies. These changes could not be explained by alterations in genes known to be involved in circRNA biogenesis nor by changes in the cognate linear host genes of the circRNAs. While we believe that a subset of circRNAs may be directly involved in psoriasis potentially through functions in epidermal stem cell differentiation or through binding of psoriasis-related microRNAs, our in vitro data also point towards a direct link to proliferation rates of the keratinocytes. In particular, we believe that many circRNAs are subject to a dilution effect where they do not reach steady-state levels in fast proliferating cells due to their slow biogenesis but may accumulate in slowly differentiating cells due to their exceptionally high stability. Finally, we find that many circRNAs correlate strongly with the psoriasis area and severity index (PASI) score, that circRNA expression changes in psoriatic skin predate clinical and histological improvements upon anti-IL17A treatment and that specific circRNAs potentially could be used to distinguish atopic dermatitis from psoriasis.

Outcomes of Vismodegib for Periocular Locally Advanced Basal Cell Carcinoma from an Open-label Trial

Meydan Ben Ishai

Importance: The outcomes of vismodegib treatment in a relatively large cohort of study participants with periocular locally advanced basal cell carcinoma (POLA-BCC) may guide physicians when considering this treatment.

Objective: To report the outcomes of vismodegib treatment in patients with POLA-BCC in the Safety Events in Vismodegib (STEVIE) study.

Design, setting, and participants: This post hoc subgroup analysis from the STEVIE single-arm, multicenter, open-label cohort study screened all 1215 participants for ocular or periocular involvement and identified 244 participants with POLA-BCC or metastatic BCC. Data for the first STEVIE trial were collected from 167 treatment locations in 36 countries from June 30, 2011, to June 14, 2017. This post hoc analysis was performed from April 1 to August 31, 2019.

Main outcomes and measures: Response to treatment and adverse events.

Results: Ocular or periocular involvement was found in 244 of 1215 STEVIE participants (20.1%), who constituted the analytic sample. The median age of the study participants was 72.0 (interquartile range [IQR], 60.0-82.0) years, and they included 143 men (58.6%). Locally advanced BCC was diagnosed in 238 of the 244 participants (97.5%) and metastatic BCC, in 6 (2.5%). The median duration of exposure to vismodegib was 40.0 (IQR, 20.0-78.0) weeks, specifically 39.7 (IQR, 19.9-76.0) weeks for POLA-BCC and 92.4 (IQR, 53.2-163.0) weeks for metastatic BCC. Sixty-nine participants (28.3%) sustained serious adverse events (alopecia, muscle spasms, dysgeusia, weight loss, decreased appetite, asthenia, ageusia, nausea, fatigue, and diarrhea). Two hundred thirty-two study participants (95.1%) sustained more than 1 adverse effect. The overall mean (SD) number of drug-related adverse effects per study participant by first adverse event, regardless of the severity, was 5.48 (3.84). Discontinuation of vismodegib treatment owing to an adverse event was recorded in 58 participants (23.8%). During the study, 22 participants (9.0%) died, 70 (28.7%) achieved complete response, and 94 (38.5%) achieved partial response.

Conclusions and relevance: Vismodegib was well tolerated by the study participants with POLA-BCC. The safety of vismodegib treatment according to the STEVIE trial findings is consistent with that reported in previous studies. These data may be helpful when considering vismodegib for patients with POLA-BCC.

Severe Forms of Acne, Impact on Patients Quality of Life, Treatment's Possibilities

Zuzana Nevoralová

Acne is a chronic inflammatory disease of sebaceous glands that is estimated to affect approximately 85% of the population at some point in their lives. Clinically, acne has a variable presentation with lesion types including open and closed comedones, papules, pustules, nodules, and cysts. The face is involved in most cases, and the trunk is affected in up to 61% of patients, more often with men. Acne lesions can progress to scars and postinflammatory hyperpigmentation. The pathogenesis is multifactorial, involving increased sebum production, disturbed keratinization, inflammation, and hypercolonization by *Cutibacterium acnes*. There is no standardized acne grading or classification system, however, acne is often categorized as mild, moderate, and severe. Acne fulminans is an uncommon and incompletely understood severe variant of inflammatory acne. Its onset is often abrupt, with rapid development of painful erosions and hemorrhagic crusts that lead to severe and often disfiguring scars. Peroral isotretinoin is the most effective drug in the treatment of acne. It is the only medicine which affects all the main aetiological factors implicating in acne. Its use is indicated in the treatment of severe and resistant forms of acne. Isotretinoin is generally well tolerated but several potential side effects have to be kept in mind in case the drug is prescribed. Teratogenicity is the most serious consideration, special recommendations for women's treatment are established. A good choice of dermatocosmetics during the therapy is important. With some patients, drug-induced form of acne fulminans- acne fulminans without systemic symptoms, can be observed, more often with young men. Corticosteroids are necessary in the beginning of isotretinoin treatment to prevent this entity.

Acne is a chronic disease that frequently interferes with the quality of life. Successful treatment of acne may improve a patient's quality of life. To investigate this issue, we conducted a prospective, uncontrolled study. The participants in the study were recruited between November 2018 and March 2021 among the outpatients of the Acne Clinic of Dermatovenereologic Department, Hospital of Jihlava, Czech Republic. Before and after finishing of orally administered isotretinoin, acne severity was assessed by grading and physical dermatological examination. All patients completed DLQI and CADL scores before treatment and after finishing isotretinoin therapy. Statistic analyses of DLQI and CADL scores were performed. Our prospective study indicated that there was a deterioration of quality of life before treatment. A significant improvement of quality of life was observed after successful isotretinoin therapy. Details of the study will be demonstrated. Some interesting casuistics of patients with severe forms of acne will be presented.

Dermatologic emergencies

Maria del Pilar Simon Diaz

Dermatologic emergencies represent about 8 to 10% of the diseases seen in the Emergency Department of hospital. They can be a challenge for primary care physicians. Sometimes they are life threatening conditions than need immediate intervention. In the

presentation we will include the following conditions: Stevens Johnson disease, Toxic Epidermal Necrosis, urticaria/angioedema, Pemphigus Vulgaris, Fasciitis Necrotising and Toxic Shock Syndrome.

DENTISTRY

The interactive association of smoking and drinking levels with presence of periodontitis in South Korean adults

Mira Lee

Objectives: This study aimed to assess whether there is an interactive effect of smoking and drinking on the presence of periodontitis.

Methods: We conducted a cross-sectional study design with data from the fourth and fifth the Korean National Health and Nutrition Examination Survey (KNHANES) sessions (2008-2010). A total of 18,488 subjects, aged over 19 answered the smoking and drinking questionnaire and were given the periodontal and metabolic syndrome examination, were included. The Community Periodontal Index (CPI) defined by the World Health Organization was used to assess the presence of periodontitis.

Results: Prevalence of periodontitis for self-reported smokers or drinkers was 35.0 or 28.0%, respectively. We observed 1.20 of Prevalence of Odds Ratio (POR) for those smoked <13 pack-year (PY) and drank ≥ 6.8 glass-year (GY) and 1.91 for POR for those smoked ≥ 13 PY and drank <6.8 GY, compared to those nonsmoking nondrinkers. The observed POR of 2.41 ($p < 0.05$), for those smoked ≥ 13 PY and drank ≥ 6.8 GY, was higher than a multiplicative effect estimated, i.e., 1.20×1.91 , or 2.29.

Conclusions: We observed a multiplicative interactive effect of smoking and drinking on the presence of periodontitis among Korean adults.

Access to Denture Restoration Services Under Removable Dentures Subsidy Program for The Elderly in Taiwan

Kuan-Yu Chu

Background: Access is an important issue in health equality. Availability of dental services and cost subsidies is an important factor affecting access to denture restoration for the elderly. This study aims to explore access to denture restoration services in the elderly removable denture's subsidy program of Taiwan.

Methods: Access to the elderly removable dentures' subsidy program was measured from two aspects, that is, availability of subsidies and payment for these services and the characteristics of patients and their treatment needs. The first aspect included reimbursements and the number and location of subsidy clinics, and the second aspect included the age and gender distribution of patients and denture types. Information on reimbursement regulations and the number and location of dental clinics providing subsidized services were obtained from the website of the Taoyuan City Public Health Bureau, Taoyuan Hospital, Department of Statistics and Ministry of Health and Welfare. Data on patient characteristics and denture type were obtained through a retrospective survey. We selected individuals who participated in the elderly removable denture's subsidy program from 2015 to 2018 at the Geriatric Dentistry Department of Taoyuan Hospital. We conducted data analysis using an interpretive approach.

Results: This study found that reimbursement amounts are inadequate, and the availability of subsidized services is low. Moreover, the proportion of male applications is slightly

higher than that of females. In addition, among the applicants, removable partial dentures for single or two arches are the most common. Conclusions: Problems of insufficient numbers of contracted hospitals and low reimbursement amounts are observed in the subsidy program, which are the key factors affecting access to denture restoration services among the elderly. Policymakers should exclude wealthy individuals and offer subsidy only to low-income elderly individuals with missing teeth who are in dire need of financial support to improve their dental health.

Key words: access, removable dentures, government subsidy, geriatric dentistry

Prognostic Factors in Cervical Necrotizing Fasciitis

Guido Lorenzini

Necrotizing Fasciitis is a rapidly progressive soft tissue infection potentially life-threatening; it can lead to septic vascular thrombosis, sepsis, organ failure, septic shock and even death. When it occurs in cervical region the most dangerous complication is Mediastinitis.

Microbes, usually Gram-, penetrate the tissues via trauma, head and neck surgery, odontogenic infections or abscess. Dental infections are quite common, but progression to Necrotizing Fasciitis is relatively rare.

The aim of this study is to develop a score so that when a patient present with serious dental infection we are able to set the risk of developing dangerous complications and, therefore, death.

We conducted a literature search on Pub Med of clinical cases of "Odontogenic Necrotizing Fasciitis" and found 74 papers for a total of 108 patients. Every single case was analysed and demographic information, symptoms, habits and co-morbidities were recorded and inserted in a table for each patient. The presence or absence of any conditions assigned one point.

We observed that the score registered in the "Dead Group" (A) is higher than in "Alive Group" (B) and T test demonstrated that the higher score in Group A had a statistical relevance, up to 97,5%, compared to the score of all patients analysed; moreover, the score of Group A is higher, with relevance up to of 99%, than Group B.

In order to assess the score discriminating of death risk in patients, we compared the total of patients with Group A and B (Z test); results demonstrated that a score ≥ 6 occurs, significantly, with higher frequency in the "Dead Group" than in "Alive Group".

Therefore, this score is an effective tool for assessing the risk of CNF complications and may be useful in clinical routine for rapidly discriminating life-threatening conditions.

Tooth Wear: Erosion and Attrition, The Bigger Picture.

Prema Sukumaran

Tooth wear comprises of erosion, attrition, and abrasion. In most tooth wear cases, erosive wear lesions and attrition exist in combination, one predominating the other. In this presentation, we look at clinical features of these lesions and how to detect them early. Early detection provides for a more conservative management, less complicated and less costly. This leads to improved longevity of teeth with erosive wear lesions or attrition.

Thickness Change of Masseter Muscles and The Surrounding Soft Tissues in Female Patients During Orthodontic Treatment: A Retrospective Study

Si Chen

Background: Facial esthetics is a major concern of orthodontic patients. This study aims to evaluate orthodontic treatment-related thickness changes of the masseter muscles and surrounding soft tissues and the potential factors that would influence these changes during orthodontic treatment in female adults.

Methods: Forty-two female adult patients were included in this retrospective study and were divided into

extraction (n = 22) and nonextraction (n = 20) groups. Pretreatment and posttreatment cone-beam computed tomography (CBCT) images were superimposed and reconstructed. The thickness changes of the masseter area of facial soft tissue (MAS), masseter muscles (MM) and surrounding fat tissue (FT) were measured. Pretreatment age, treatment duration, sagittal relationship (ANB), and vertical relationship (Frankfort-mandibular plane angle, FMA)-related MAS, MM and FT changes were compared between extraction and nonextraction groups. Spearman's correlation coefficient was calculated between the above variables. Regression analysis was conducted to confirm the causal relations of the variables.

Results: The thickness of MAS and MM significantly decreased in both groups, with larger decreases (> 1 mm) in the extraction group. There were strong correlations ($r > 0.7$) between the thickness decrease in MAS and MM in both groups and moderate correlations ($r > 0.4$) between MAS and FT in the nonextraction group. A significantly greater decrease of MAS and MM were found to be moderately correlated with a smaller FMA ($r > 0.4$) in the extraction group. Scatter plots and regression analysis confirmed these correlations.

Conclusions: Masseter muscles and the surrounding soft tissue exhibited a significant decrease in thickness during orthodontic treatment in female adults. Low-angle patients experienced a greater decrease in soft tissue thickness in the masseter area in the extraction case. But the thickness changes were clinically very small in most patients.

Keywords: Masseter muscles, CBCT, Machine learning, Computer-assisted image processing

Orthodontic Treatment in Childhood - Reversed Occlusion Treated by Mini-screw

Yasushi Nishii

One of the main goals of orthodontic treatment in children is to control the growth of the maxilla, which is called orthopedic treatment. However, conventional orthodontic treatment does not adequately control the growth of the jawbone. TADs have improved the outcome of jaw growth control in orthodontic treatment. However, the surgical invasiveness of TAD implantation is problematic. Therefore, we propose a less invasive orthodontic treatment using TADs.

Alternative Methods for Attenuating Orthodontic Treatment-Related Pain.

Kazunori Adachi

Orthodontic treatment has been applied to dissolve the functional and aesthetic issues in the orofacial region. However, among many dental treatments, orthodontic treatment

induces pain during tooth movement. Since inflammatory eicosanoid (prostaglandin) increases osteoclast activity, commonly prescribed acidic nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., aspirin), which inhibit eicosanoid production, are not recommended for tooth movement-related pain. We have established the animal model of tooth movement-related pain to investigate the etiology of orthodontic pain and alternative analgesic methods. In this animal model, orthodontic apparatus was attached to the right maxillary first molar, and electrical stimulation was applied to the bilateral maxillary first molar to evaluate the threshold intensity for inducing jaw-opening reflex (JOR TH). The orthodontic force application significantly decreased JOR TH in one day (D1), then recovered in seven days. To elucidate the analgesic effect of the low-level laser therapy on orthodontic pain, irradiation by CO₂ or diode laser was applied to the right maxillary first molar region. CO₂, but not diode, laser irradiation by a certain method significantly increased JOR TH at D1. Since CO₂ laser also increased gingival temperature up to 45°C, the range for TRPV1 activation, the involvement of TRP channels in orthodontic pain was investigated. General administration (i.p.) of TRPV1 antagonists (A-889425: 1.25 – 10 μmol/kg, AMG9810: 5 – 15 μmol/kg) for one day significantly increased JOR TH at D1 in a dose-dependent manner. These results suggested that the involvement of TRPV1 in orthodontic pain and the efficacy of TRPV1 antagonism for treating tooth movement-related pain. However, there are issues to using TRPV1 antagonists for analgesic purposes, such as the increasing heat pain threshold and hyperthermia in healthy human volunteers. To reduce such adverse effects of TRPV1 antagonists, the effects of local administration of TRP channel antagonists on both tooth movement-related pain and body/local temperature were investigated. In addition, the cocktail application of TRPV1 (AMG9810) and TRPA1 (A-967079) antagonists was also investigated because their cooperative function has been reported. TRP antagonist(s) were applied to cervical gingiva immediately after (D0) or one day after (D1) orthodontic force application, and JOR TH was examined on D1. When applied alone, TRP antagonists significantly and dose-dependently increased JOR TH the next day in both D0 and D1. Furthermore, the TRPV1 and TRPA1 antagonists (4% each) cocktail application showed a cooperative/synergistic analgesic effect in D0 and D1. Moreover, rectal or gingival temperatures did not alter across the experiment. Taken together, topical application of TRP antagonists' cocktail may be useful for clinical orthodontic pain.

Children's dental fear in relation to dental health and parental dental fear

Jana Olak

Dental fear IS A problems is a problem for dentists, parents and patients alike. Prevalence of dental fear and anxiety among children and adolescents in different countries ranged from 5 to 33%. They are Dental fear is a significant predictor of dental caries and is related

to increased occurrence of caries among children and adolescents. Among adults, dental anxiety is associated with poor dental health, poor oral health habits and irregular dental attendance. Children may acquire dental fear through social learning from siblings and other relatives. Parental dental anxiety affects dental anxiety in children. Family can be a reason for the development of dental fear and anxiety in children. A strong association between parental and child dental fear has been shown and parental dental fear is associated with increased occurrence of caries in children. Fearful patients avoid dental treatment and postpone their dental appointments. Children with poor dental attendance and poor dental health have a parent with dental fear more often than children with better dental health. Dental fear can be harmful for patients but also to the dental professionals who are working to offer care for them. Dental team should practice effective ways to help patients deal with dental anxiety to improve their dental health.

DIABETES

Management of Hyperglycemia in Type 2 Diabetes

Nisa M. Maruthur

The management of hyperglycemia in type 2 diabetes has become increasingly complex. Therapy for glucose-lowering in type 2 diabetes should include healthy lifestyle behaviors and referral to DSMES. Glycemic goals and cardiorenal risk and weight should all be considered. Important co-morbid conditions to consider in the selection of therapy include (but are not limited to) atherosclerotic cardiovascular disease, chronic kidney disease, heart failure, and obesity. To implement evidence-based recommendations on the management of hyperglycemia in type 2 diabetes, the use of language should be considered, providers must see and treat each person with diabetes as an individual, and they must know their health care team, local resources, and stay up-to-date on diabetes pharmacotherapy. We must incorporate continuous quality improvement at the local and system level in order to improve the care of type 2 diabetes.

Dorzagliatin monotherapy in Chinese patients with type 2 diabetes: a dose-ranging

Li Chen

Glucose sensitivity is often referred to glucose intolerance and the function of glucose stimulated insulin secretion (GSIS). Glucokinase GK, a Hexokinase 4, was discovered half century ago and was considered as a glucose sensor that plays a central role in glucose homeostasis [1]. The defect of the GK has shown clear impact of the glucose sensitivity in stimulating insulin release from beta cells and glucagon release from alpha cells of pancreatic islets. Its defect has also associated with hepatic insulin resistance and reduction of hepatic glycogen content. The loss of glucose response of GLP-1 secretion in T2D and obese subjects are the other forms of loss of glucose sensitivity. Dorzagliatin, a novel glucokinase allosteric modulator demonstrated its effects on the improvement of glucose sensitivity and sustained glycemic control in T2D patients in various clinical studies and will be presented [2-10]. Significant increase in early insulinogenic index, disposition index

together with HbA1c reduction suggested the role of Dorzagliatin in improvement of glucose sensitivity and treatment of root cause of diabetes.

Type 2 Diabetes and Plasma Levels of Direct Oral Anticoagulants in Patients with Atrial Fibrillation

Matej Samos

Type 2 diabetes (T2D) is a strong, traditional risk factor of stroke and systemic embolism (SE) in patients with atrial fibrillation (AF). In addition, T2D patients who suffer AF-associated embolic event seem to have worse clinical outcome compared to non-diabetic ones. Long-term anticoagulation is needed in majority of T2D patients with AF. Direct oral anticoagulants (DOACs) should be preferred for long-term prevention of stroke and SE in AF patients. These agents offer potent and predictable anticoagulation and a favorable pharmacology with low risk of interactions. However, it is not entirely clear whether T2D affects the plasma levels of DOACs, the efficacy and/or safety of long-term DOACs therapy. This speech reports the results of our pilot study aiming to determine the effect of T2D on plasma levels of DOACs in patients with AF and reviews the current data regarding the use of DOACs in individuals with T2D and AF.

Emerging Areas of Type 2 Diabetes Drug Discovery

Bhatt Harikrasha

Type 2 Diabetes Treatments are in need of more efficacious and safe treatment options in order to better individualize therapy for our patients.

Contraception, Pregnancy Planning and Preconception Care in Women with Diabetes Mellitus

Emily Hibbert

Pregnancy outcomes in women with type 1 or type 2 diabetes are poorer than for women without diabetes. Women with diabetes have higher incidences of maternal, fetal and neonatal complications, including increased risk of congenital malformations. High glucose levels from early pregnancy increase the risk of adverse outcomes, including congenital malformations. Congenital malformation risk increases exponentially as early pregnancy glucose levels rise.

Many of these risks can be reduced through tight glycaemic control before and during pregnancy. However, Australian data demonstrate that the incidence of infant morbidity or mortality in women with diabetes is over four times higher than in women without diabetes (13.6% vs. 3.1%) with an odds ratio of 5 (OR= 5.0, 95% CI 4.2-5.8). Pregnancy outcomes are similarly poor in many other countries.

Many women with diabetes are unaware of the need for diabetes-specific pre-pregnancy planning. A major issue is that up to half of pregnancies in women with diabetes are unplanned, which is the same as for women without diabetes. Foetal damage may occur before a woman realises she is pregnant.

Safe, effective contraception is key to pregnancy planning. However, there are major gaps in the knowledge of both women and their healthcare practitioners. Education of both

women and health care practitioners around the need to carefully plan pregnancies is lacking. Women are uncertain about which contraceptive methods are most effective and which methods are safest in diabetes. Conversations initiated by health care practitioners with women around contraception and pregnancy planning are not routinely performed.

How can we ensure that women with diabetes and all health care practitioners receive the message about the importance of safe and effective contraception and pregnancy planning in diabetes and act on it? How can we change women's contraceptive practice and health care practitioner practice?

This presentation will examine the most effective contraceptive methods which are also safe in women with diabetes and components of pregnancy planning in women with diabetes. It will explore evidence-based strategies and potential strategies to improve effective contraceptive uptake and pregnancy planning in women with diabetes in order to improve their pregnancy outcomes.

Lead (Pb) Exposure Promotes Diabetes in Obese Rodents

Todd Leff

Pb (lead) exposure occurs at elevated frequency in urban inner-city populations that also have high rates of obesity and diabetes. To determine if Pb can promote the development of diabetes in a setting of obesity, we examined the effect of Pb exposure on glucose metabolism in a rodent model of obesity. Adult female ZDF rats and high fat fed C57BL6 male mice were exposed to Pb in drinking water for varying times. Fasting blood glucose, insulin, and glucose tolerance were measured at regular intervals. Expression of hepatic gluconeogenic genes was measured in exposed and control animals and in cultured hepatoma cells treated with Pb. In both obese rats and high fat fed mice, Pb exposure induced fasting hyperglycemia and glucose intolerance. In addition, Pb-exposed animals showed elevated hepatic triglyceride levels and increased expression of the gluconeogenic genes PEPCK and glucose-6-phosphatase. In cultured rat hepatoma cells treatment with Pb stimulated PEPCK and glucose-6-phosphatase gene expression, suggesting a possible direct effect of Pb on hepatic gluconeogenic gene expression, which likely contributes to the observed hyperglycemia.

Yoga-based lifestyle treatment and composite treatment goals in Type 2 Diabetes in a rural South Indian setup- a retrospective study

Majumdar Vijaya

Lifestyle management plays an essential role in the efficient control of diabetes status. Yoga, as a lifestyle intervention has been reported to lead to beneficial health outcomes related to cardiovascular and metabolic disorders including T2D. Based on its high reported receptivity and cost-effectiveness, yoga holds a strong potential as a lifestyle management skill in Indian scenario. This is the first multicentric report wherein the efficacy of yoga treatment was assessed in aiding the cardiovascular fitness with respect to achievement of ADA laid primary treatment goals of T2D in rural Indian settings. Records were extracted for 146 T2D patients, aged ≥ 20 -70 years, and treated under the "Apollo Total Health Programme" for rural diabetes management, for the period April 2016 to November 2016.

The study cohort comprised two treatment groups (n = 73 each); non-yoga group (standard of care) and yoga group (adjunct yoga-treatment). Propensity score matching was applied between the study groups to define the cohort. Composite cardiovascular scores were based on the combination of individual ADA goals; A1c < 7%, blood pressure (BP) < 140/90 mmHg, stringent BP (<130/80 mmHg) and lipid, LDL-C < 100 mg/dl [risk factor for atherosclerotic cardiovascular disease]. Logistic regression was used to compare between the two treatment groups. Compared to standard of care, adjunct yoga-treatment was found to significantly facilitate the attainment of ADA composite score by 8-fold; A1c, ~2-fold; LDL-C, ~2-fold; BP < 140/90 mmHg and <130/80 mmHg by ~8-and ~6-fold respectively. This study provides the first evidence for significant efficacy of adjunct yoga-treatment for the attainment of favourable treatment goals for T2D in rural Indian settings. Clinical Trial Registration Number: CTRI/2020/02/0232790

Outline of Proposed Presentation on Remote Monitoring and Management in Diabetes Care

Steven B. Leichter, M.D., F.A.C.P., F.A.C.E.

Remote monitoring of diabetic patients was first reported in the early part of the previous decade. Our study of remote monitoring of blood sugars and the remote transmission of other data about diabetic patients was one of the first (Leichter et al. J Diabetes Technol and Therapeutics 15: 1089, 2013). In that study, we compared two groups of patients with diabetes, who were carrying out blood sugar monitoring with an Accucheek glucose monitor. Glycemic control, blood pressure control, and control of hyperlipidemia was the same in both groups. The remotely monitored group had significantly more weight loss than the group in usual care. Since then, there have been numerous studies on remote transmission of data from diabetes care devices, including blood sugar monitors, insulin pumps, and glucose sensors. Most have shown similar outcomes via remote care versus usual care, emphasizing the feasibility of a growing technology providing the opportunity for remote monitoring of diabetic patients versus usual care.

From the perspective of rendering best care to diabetic patients, the growing experience with opportunities for remote monitoring have also pointed out some caveats in the use of remote monitoring. Patients with lower socioeconomic resources and/or less education are not as suited for this form of care as people with higher levels of education and more substantial socioeconomic resources. Less educated or less affluent patients are less likely to have the technical capability or equipment to participate effectively in remote care. They are also less likely to accumulate the data necessary for remote care than other patients.

Until the onset of COVID 19, there were many administrative, economic, and medical-legal obstacles to carrying out remote care of patients. In the United States, many insurance plans, such as Blue Cross, required a separate credentialing process to qualify health providers for remote care. This was often tedious and difficult to obtain. In addition, most insurance plans established different reimbursement schedules for remote visits versus usual visits, and these altered fee schedules were significantly lower than the fee schedules for usual care. Similar obstacles existed in many countries. One of the few benefits in medicine from COVID 19 was that this epidemic rapidly and markedly expanded the

opportunities to carry out remote care, both in terms of the elimination of separate credentialing processes, and discounted fee schedules. In the United States, all health insurance companies and government insurance plans adopted simple modifier codes to indicate that the visit was carried out remotely, so long as it was a telemedicine visit.

Because of this change, a number of different technologies have become available to expand the opportunity for remote monitoring. These include: the remote transmission of data from insulin pumps and glucose sensors; the ability to transmit data from insulin pens; and more sophisticated systems to transmit data, coordinating insulin pens and glucose sensors together. However, these sorts of systems are currently beset by different rules for carrying out communication with patients by mechanisms that are not telemedicine visits, such as telephone visits. Reimbursement for these sorts of interactions is less certain in the United States. In other countries, rules allowing these sorts of visits are less developed. Perhaps, a bigger problem is that these visits tend to take the same amount of time as in person visits were telemedicine visits, but they do not qualify for the same rate of reimbursement.

Telemedicine visits in many countries are now an established form of care, and that has significantly expanded opportunities to render care to patients. Other sorts of interactions with patients, using remote transmission of data have yet to clearly establish that place as a major component of the system of care for people with diabetes.

Effect of Health Information Technologies on Type 2 Diabetes and Cardiovascular Risk Factors among Patients with Diabetes

PI: Eduardo J. Simoes, MD, MSc, MPH

Background: In 2019, it is estimated that 19.3% of people aged 65–99 years (135.6 million, 95% CI: 107.6–170.6 million) live with diabetes. It is projected that the number of people older than 65 years (65–99 years) with diabetes will reach 195.2 million by 2030 and 276.2 million by 2045.

Health Informatics in Diabetes Research (HIDR) Results

The University of Missouri Health Informatics in Diabetes Research Core of the Washington University Center for Diabetes Translation Research combined research (implementation, informatics, endocrinology & diabetes education) showed that effect of health information technology (HIT) applications, especially mobile apps and handheld messaging, on clinical control of glycemia (HbA1c) is both statistically and clinically significant. Research also shows that HIT effect on risk factors for cardiovascular diseases (CVD) in Type 2 diabetes (T2D) patient was both clinically and statistically significant. This type of research has contributed to the gained popularity of mobile apps and handheld messaging. However, HIDR additional research shows those technologies lacked many foundational domains of effective health communication, self-education, and marketing to have such impact, especially those expected in the diabetes self-management and education (DSME). In addition, HIDR research demonstrated that HIT interventions researched lacked the necessary internal and external validity for feasibly scaling them up in the real world. There is a need to test postulated effects of HIT by improving domains of theoretical models for

effective communication and marketing in diabetes management and minimizing barriers to adoption and maintenance of strategy.

This presentation summarizes findings of the (1) efficacy of HIT on the reduction of A1c and risk factors for CVD among diabetes patients; 2) evidence that HIT interventions promotes diabetes self-management and education (DSME) through apps and messaging on diabetes, (3) a summary of internal and external validity of the HIT intervention measured by validated RE-AIM framework, (4) specific aspects of mobile apps and messaging that address domains of theoretical models for effective health communication, self-education and marketing; and 5) proposed areas of future research.

Future Work: We propose an eHealth approach that engage patients with appropriate DSME approach in communication and education, provides provider with critical patient care information, provides individualized treatment goals; and allows for the collection of objective data from the client, as well as the input of self-reported data.

Current State of the Art for Revascularization and Amputation Prevention in the Diabetic Foot

Joshua Gabel

The lifetime risk of a person with diabetes developing a foot ulcer can be as high as 34%, effecting 131 million people globally. Diabetic foot ulcers (DFUs) increase the risk of hospitalization 10-fold and represent the underlying etiology in 80% of amputations worldwide. DFUs are caused by a combination of peripheral artery disease (PAD), microangiopathy, neuropathy, and increased susceptibility to foot infections. Diabetic PAD often takes the form of tibial disease with or without pedal sparing. The Society for Vascular Surgery (SVS) Wound, Ischemia, and foot Infection (WIFI) classification system has emerged as a valuable resource, independently predicting wound healing, benefit from revascularization, risk of amputation, and costs of care in diabetic patients. Multidisciplinary treatment teams have shown increasing success in the complex management of DFUs. These teams are comprised of podiatrists and vascular surgeons with the addition of other specialists, including infectious disease, endocrinology, orthotics, and nutrition. Key considerations in the revascularization of diabetic patients include time to revascularization, direct versus indirect revascularization, bypass versus endovascular approaches, and determining those for whom primary amputation offers the greatest benefit. Finally, focusing on patient-centered metrics of success help us to better improve our patients' quality of life and lead to a higher level of medical decision making that optimizes care for both the patient and the system at large.

Type 2 Diabetes and Vascular Health in Youth

Sarah Henson

The prevalence of youth-onset type 2 diabetes continues to rise putting these children at risk for early onset cardiovascular disease, morbidity and mortality. Cardiovascular risk factors, including diabetes mellitus, have been shown to be associated with accelerated cardiovascular aging in longitudinal adult studies. Similarly, publications addressing early vascular aging in at risk youth have shown that adolescents with type 2 diabetes have

higher vascular thickness and stiffness in addition to lower endothelial function when compared to non-diabetic youth. The most current published data consistently show non-invasive arterial stiffness measures predict target organ damage and that target organ damage is higher in those with type 2 diabetes than type 1 diabetes. The use of noninvasive techniques to assess vascular disease in this population may help in developing better risk stratification techniques, identification of treatments aimed at improvement or reversal of vascular dysfunction and decrease diabetes related cardiovascular disease.

Intraocular Inflammation in Diabetic populations

Rola Hamam

Both uveitis and diabetes are individual risk factors for blindness but is there an association between the two diseases?

Review of the prevalence of uveitis in the diabetic population show that:

Diabetes is reported in 5.9% of anterior uveitis versus 1.4% in the normal Dutch population (P value < 0.001)

Furthermore, Diabetes was reported in 14.3% of idiopathic anterior uveitis patients versus 0% in the anterior uveitis with an established diagnosis (Prevalence of DM in the idiopathic anterior uveitis group was higher than that in the normal Spanish population).

As for the clinical features of the uveitis and diabetes when coexisting, it is typically a fibrinous anterior uveitis in the presence of poorly controlled DM and in the absence of any other underlying cause.

We will also discuss pathophysiology of a possible correlation related to breakdown of blood retina barrier and inflammatory markers in both diseases.

We will also discuss the results from the Royal College of General Practitioners Research and Surveillance Center database which shows uveitis is more common in diabetic population especially type 1 and that it is more likely with worse glycaemic control.

They established the prevalence of acute uveitis among populations without (n = 889,856) and with diabetes (n = 48,584) over a six-year period.

Incidence of acute uveitis was higher among patients with diabetes; Type 1 OR:2.01 (95% CI 1.18–3.41; p = 0.009), and Type 2 OR:1.23 (1.05–1.44; p = 0.01). Acute uveitis was significantly more common in people with type 1 diabetes and type 2 diabetes, than in those without diabetes after adjusting for confounders.

Glycaemic control was established as an important effect modifier for uveitis risk. Results confirmed a dose-response relationship such that very poor glycaemic control OR:4.72 (2.58–8.65; p < 0.001), poor control OR:1.57 (1.05–2.33; p = 0.03) and moderate control OR:1.20 (0.86–1.68; p = 0.29) were predictive of uveitis.

Analysis of outbred mouse multi-tissues' expression profiles supports a new angle of earlier prediabetes detection and treatment

Lei Li

Type 2 diabetes (T2D) is a complex and polygenic disease yet in need of a complete picture of its development mechanisms. To better understand the mechanisms, we examined gene expression profiles of multi-tissues from outbred mice fed with a high-fat

diet (HFD) or regular chow at weeks 1, 9, and 18. To analyze such complex data, we proposed a novel dual eigen-analysis, in which the sample- and gene-eigenvectors correspond respectively to the macro- and micro-biology information. The dual eigen-analysis identified the HFD eigenvectors as well as the endogenous eigenvectors for each tissue. The results imply that HFD influences the hepatic function or the pancreatic development as an exogenous factor, while in adipose HFD's impact roughly coincides with the endogenous eigenvector driven by aging. The enrichment analysis of the eigenvectors revealed diverse HFD impact on the three tissues over time. The diversity includes: inflammation, degradation of branched chain amino acids (BCAA), and regulation of peroxisome proliferator activated receptor gamma (PPAR γ). In particular, we reported remarkable pancreatic angiogenesis as downstream of the HIF signaling pathway in the T2D development. The discoveries provide new thinking in T2D prevention and therapy.

By integrating our discoveries and other relevant reports in the literature, we propose a scheme of earlier detection and treatment of prediabetes. We suggest that hyperinsulinemia rather than hyperglycemia is an "early warning signal" of T2D. Therefore, only testing the blood glucose levels is not enough whereas testing and monitoring the blood insulin levels is much needed. We also suggest that metformin, as an agent directly acting against insulin resistance, shall be administrated as early as in the prediabetes stage, and sufficient dose of this medication shall be applied upon correcting hyperinsulinemia. To examine and prove the above hypothesis, further comprehensive basic research and clinical study, with the assistance of computational and systems biology to analyze big data, are recommended. Once such studies provide sufficient evidences supporting the above suggestions, the current clinical guidelines should be updated and modified. These efforts may make a breakthrough in tackling the problems of curing T2D and in reducing its incidences.

Diabetic foot in Algeria – Gangrene of the extremities during COVID 19

Dr. Nadia Boudjenah

The purpose of this presentation is to publish a catalog of the lesions encountered during the attack of the limbs by COVID 19. It does not claim the explanation. We preferred to stay open for our patients and therefore not to close our diabetic foot center since the start of the pandemic to date. These direct face-to-face visits were made possible thanks to all the health precautions taken to protect our patients, carers, and the entire active team at our center.

We are bringing to you our experience of the diabetic foot. After having taken care of more than 120.000 patients over the past 17 years, we were able to clearly define specific particularities as well as strong points of our therapeutic strategy.

More than 95% of our patients suffer from severe Neuropathy. Treating Diabetic Neuropathy is a big challenge. More than 50% of diabetics worldwide are affected. Neuropathy is a consequence of microcirculatory damage in diabetics. The damage caused destroys the nerves. It is caused by the aggression of hyperglycemia. The diagnosis is both clinical and paraclinical: ENMG.

Diabetes and Driving: Evidence and Recommendations

Catarina Senra

In recent years there was an increasing concern about Diabetes and driving. As a result, most countries impose strict rules to diabetic drivers.

Diabetes could impair the ability to driving due to side effects from the treatment (mainly hypoglycaemia) and the potential risk subsequent to complications such as retinopathy or cataract formation impairing vision and neuropathy affecting the ability to feel foot pedals.

The increased crash risk for diabetic patients isn't fully established. Some studies have reported increased road traffic accident rate while other studies haven't reported an increased risk. Research studies have demonstrated that hypoglycaemia is a significant factor in impaired driving. As driving performance decline at lower levels of glycaemia, patients' decisions concerning driving or taking corrective action may also be compromised.

To avoid car crashes patients who are at risk for disruptive hypoglycaemia should be counseled to: carry a blood glucose meter and some sugar source in their vehicle; always measure blood glycaemia before start driving; never begin an extended drive with low normal blood glucose (70- 90 mg/dl) without prophylactic carbohydrate consumption; stop the vehicle as soon any of the symptoms of low blood glucose are experienced, and measure and treat the blood glucose level; not resume driving until their blood glucose and recognition have recovered.

The European Union published in 2009 a directive in order to harmonize rules about driving licensing in member states. As a result, regulations for driving licenses have changed across Europe.

We will revise the evidence on this subject and also driving regulations for patients with type 2 diabetes.

Ultrasound diagnosis of insulin-derived subcutaneous degeneration

Minoru Kikuchi

Diabetes patients often suffer from subcutaneous degeneration at insulin injection sites during self-administered insulin therapy (SAIT). Among the distinct types of subcutaneous complications resulting from SAIT, lipohypertrophy (LH) and insulin-derived amyloidosis (IDA) are defined as tumor-like enlargements of the adipose tissue and are caused by repeated injections at the same site. Nagase et al. (2009) were the first to report on a condition called the "insulin ball," which is an IDA with a palpable mass or nodule. Recently, several reports have indicated that IDA is caused by an increase in the administration of insulin at the same site and is associated with poor glycemic control. The early detection and prevention of these lesions are therefore important to diabetic patients. However, these lesions are difficult to diagnose because some IDA cases are non-palpable. IDA can be detected using image inspection (MRI, CT, and ultrasonography), but MRI and CT are probably unwarranted for observing subcutaneous tissue. By contrast,

ultrasonography is a simple, noninvasive, and high-resolution imaging modality that is more suitable for examining subcutaneous induration as it enables the detailed observation of subcutaneous tissues without being influenced by physical conditions. Considering that amyloid deposits in subcutaneous lesions can change the normal dermis plus the subcutaneous structure and echogenicity, anomalies can be easily identified with ultrasonography. Both palpable and non-palpable types of IDA can cause poor glycemic control and increase the required dose of insulin. In our study, injection sites were shifted after a subcutaneous lesion was confirmed by ultrasonography. This approach significantly decreased the necessary insulin dose and led to improvements in glycemic control. IDA leads to poor glycemic control because it impairs insulin absorption. To improve glycemic control in patients undergoing SAIT, the accurate identification of injection site induration is important (i.e., ultrasound diagnosis may contribute to better glycemic control in patients undergoing SAIT). We believe that the presence of non-palpable lesions characterizes the preliminary stage of IDA, whereas the presence of an “insulin ball,” which is palpable, characterizes an advanced stage of IDA. Therefore, we recommend ultrasonography for detecting non-palpable IDA. Ultrasonography should also be used to screen subcutaneous lesions in diabetes patients who are undergoing SAIT. We speculate that some diabetes patients may be unaware of abnormalities at their insulin injection sites. The use of ultrasonography in clinical practice can improve diabetes care by enabling the early detection of IDA.

Diet and Parasitism Influence Risk and Evolution of Type 1 Diabetes In Mexican Children Inducing Bacterial Dysbiosis

Calderón de la Barca Ana M., Mejía-León M. Esther, López-Domínguez Lorena, Aguayo-Patrón Sandra V.

Understanding the type 1 diabetes (T1D) etiology, the second most frequent autoimmune disease in childhood will allow the designing of strategies to avoid or delay the T1D onset and to maintain control if developed. Our group has focused on the relationship between perinatal history, diet, and gut microbiota structure in Mexican children with genetic predisposition or developed T1D.

After gene sequencing, we found that newly diagnosed T1D cases had high levels of *Bacteroides* ($p < 0.004$), whereas in healthy children the dominant genus was *Prevotella*. Children with T1D treated for ≥ 2 years had levels of *Bacteroides* and *Prevotella* with a trend to those in healthy children.

The differences in microbiota between healthy and newly diagnosed children could be attributed to the autoimmune process. However, subsequent changes in the microbiota could depend on factors such as diet. We evaluated diet and microbiota in children with T1D, during the first year after diagnosis. T1D children decreased intake of energy ($p=0.028$), protein ($p=0.012$), and saturated fat ($p=0.031$) from baseline to 3 months, without posterior changes. *Bacteroides* proportion increased in the first month and tended to decrease at 9 months ($p > 0.05$) and was positively correlated with saturated fat ($\beta = 3.70$, $p=0.009$) and total carbohydrates ($\beta = 0.73$, $p=0.005$) intake at 3 months. Carbohydrate consumption was related to decreased *Bacteroides* abundance over time ($\beta = -14.9$, $p=0.004$), after adjusting for glycosylated hemoglobin.

Seeking to better understand the factors involved prior to T1D diagnosis, we evaluated the effect of enteropathogenic parasites (*Cryptosporidium* spp., *Cyclospora* spp., *G. lamblia*, and *Blastocystis* spp.) on the bacterial structure of feces from children with autoantibodies for T1D. We detected that *Cryptosporidium* spp. and *Cyclospora* spp. affected the bacterial structure at family and genus levels, decreasing the ratio between Firmicutes and Bacteroidetes. Therefore, intestinal parasitic infection could increase the risk of T1D onset. In conclusion, in Mexican children, the T1D associated dysbiosis is dominated by *Bacteroides* spp. Besides autoimmunity, diet and parasitism could have a central role in determining the T1D onset, and diet is clearly associated with dysbiosis evolution and disease control.

Type 2 diabetes and plasma levels of direct oral anticoagulants in patients with atrial fibrillation

Matej Samoř, M.D. PhD.

Acknowledgments and Funding

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Type 2 diabetes (T2D) is a strong, traditional risk factor of stroke and systemic embolism (SE) in patients with atrial fibrillation (AF). In addition, T2D patients who suffer AF-associated embolic event seem to have worse clinical outcome compared to non-diabetic ones. Long-term anticoagulation is needed in majority of T2D patients with AF. Direct oral anticoagulants (DOACs) should be preferred for long-term prevention of stroke and SE in AF patients. These agents offer potent and predictable anticoagulation and a favorable pharmacology with low risk of interactions. However, it is not entirely clear whether T2D affects the plasma levels of DOACs, the efficacy and/or safety of long-term DOACs therapy. This speech reports the results of our pilot study aiming to determine the effect of T2D on plasma levels of DOACs in patients with AF and reviews the current data regarding the use of DOACs in individuals with T2D and AF.

Barriers to Weight Management in persons with and without Type 2 Diabetes

Robert R Dent

Objective: To report on our studies dealing with barriers to weight loss, and to put them in context of a list of barriers in persons living with obesity and type 2 diabetes.

Methods: In 1992, we established a weight management clinic at a University of Ottawa teaching hospital for the study and treatment of obesity. This was a 6-month course with weekly 1.5-hour interactive teaching sessions to build skills for long-term weight management. For weeks 2 – 14 patients were on a total meal replacement for a timely and safe weight loss. The data-gathering system collected information on the standardized initial history, physical exam, lab testing protocol, and weights measured weekly for the first 26 weeks and long-term for a mean of 10 years. This was a modified intention to treat study on 5057 patients and has resulted in 60 papers in peer-reviewed journals. Here we report on these studies:

- Is Type 2 diabetes a barrier in and of itself to weight loss? This is a study of persons with T2DM who were treated with diet only or diet and metformin.

- Is Beta-Blocker usage, a significant barrier?
- Is suboptimal weight loss only due to non-adherence? Here we report on a diet resistance state due to a problem of energy expenditure. (Reviewed by Dent et. al. Metabolism 2020).

Conclusions: We see these studies as reinforcing a non-judgemental approach to persons who lose sub optimally with dietary restriction.

EMERGENCY MEDICINE

Caring for Older Adults in the Emergency Department - The Importance of a Team Based Approach

Osama Loubani

Around the world, the population is aging. As such, older adults will make up a greater number of visits to the emergency department in the coming years. Emergency department management of older adults is challenging as these patients often have complex co-morbidities, are at higher risk of serious illness, and often have cognitive issues. Current models of care involving an emergency physician seeing the patient and deciding on disposition are not well suited for older adults. A multi-disciplinary approach involving medication review, mobility assessment, cognitive assessment, and discharge planning can improve outcomes. This session will review the importance of a multi-disciplinary approach in caring for older adults and steps that can be taken to achieve this.

EPILEPSY

Short-Term Risk of Recurrence After a First Unprovoked Seizure

Walid Alesefir

Objective: To evaluate the incidence of short-term recurrence (<1 month) after a first unprovoked seizure (FUS) and the associated risk factors. Methods: This is a prospective monocentric one-year observational study on all consecutive adult patients admitted to the Emergency Department (ED) and diagnosed as FUS. Patients underwent neurological consultation at one and three months after the FUS. Demographic information, clinical examination and seizure features, seizure recurrence at 1 and 3 months, electroencephalogram (EEG), brain imaging, precipitating factors, seizure type, and prescribed antiepileptic drugs (AED) were prospectively collected. Results: Among 140 patients diagnosed as FUS, 109 patients attended the neurological consultation at 1 month. FUS diagnosis was confirmed in 80/109 cases. Nine patients (11.2%) had seizure recurrence before the consultation at 1 month. Identified specific risk factors of short-term recurrence were focal seizure ($P=0.015$) and abnormal EEG in the first 48hours ($P=0.048$). In the group of patients followed for three months (38 patients), the risk of seizure relapse was 15.7%. Conclusion: Most patients with FUS diagnosed in the ED did not present seizure recurrence within the first month, especially if no specific risk factors were present (focal seizure, abnormal EEG within first 48hours). The systematic use of prophylactic AED (benzodiazepines) is not recommended in the ED in the clinical setting of FUS. A specialized consultation within a one-month period is safe and adequate for FUS follow-up.

Influence of Ketone Supplements on Epileptic Seizures and Anxiety in WAG/Rij Rats

Zsolt Kovács, PhD

It has been demonstrated that the state of therapeutic ketosis can be induced and maintained by administration of exogenous ketone supplements (EKSs), such as ketone ester (KE) and KSMCT (ketone salt/KS + medium chain triglyceride/MCT). Moreover, adenosinergic system may be involved in the alleviating effects of EKSs on both different types of epilepsies and anxiety, likely through adenosine A1 receptors (A1Rs). Thus, we tested whether administration of EKSs for 7 days by intragastric gavage can modulate absence epileptic activity and level of anxiety in an animal model of human absence epilepsy Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats by using electroencephalography and elevated plus maze (EPM) test. Levels of blood beta-hydroxybutyrate (β Hb) were significantly increased after both KE and KSMCT gavage (2.5 g/kg/day), compared to control levels. Number of spike-wave discharges (SWDs) decreased after both KE and KSMCT treatment between 3rd and 7th days of administration. KSMCT increased the time spent in the open arms, decreased the time spent in the closed arms and resulted in more entries to open arms and less entries to closed arms suggesting anxiolytic effect of the treatment. Moreover, combined administration of a specific A1R antagonist DPCPX (1,3-dipropyl-8-cyclopentylxanthine; intraperitoneal/i.p. 0.2 mg/kg) with KSMCT (2.5 g/kg/day, gavage) abolished the KSMCT-evoked decrease in SWD number and anxiolytic effect. Thus, we concluded that (i) administration of EKSs can decrease both absence epileptic activity and anxiety level in WAG/Rij rats and (ii) A1Rs may modulate the EKSs-induced beneficial effects on absence epilepsy and anxiety.

Keywords: ketone supplements, ketosis, SWD, EPM, anxiety, adenosine, WAG/Rij rats

Therapeutic Drug Monitoring (TDM) of Anti-epileptic Drugs (AEDs) in a Tertiary Hospital in Malaysia

Allan Mathews

Epidemiological studies have shown that approximately 70 million people would have epilepsy at any particular time globally. Pharmacotherapy with AEDs is the mainstay of treatment resulting in seizure control in 70% of cases. However, AEDs pose challenges in that they possess narrow therapeutic ranges and in the case of Phenytoin zero order kinetics, thus necessitating the need for TDM. A case controlled retrospective study was carried out to evaluate the association between measured drug levels of four AEDs i.e. Phenytoin, Carbamazepine, Phenobarbitone and Valproic Acid and indications for TDM requests, was carried out in a tertiary hospital in Malaysia. Only samples that reflected steady-state concentrations of the drugs were included in the study. Data was collected over a period of one year and 780 samples were studied. % of sample contribution of the drugs was 27.7% Phenytoin, 11.5% Carbamazepine, 4.0% Phenobarbitone and Valproic Acid 56.8%. 39.6% of samples were for breakthrough seizures, 37.4% for dosing adequacy, 15.0% for compliance and 8.0% for suspected toxicity. 39.6% of samples were found to be in the therapeutic range, 49.2% in the sub-therapeutic level and 11.2% in toxicity level. Odds Ratio (OR) with 95% confidence interval which reflects the strength of association was used in the analysis. The comparison of measured drug levels that was in the sub-therapeutic range with those not within the range had an OR of 1.318 indicating there was no significant increase in risk on occurrence of breakthrough seizures. The OR for dosing adequacy was 1.739 among measured drug levels within the therapeutic range and those not, indicating the measured drug levels correlates with patients having appropriate dosage

regimen. The OR for compliance was 2.046 among measured drug levels in the sub-therapeutic range indicating that the levels are significantly associated with patients having compliance problem. The OR for suspected toxicity was 4.627 indicating a significant increase in risk of toxicity to be in the toxic level. This study implied that TDM requests for breakthrough seizures can be reviewed. This study also revealed that the therapeutic ranges for each of the AEDs must be viewed as a guideline and that clinical response and pharmacotherapeutic outcomes remain the main focus when treating epileptic patients.

Quality of Life in Epilepsy: The Impact of Traumatic Brain Injury and Multimorbidity

Mary Jo Pugh PhD, RN

Co-authors: James J. Gugger MD, PharmD, Eamonn Kennedy PhD, Samin Panahi MS, David F. Tate PhD, Ali Roghani PhD, Anne C. Van Cott MD, M. Raquel Lopez MD, Hamada Altalib MD, MPH, Ramon Diaz-Arrastia MD, PhD

Background

Epilepsy is defined by the occurrence of multiple unprovoked seizures, but quality of life (QOL) in people with epilepsy is determined by multiple factors, in which psychiatric comorbidities play a pivotal role. It is well known that QOL is lower in people with epilepsy, but little is known about QOL in those with a history of traumatic brain injury (TBI)—the most common cause of new onset epilepsy in younger adults. Therefore, understanding the interplay between comorbidities and QOL across epilepsy phenotypes is an important step towards improved outcomes. Here, we report the impact of QOL across distinct epilepsy phenotypes in a cohort of post-9/11 veterans with high rates of traumatic brain injury (TBI) who responded to a national survey from the Military INjuries—Understanding post-Traumatic Epilepsy [MINUTE] study. We describe results of the MINUTE study which examined the association of epilepsy and quality of life in a cohort from which we developed epilepsy phenotypes based on lifetime history of TBI, current seizure and seizure medication use.

Methods

Using combined survey and health record data, the MINUTE study (n=2603) revealed high rates of undocumented lifetime TBIs among Veterans with epilepsy who had no evidence of TBI in VA medical records. We developed 6 measures of quality of life using the SF-12, Quality of Life in Brain Injury overall score (QOLIBRI), and Quality of Life in Epilepsy (QoLIE 10). We then classified veterans with epilepsy (VWE n=529) as Epilepsy, Refractory Epilepsy (RE; seizures in the past year or receiving ≥ 2 antiseizure medications) TBI+Epilepsy, TBI+RE.

Results

Data from the full cohort found worse physical and mental component scores of the SF-12 and QOLIBRI for individuals with Epilepsy+TBI compared to those with either epilepsy or TBI alone. RE was more common in those with PTE compared with non-traumatic epilepsy (45% vs. 33%, odds ratio 1.6 (95% CI: [1.1-2.4], $p=0.01$)). Those with RE and RE+TBI had significantly more comorbid conditions than those without RE. Those with RE with or without TBI history had significantly lower scores on SF-12 physical and mental component scores, QOLIBRI, QoLIE 10, quality adjusted life years (QALY), and quality adjusted life expectancy (QALE) even after controlling for comorbid conditions. Scores were significantly lower for those with TBI+RE than those with RE alone.

Discussion

These findings suggest that people with epilepsy+TBI are distinctly vulnerable to the comorbidities associated with TBI and epilepsy and that those with RE had even more comorbidities. Those with RE and RE+TBI should be the focus of future studies aimed at elucidating the factors associated with adverse health outcomes and developing anti-epileptogenic therapies. These insights provide valuable opportunities to optimize the resilience, delivery of health services, and community reintegration of patients with epilepsy and complex comorbidity.

ENDOCRINOLOGY

Short Telomere Length is Associated with Arterial Aging in Patients with Type 2 Diabetes Mellitus

Katharina Gin

It is known that glucose disturbances contribute to micro- and macro vascular complications and vascular aging. The length of telomere (TL) is considered as a biomarker for cellular aging. It is crucial to determine the role of the telomere length in structural and functional vessels changes in patients with DM.

The aim of our study was to determine the role of the telomere length in vascular aging in patients with T2DM.

Methods: The study group included 50 patients with T2DM in mean age 58.4 ± 7.83 years. The duration of diabetes was 3.3 ± 0.34 years. Mean blood pressure: SBP 131.76 ± 1.4 mm Hg, DBP 83.02 ± 11.3 mm Hg.

Carbohydrate metabolism was assessed by fasting plasma glucose and Glycated hemoglobin (HbA1c) measuring.

TL and telomerase activity (TA) was assessed by quantitative polymerase chain reaction (PCR).

Intima-media thickness (IMT) and plaque presence (PP) were determined by ultrasonography in both left and right carotid arteries. Arterial stiffness (AS) was appreciated by aortic pulse wave velocity (PWV) measuring by SphygmoCor (AtCor Medical).

Endothelial dysfunction was assessed by flow-mediated endothelium-dependent dilation (FMV) in response to reactive hyperemia and endothelium-independent vasodilation in response to nitroglycerine (NDV); by homocysteine, von Willebrand factor measuring.

Oxidative stress was assessed by malondialdehyde measuring, inflammation was estimated by interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen measuring.

Results: All patients were divided into 2 groups by the median of TL (9.75): «short» telomeres (mean TL 9.19 ± 0.32) and «long» telomeres (mean TL 9.97 ± 0.43). Patients were similar in blood pressure and HbA1c. Vessels changes were more pronounced in patients with «short» TL than patients with «long» TL: PWV 14.11 ± 3.22 m/s vs 11.78 ± 3.26 m/s ($p=0.016$), IMT 1.00 ± 0.15 mm vs 0.84 ± 0.16 mm ($p=0.0010$), PP 2.63 ± 0.31 vs 1.36 ± 0.26 ($p=0.0032$), FMV 7.93 ± 3.40 vs 10.95 ± 3.10 ($p=0.0022$), NDV 12.63 ± 4.25 vs 15.68 ± 4.51 ($p=0.0186$), homocysteine 14.39 ± 2.68 mkmol/l vs 12.32 ± 2.52 mkmol/l ($p=0.0077$), von Willebrand factor 120.0 ± 36.7 % vs 87.91 ± 31.76 % ($p=0.0020$). There were now no significant differences in AT between two groups. We found significant increasing of oxidative stress and chronic inflammation in diabetic patients with «short» TL:

malondialdehyde 3.43 ± 1.06 mkmol/l vs 2.94 ± 0.87 mkmol/l ($p=0.058$); CRP 9.43 ± 2.01 mg/l vs 3.30 ± 0.37 mg/l ($p=0.0062$).

Correlation analysis showed in diabetic patients significant association between telomere length and next parameters: PWV ($r=-0.50$, $p=0.0003$), IMT ($r=-0.39$, $p=0.0059$), FMV ($r=0.49$, $p=0.0003$), NDV ($r=0.41$, $p=0.0035$), fasting plasma glucose ($r=-0.42$, $p=0.0027$), CRP ($r=-0.40$, $p=0.0039$), reduced TA ($r=-0.32$, $p=0.0353$), homocysteine ($r=-0.39$, $p=0.0063$), von Willebrand factor ($r=-0.42$, $p=0.0026$).

Conclusion: In patients with T2DM and "short" telomeres signs of vascular aging, chronic inflammation and oxidative stress were more pronounced. Perhaps long telomeres protect patients with short duration of diabetes from the damaging effect of oxidative stress and chronic inflammation, leading to the development of subclinical atherosclerosis and increased vascular stiffness.

Management of Type 2 Diabetes Mellitus in Adolescents and Young Adults in Primary Care **Ana Guadalupe Olivares Loro**

The prevalence of type 2 diabetes (DM2) diagnosed in childhood and adolescence is currently increasing, and is characterised by a rapidly progressive decline in beta-cells and insulin resistance. Physical inactivity and obesity are the main risk factors for its development. Diagnostic criteria are similar to those used in adults, although HbA1c as a diagnostic method is questioned. Diabetes-related complications are more aggressive than in adults. Diabetic nephropathy is the most frequent complication in the young population and macrovascular complications appear early, leading to high mortality rates.

Healthy lifestyles are the basis of the treatment, and metformin, insulin and liraglutide (approved by FDA for its use in the United States) are the pharmacological options indicated in this population. It is important to establish models of health care transition from paediatric to adult care to ensure continuity of care and avoid patient disengagements.

Is the decision on the use of biosimilar growth hormone based on high quality scientific evidence? A systematic review

Linda Fryklund, Martin Ritzén, Göran Bertilsson, Marianne Heibert Arnlind

Background: The authors carried out a systematic and critical review of the scientific literature regarding the possible development of neutralising antibodies developed in patients treated with growth hormone biosimilars as compared to the reference drug. As a consequence, we discovered two major issues namely the poor quality of the comparative clinical trials and the poor quality of the antibody assays used during the trials.

Methods: The literature review was performed according to the principle of the Cochrane Collaboration and SBU. The electronic literature search included the databases PubMed, EMBASE and The Cochrane Library up to December 2012. Two independent reviewers assessed abstracts and full-text articles.

Results: The search identified 1 553 abstracts related to the subject. Only six articles contained data on biosimilar growth hormone or antibody results obtained with appropriate

methods. None of the studies fulfilled the criteria for high quality randomised controlled trials. Qualitative rather than quantitative assays were used for monitoring antibody formation.

Conclusions: It is our firm opinion since, that biosimilars are not identical, emphasis must be placed on the quality of the comparative clinical trials performed and the quality of the analytical to guarantee patient safety. Clinical trials should follow established quality rules for controlled comparative randomised clinical trials.

Understanding Human Physiological Limitations and Societal Pressures in Favor of Overeating Helps to Avoid Obesity

Katarina T. Borer

Can behavioral approaches including timing of meals, of exercise with respect to meals, and macronutrient modifications, ameliorate or prevent insulin resistance in the face of human physiological limitations and social barriers that promote obesity? Insulin resistance (IR) is the major underlying link between physical inactivity, unhealthy eating habits, and the metabolic syndrome (MS). In developed societies, and to an increasing extent in developing ones as well, mechanization in transportation and in activities of daily living have dramatically reduced physical activity. Human obesity is facilitated by limitations of human physiology that include an absence of a mechanism regulating adult body weight coupled with a large capacity to accumulate body fat and to increase stomach size by binging. Many environmental societal features contribute to obesity by facilitating overconsumption of energy-rich and nutrient-poor diet. Obesity has tripled in the US in the past 50 years as a consequence of the combination of low activity and overeating. Obesity leads to insulin resistance and precipitates the MS. Insulin resistance is a pathology which prevents the hormone to efficiently carry out its four actions, maintenance of (1) normal blood glucose levels through increased glucose uptake by the muscle and (2) by stimulation of carbohydrate oxidation, (3) suppression of excess glucose and free fatty acid release into circulation, and (4) control of glycogen, fat, and protein synthesis. Metabolic syndrome is a cluster of physiological abnormalities that include excessive concentrations of blood glucose, insulin, and lipids that facilitate ectopic fat deposition, malfunction of a number of vital organs, and progression to cardiovascular disease and type 2 diabetes. Although it has been known for some time that increased physical conditioning will partially reduce some symptoms of MS, simply improving physical fitness is not sufficient to fully reduce IR. Fortunately, two behavioral modifications have proven to be very effective in reducing IR, and the third one to ameliorate or prevent obesity. A change in dietary macronutrients reduces IR by 30% within 24 h after eating three modified meals. A modification in the timing of meals and moderate-intensity exercise reduces IR by 50% within one day of exercise. A deliberate reduction in the number of hours with access to food leads to weight loss or prevents excessive weight gain. The details of the first two behavioral experiments and the probable mechanisms of action of all three behavioral modifications will be discussed and may provide a useful non-pharmacological approach to amelioration or prevention of IR and MS.

Effect of antithyroid drugs on the occurrence of antibodies against type 2 deiodinase (DIO2)

Ildikó Molnár

Graves' hyperthyroidism is an organ-specific autoimmune thyroid disease characterized by endocrine and autoimmune features. The overproduction of thyroid hormones (T3 and T4) is mediated by type 1 (DIO1) and type 2 (DIO2) deiodinase enzymes via the conversion of T4 to T3. Antithyroid drugs inhibit the thyroid hormone synthesis via blocking deiodinase activities, iodination and the coupling mechanisms.

In our study, the occurrence of autoantibodies against cys- and hom-peptides corresponding to amino acid sequences of DIO2 was investigated in 78 patients with Graves' disease and 30 controls. The frequency of anti-peptide antibodies was studied with respect to thyroid function, the treatment of antithyroid drugs [methimazole (MMI), propylthiouracil (PTU)] and the presence or absence of ophthalmopathy,

In euthyroidism, the frequency of cys-peptide antibodies was greater than those found by hom-peptide ones. Cys-peptide antibodies demonstrated an inverse correlation with serum FT4 levels. Only the presence of both anti-peptide antibodies was able to decrease anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibody levels in all Graves' patients and in patients with ophthalmopathy. Anti-peptide antibodies showed a strong relationship with TSH receptor antibodies. MMI treatment in the presence of cys-peptide antibodies resulted more decreased serum FT3 levels and ratio of FT3 to FT4. Anti-peptide antibodies were rather connected to the new onset of Graves' disease than its relapse.

In conclusion, the occurrence of anti-peptide antibodies corresponding to DIO2 amino acid sequences are present in Graves' hyperthyroidism. Their presence was connected to reduced anti-TPO and anti-Tg antibody levels, as well as lower TSH receptor antibody and FT3 levels during MMI treatment.

GASTROENTEROLOGY

Recent Advances in the Regulation of Cholangiocyte Proliferation and Function During Extrahepatic Cholestasis

Romina Mancinelli

Cholangiocytes, the bile duct epithelial cells, line the intrahepatic and extrahepatic biliary system of the liver. They represent the target cells of a number of human cholestatic liver diseases, known as cholangiopathies (1). A number of studies have defined three types of cholangiocyte proliferation: "typical", "atypical" and oval cell proliferation (2). "Typical" cholangiocyte proliferation is a hyperplastic reaction, which induces an increase in the number of intrahepatic bile ducts around the portal areas. The "atypical" proliferation is commonly seen in patients with prolonged cholestatic liver diseases such as primary sclerosing cholangitis (PSC) or primary biliary cholangitis (PBC) with a characteristic irregular proliferation of intrahepatic bile ducts sprouting into periportal and parenchymal regions. The third one, oval cell proliferation represents the growth of the stem cell compartment of the liver characterised by a disorganised proliferation of biliary structures with a poorly defined lumen (3). Several studies have provided insights into the key mechanisms that regulate the proliferation and function of cholangiocytes during the pathogenesis of

cholestatic liver diseases (4). In the present work, we have summarised the most important findings with a focus on those performed in the animal model of extrahepatic bile duct ligation (BDL). Firstly, we provide a relevant background on the biliary ductal system. Then, we proceed with a general discussion of the factors regulating biliary proliferation in the cholestatic liver injury: In fact, various pathways and axes are associated with cholangiocyte proliferation and response to biliary damage. These pathways and axes could be potential therapeutic targets for novel treatments.

GENETICS

Management of Hemophilia: Recent advances

Dr Samriti Gupta

Hemophilia is an inherited disorder characterized by clotting factor 8 or 9 deficiency and bleeding manifestations, hemoarthrosis being the most characteristic. The mainstay of the treatment is replacement of deficient clotting factor. However, despite widespread availability of effective standard factor concentrates, people with haemophilia experience huge burden of treatment, recurrent breakthrough bleeding and development of progressive arthropathy as well as high risk of development of inhibitors which pose challenges to the current standard treatment. Various advances have been made in last two decades in the field of haemophilia management which include long acting factor products, non factor agents including monoclonal antibodies as well as therapies with curable potential like gene therapy which may mitigate the challenges of standard factor therapy. These advances, in combination with better diagnostics, are now enabling clinicians to improve the standard of care for people with haemophilia. Though they may appear exciting treatment options, their use should be balanced with their utility and adverse effects. More data is required regarding the efficacy and safety of these newer modalities as well as long term sustainability in case of gene therapy, especially in children. Advances have also been made in management of most debilitating complication of haemophilia i.e. hemophilic arthropathy. Use of modalities like musculoskeletal ultrasound and MRI have the potential for early detection of arthropathy. Scores like FISH are helpful for functional assessment of musculoskeletal function in these patients. Appropriate use of factor concentrates, screening for inhibitors and judicious use of other newer modalities to treat and prevent bleeding along with physiotherapy and rehabilitation help in improving the quality of life in people with hemophilia.

Keywords: Hemophilia, factor concentrates, advances, hemophilic arthropathy, musculoskeletal assessment, physiotherapy

A novel transfection method for short interference RNA with the lipid-like self-assembling nanotube, A6K

Daizo Yoshida, K Koketshu, K. Kim and A. Teramoto

The aim of the present study was to develop a novel transfection method for short interference RNA (siRNA). A nanotube with surfactant activity, A6K, consisting of six alanine residues and a hydrophilic head, lysine, was compared to the conventional cationic transfectant reagents, siFECTOR and Lipofectamine 2000. The cytotoxicity for the human

glioblastoma cell lines, U87MG, A172, and T98G was examined with the MTS assay. The transfection efficiency was analyzed with FITC-labeled siRNA targeting MMP-2 mRNA by fluorescent activity on microscopy. The ultrastructure of A6K was evaluated by electron microscopy.

The level of cytotoxicity associated with A6K, in the U87MG cells (IC₅₀, 285.5 µg/ml) was significantly lower than with siFECTOR ((IC₅₀, 25.03µg/ml) and Lipofectamine 2000 (IC₅₀, 42.49 µg/ml). The transfection efficiency for the siRNA was increased in a dose- and time-dependent fashion. The relative expression of MMP-2 mRNA to β-actin was reduced in a dose-dependent manner by real-time RT-PCR analysis. The ultrastructure of the A6K was transformed to micelle formation when mixed with the siRNA.

The lipid-like self-assembling peptide, A6K, has genes in the micelle associated with the hydrophilic tail. This transfection method is a novel and stable technique with lower cytotoxicity than the current standard methods.

Coevolution Theory Of The Genetic Code At Age Forty

J. Tze-Fei Wong , Hong Xue

Molecular biology, addressing the fundamental relationships between nucleic acids and proteins, has been translated into stunning breakthroughs in genome-based molecular medicine over the past decades. Moreover, the evolutionary roots of a wide spectrum of the elements of molecular biology have been either resolved or brought to near resolution:

(a) Based on the Coevolution Theory, the 20 proteinous amino acids are known to enter into the genetic code in two phases, viz. Phase 1 amino acids found on primitive Earth, and Phase 2 amino acids derived from amino acid biosynthetic pathways.

(b) Instead of being a frozen accident, the genetic code has now been altered experimentally to reject some old, or admit some novel, amino acids in synthetic lifeforms.

(c) The oldest living organism on Earth is identified to be *Methanopyrus kandleri* which inhabit marine hydrothermal vents, suggesting that comparable vents on other planets might also be attractive sites to look for life.

(d) Evidence suggest that the earliest genes consisted of functional RNA molecules which managed to keep replicating in the presence of their metabolite ligands while non-functional RNA molecules would perish in the form of double helices that failed to unwind to replicate.

(e) The future genetic codes will enable the introduction of novel types of macromolecules into body tissues.

(f) Search for genetic interactions between human host and intestinal microorganisms need to be intensified to find microorganisms that could contribute to the fight against chronic diseases.

More research has to be directed toward the elimination or minimization of methanogenic archaea among the ruminant microbes in order to reduce emission of methane by ruminant farm animals.

Epilepsy Genetics: Advancements in the Field and Impact on Clinical Practice

Yael Shiloh-Malawsky

During the first decade of the 21st century, epilepsy related genes were discovered. These genetic discoveries opened the field of epilepsy genetics and advanced our understanding of the cellular mechanisms involved in epilepsy. Over the subsequent ten years, the

availability of clinical genetic testing along with rapidly growing knowledge of epilepsy genetics transformed patient care. This has dramatically changed how childhood onset epilepsy is treated. This new genomic era offers a great opportunity for the advancement of health outcomes and epilepsy research. It has also created new demands and challenges for physicians, requiring specialized expertise in epilepsy genetics in order to provide best care for patients and their families.

The Genetic and Pharmacogenomics Literacy of The Community in The United Arab Emirates

**Azhar T. Rahma, Ifat Elbarazi , Bassam R. Ali , George P. Patrinos , Luai A. Ahmed , Mahanna Elsheik , Maram , Farah Afandi, Aysha ,Aminu Abdullah ,and Fatma Al Maskari
United Arab Emirates**

Introduction: Public Health Genomics is a recent trend in the discipline of public health comprising the use of genetic epidemiology, biostatistics, health policy, health education, and state-funded programs focused on surveillance and prevention of heritable disorders as well as provide the necessary set up needed to achieve the ultimate aim of improving population health. Insufficient genomics education and lack of genomics awareness among the general public are two perspectives which hinders the smooth incorporation of genomic medicine into clinical practice. we aim to assess the general public genomics awareness in United Arab Emirates.

Method: We conducted a cross sectional study design using a validated questionnaire to assess the knowledge attitude and interest in Genomic medicine and pharmacogenomics among community in United Arab Emirates (UAE). The questionnaire was in both languages: Arabic and English to allow recruiting a representative sample, The questionnaire is composed of three sections : socio-demographic data as well questions to estimate the relative risk of a disease using pictograph to assess their genetic literacy as well as questions related to their reliable source of information regarding genomic and pharmacogenomics and if they are willing to pay out of pocket for the test as well as their willing to be part of a research and/or genomic bank. We piloted among 57 participants, and a total of 915 responded to our survey. We used SPSS for statistical analysis chi-square test and ANOVA. This research had been approved by the social science research ethic committee of ERS_2017_5671.

Results: 80 % of our sample is female, and we had good representation of both the citizen of UAE and the expatriates (53% vs 47%). 63% are married.53% of the community trusted governmental genetic laboratories over abroad laboratories.76% of the community are willing to undertake a genetic test to know their genetic susceptibility to diseases. 32% are willing to proceed with marrying partner with higher risk of dominant and recessive disease. 63% believe that genetic tests are expensive. 17% thinks that religion doesn't endorse genetic medicine. Only 38 % of the community recognize the role of genetic counselors and only 34% will disclose results of their disease susceptibility to their children.

Conclusion: The detailed assessment and exploration of the knowledge and attitudes of the community will serve as bottom-up approach to guide the strategic and logistic planning of implementation of personalized medicine in UAE. Cultural and religious aspects had to be addressed to streamline the implementation process.

Genomic Bases of Symptomatic Dimensions in OCD**María Alemany-Navarro**

The genomic characterization of OCD has been mainly approached by genome-wide association analyses (GWAS)¹⁻³. However, the heterogeneity of the disorder has seemed to hamper the identification of replicable single-nucleotide variants (SNVs) associated with OCD. The existence of multiple symptomatic profiles has been consistently proven in OCD from clinical, heritability, neurobiological, and genetic approaches⁴⁻⁸. In this study, we analyzed genetic associations with the presence of different OCD dimensions from an exploratory genomic approach at SNP-, gene-, gene ontology-, and pathway-levels in a final sample of 399 OCD probands. OCD dimensions were assessed with the Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS9). Gene-based analyses included common and rare SNVs, and gene ontology and pathways were analyzed from the gene-based analyses' results. No SNP reached genome-wide significance, but suggestive signals ($P < 1E-05$) were observed for Aggressive, Order, Contamination, and Hoarding. Order Dimension presented one single peak of association formed by 6 exonic SNPs distributed in two LD clusters covering IPO8 and CAPRIN2 genes in chromosome 12. Gene-based analyses reported two genome-wide associated genes: CPE (Aggressive Dimension; $P = 4.42E-06$), and SETD3 (Hoarding, $P = 1.89E-08$). Enrichment analyses reported biological processes and/or pathways associated with Aggressive (Zinc ion response and Peroxisomal lipid metabolism; $FDR = 0.002; 0.020$), Order (Sphingolipid signaling pathway; $FDR = 0.025$), Sexual/Religious (G alpha (12/13) signaling events; $FDR = 0.032$), and Hoarding (two clusters formed by metabolic processes and anion transport pathways) dimensions. The specific genomic signals found for the different OCD dimensions align with the differences in heritability, genetic, and neurobiological aspects previously reported for different symptomatic profiles in OCD. Further research in greater samples and from different genomic approaches is necessary to elucidate the genetic characterization of the different OCD dimensions.

Genome-wide profiling and haplotyping of cell-free DNA enables non-invasive prenatal screening for aneuploidy and monogenic diseases**Huiwen Che**

In the past few years, technological advances have permitted the use of cell-free DNA (cfDNA) as a minimally invasive biomarker for the detection of disease. Non-invasive prenatal testing (NIPT) based on the cell-free fetal DNA (cffDNA) analysis has been shown to be very accurate for the screening of the most common fetal aneuploidies. While some studies have also been exploring the potential of cffDNA to detect monogenic diseases, the analysis of monogenic diseases is less accessible. With increasing societal awareness of genetic diseases, the increase in in vitro fertilization methods and the rapid uptake of carrier screening, there is an increasing need for generic approaches for non-invasive prenatal screening. Here, we present a cost-effective, generic approach allowing for simultaneous non-invasive prenatal testing for any monogenic disease as well as aneuploidy. The approach presented can be easily adopted in genetic testing laboratories

Multiple and Overlapping Functions of Quorum Sensing Receptors in the *Bacillus cereus* group.

Mayra de la Torre

Quorum sensing (QS) refers to cell-to-cell communication processes that microbes use to interact with each other and regulate collective behaviors, including pathogenesis. QS depends on the synthesis and secretion of small signaling molecules, which bind to specific protein receptors for regulating gene expression. Gram positive bacteria use mainly peptides as signaling molecules, while Gram negative utilize homoserine lactones or other molecules whose production depends on S-adenosyl methionine.

Dozens of clinically relevant bacteria have been shown to use QS to regulate the production of virulence factors and toxins. Here, we focus on the *Bacillus cereus* group, which includes potential pathogenic species of *B. anthracis*, *B. cereus* and *B. thuringiensis*. *B. cereus* produces toxins, causing emetic and diarrheal syndromes; *B. anthracis* causes anthrax, an acute infectious disease of wild and domestic animals, and infects humans; *B. thuringiensis* is highly pathogenic for insects, but is rarely associated with disease in humans. Here, first we outline the QS systems that include the cytoplasmic receptors PlcR, Rap and NprR in this bacterial group. PlcR is a pleiotropic transcriptional regulator controlling expression of 45 genes including enterotoxins, cytotoxins and hemolysins; Rap proteins modulate sporulation setup, transfer of mobile genetic elements and competence, through protein-protein interactions; NprR is a bifunctional protein, acting as a response regulator for sporulation initiation and as a transcriptional regulator. We discuss how the multiple functions of these regulators are interconnected, and the structural changes that allow Rap and NprR switch between functions and connect distinct signal pathways. Finally, we will speculate on the relevance of interconnection among signal transduction pathways, as well as multifunctionality and redundancy of QS systems for bacterial species adaptation and survival in its environment.

Paleolithic genetic link between Southern China and Mainland Southeast Asia revealed by ancient mitochondrial genomes

Fan Bai

Since Southern China is the crossroads of East and Southeast Asia, the genetic history of Southern East Asian is important for understanding the early human genetics and population movements between East and Southeast Asia. However, the genetic history of Southern East Asians is unclear, especially prior to the Neolithic period. Only a few ancient genomes were published in this region, partly due to the poor preservation of ancient DNA in the hot and humid climate. Here, we will introduce the recently published ancient genomes of Dadong and Longlin individuals dating ~11,000 years old in Guangxi and Guizhou which are the oldest ancient genome data in southern China. Integrating these two mitochondrial genomes and published data, we characterized M71d, a new subhaplogroup of haplogroup M71. Our results suggest a possible early migration between Southern China and mainland Southeast Asia by at least 22,000 BP. Moreover, Longlin individual's nuclear genome revealed a previously unsampled deeply diverged East Asian ancestry in Guangxi.

All these results show how these ancient genomes reveal the complex human population history in this region over the past ten thousand years.

Infrared Laser Heating Applied to Nanopore Sensing for DNA Duplex Analysis

Joseph E. Reiner

Resistive pulse nanopore sensing is a single molecule technique of great interest for a variety of applications. It is most notable for its advancement of 3rd generation DNA sequencing and it has been utilized in a wide variety of situations with emphasis on portable device applications for remote analysis. The principle of operation is straightforward and it is based on the Coulter-counter principle applied at the nanoscale. Briefly, a nano-sized hole is formed in a partition that separates two chambers filled with electrolyte solution. An applied transmembrane potential, drives ionic current through the pore and gives rise to a stable, open-state current. Analyte molecules enter the hole and reduce the flow of current thus giving rise to well-defined current blockades. Typical measurements analyze the magnitude and duration of these blockades to infer information about the molecules of interest. To further expand the sensing capabilities of the nanopore sensor, we have demonstrated the use of infrared laser heating to rapidly control the solution temperature in and around the pore. This enables a more complete exploration of the escape free energy barrier. Specifically, temperature control allows us to independently measure the enthalpic and entropic components of the free energy barrier against escaping from the pore and this in turn provides a more detailed understanding of how molecules interact with the pore. The goal is to utilize this information to design more effective sensing devices. This presentation reports on our proof-of-concept heating demonstrations with double stranded DNA, polyethylene glycol and a variety of water-soluble peptides. We will also discuss future implications of the technology for sensing applications.

GLIOBLASTOMA GLOBAL PUBLIC HEALTH

The Study of Some Physiological and Biochemical Indices as Predictive Markers of an Unfavorable Outcome of COVID-19 Pneumonia

Svetlana Rogacheva

The study is aimed to determine via mathematical methods the significance of some physiological and biochemical indices as predictive markers of an unfavorable outcome of pneumonia caused by the SARS-CoV-2 virus.

For this purpose a retrospective analysis of the clinical data of the COVID hospital patients was carried out. A random cohort of patients with COVID-19 pneumonia numbered 209 people. In total 15 indices were studied: the physiological characteristics of patients described during hospitalization, the indices of blood coagulation, C-reactive protein (CRP) level, urea and creatinine concentration in blood. The analyzed parameters were categorized relative to the reference intervals of physiologically normal values. Correlation analysis was carried out using categorical data on the disease outcome. The algorithms for calculating statistical characteristics, as well as results visualization, were implemented in the Python language. The significance of differences in signs when comparing patient groups

was assessed using the Pearson's χ^2 test with Yates' correction. The reliability of the results was assessed using one-way analysis of variance using Fisher's F-test. The studies were carried out in accordance with international and Russian ethical principles and norms.

There were revealed maximal correlation coefficients between the level of blood oxygen saturation (-0.43), as well as the respiratory rate (0.43), and a mortal outcome. For patients over 50 years of age, oxygen saturation below 80% at the time of hospitalization turned out to be a marker of mortality. It was shown that D-dimer blood level above 625 ng/mL and an increase in the concentration of creatinine and urea in the blood by 2.5 times are associated with mortal outcomes of the old patients. No correlation was found between the CRP level and the disease outcome. The effect of corticosteroids on the disease outcome was analyzed in patients with different CRP levels. It was found that while using corticosteroids, the mortality rate in patients with CRP \leq 12.5 mg/L is 2.7 times higher than in those with CRP $>$ 12.5 mg/L ($p < 0.01$). Thus, the use of adequate mathematical methods made it possible to define more precisely some mortality-associated indices in patients with COVID-19 pneumonia.

Impact on morbidity and mortality due to COVID-19 according to the regulations on the use of face mask

Marlon Edu Saavedra-Delgado

Currently, the mask represents an incomparable symbol, whose value went from clinical work to impact the containment of the spread of the SARS-CoV-2 virus. Our work aims to establish the impact of mask use policies on COVID-19 morbidity and mortality. The policy variables for the use of face masks were obtained from the page of the scientific movement # masks4all and analyzed with the number of infections and deaths published by the Johns Hopkins University resource center and EndCoronavirus.org. The associations of the mask use policy with total cases (p 0.01), cases per million (p 0.04) and deaths per million inhabitants (p 0.02), were statistically significant; the associations of the variables with the trend of the epidemiological curve were also statistically significant (p 0.00).

Neoliberalism: what it is, how it affects health and what to do about it.

Dr Philip Bagshaw and Dr Pauline Barnett

Since the 1970s, neoliberalism has been the dominant economic and political philosophy among global institutions and some Western governments. Its three main strategies are: privatisation and competitive markets; reduced public expenditure on social services and infrastructure; and deregulation to enhance economic activity and ensure freedom of 'choice'. Generally, these measures have negatively affected the health and wellbeing of communities.

In the 1980s and 1990s successive New Zealand (NZ) governments introduced extreme neoliberal reforms to the economy and public services, including healthcare. This led to widening income inequalities and an unequal distribution of the 'determinants of health', burdens borne disproportionately by children, the poor, and by Māori and Pacific people. Failure to regulate for the protection of citizens undermined health and safety systems, the security of work and collective approaches to health improvement. Health reform in the 1990s was touted as "a shining example" internationally of how to modernize public healthcare. We feel ashamed to have been part of this regrettable experiment. Limiting

health expenditure widened inequalities in access to services, and managerialist restructuring subverted the service culture of the health system, with dire consequences.

There has been some retreat from neoliberalism in NZ in recent years but, despite this, it lingers covertly in our institutions and could be described as an 'embedded norm', with Covid-19 dramatically aggravating prior inequities. The need now is to move policy attention from equality of health inputs to equity of health outcomes. This will require: (i) redirection of resources and a focus on 'upstream' health initiatives; (ii) recognition that social investment returns benefits far in excess of costs; and (iii) adequate funding of services needed to ensure social and cultural equity goals are achieved.

We see some hope with planned health policy changes for NZ. Amongst these changes, there will be health co-governance with the indigenous population, which will have a separate funding stream. However, there is still no explicit recognition of the utility of Public Health as an upstream approach to promoting health equity or the important principle of 'proportionate universalism' to provide a strategic way of balancing targeted and population approaches.

Global Public Health Practice and Policy: Learning Lessons from the COVID 19

Robert Drury

This keynote panel will identify key public health lessons available from experiences with the COVID-19 pandemic. A brief introduction will be followed by discussions by Dr. Christopher Murray, Director of the Institute for Health Metrics and Evaluation at University of Washington and Dr. Michael Osterholm, Director of the Center for Infectious Disease Research and Prevention at University of Minnesota. While great strides have been made with medical interventions such as vaccines and medications, some of the major difficulties and drawbacks to current global public health interventions will be identified. In particular, the central role of human compliance with public health behavioral strategies and prescriptions will be discussed as well as other factors that limit the application of evidence-based scientific knowledge.

Covid-19 in Patients with Rheumatic Diseases: A Single Center Experience

Rowsan Ara, Rashedul Hassan Ishrat Jabeen, Tonmoy Biswas, Syed Atiqul Haq

Background: Patients with rheumatic diseases are susceptible to infections. Some evidence suggested that the prevalence of Covid-19 was higher among the rheumatic patients. The effect of Covid-19 in rheumatic patients is not yet clear. The aim of this study was to find out effects of Covid-19 in patients with rheumatic diseases.

Methods: This cross sectional observational study was conducted in Green Life Center for Rheumatic Care and Research from June 2021 to December 2021. The patients with known rheumatic diseases came for follow up in the center with a history of Covid-19 infection confirmed by positive RT-PCR for SARS COV 2 from oral/nasopharyngeal swabs or positive CT scan findings of chest were included. Those who were suspected but not confirmed, patients with non-inflammatory arthritis like osteoarthritis, NSLBP, FMS were excluded. Sample size was 225. Patient's interview and medical records were reviewed by the investigators. Data were collected in a preformed data sheet and analyzed by using SPSS windows version 25.

Results: Out of 225 patients, 168 (74.7%) were female and 57 (25.3%) were male. Mean \pm SD of age was 46.8 ± 14.8 years. Most common rheumatic disease was spondyloarthritis (83), followed by RA (77), SLE (46) and others (19). Most of them had mild disease 197 (87.5%) and did not require hospitalization. Twenty-eight (12.4%) patients had moderate to severe disease required hospitalization. Average duration of hospitalization was 7.8 ± 5.4 days. Among them 8 patients required high flow nasal cannula and 2 patients required ventilatory support.

Covid-19 period and competences in higher education- study on cooperation and assertivity

Sónia Galinha

Within this pandemic associated with Covid-19, psychological health occupies a prominent place as a result of a situation of forced isolation. Mental health, it is ever so pressing to know and preserve, particularly in the young adult. These changes affect more vulnerable population groups among them students. Students express and reflect their psychological health needs, their beliefs, competences and abilities, functionalities, weaknesses, vulnerabilities, and their risks and dangers within the framework of global public health. Assertiveness is conceived as a bilateral behaviour that emphasizes the importance of considering the desires, thoughts and feelings of both the sender and the recipient of the assertive message, predictive of academic success. Cooperation is conceived as the ability to jointly operationalize knowledge, attitudes and skills with a view to achieving a common purpose. OBJECTIVE to present the results of the application of the Global Assertiveness Assessment Scale (EAGA) and the findings levels of the Global Cooperation Assessment Scale (EAGA), applied in the pandemic period in higher education. SAMPLE The study used a non-probabilistic sample for convenience of 101 Portuguese higher education students. INSTRUMENTS Global Assertiveness Assessment Scale (EAGA) and Global Cooperation Assessment Scale (EAGC), Likert. ADMINISTRATION Online administered survey SOCIODEMOGRAFIC PROFILE Most of the participants are females (88%). The average age is 21.25 years old ($\pm 3,86$ years) with the youngest and oldest student respectively 19 and 27 years old. The majority of students (50%) live with their families, 26% with their friends, 13.5% other choose, and the lowest percentage of students lives in a residence/rented room (10.6%). Most of respondents are single (98%). The median travel time from the student's address to the university is 20 minutes (inter-quartile range: 40 minutes). Additionally, it appears that in students who travel daily distances in each route greater than 30 km, 72% do so in public transport, the rest being by their own vehicle. Approximate distance, in Km, of the route (one way) that the student takes daily from his address to the educational institution during the class period: 54% [0;5[km. Sociodemographic variables were also used, which seemed promising in contextualizing, interpreting, and discussing the results. The value of the sample mean obtained at EAGA=31 (± 5.53), thus revealing a high assertive competence who attend higher education and EAGC=35 (± 6.5), thus revealing a high cooperation. We argue that signaling and monitoring of less favorable cases detected is pertinent. The impact of SARS-CoV-2 on global public health has been profound. The monitoring of the student population using these scales is an element of greater value because, besides its easy applicability and low cost, it allows for the evaluation of health in this population group.

New multicentric studies, seeking to assess the geographic role (inside and outside borders) in assessing the levels of assertiveness and cooperation of students from higher education, well-being, soft skills and their relationship with peers, studying how we can reduce the global burden of diseases and preventing consequences of the next pandemic. Acknowledgements UIDB/04083/2020 - 21-CIE-RB020-UIDB.

Novel strategies to contain the spread of methicillin (oxacillin)-resistant *Staphylococcus aureus* strains: an in vitro analysis.

Barbara Azzimonti

Staphylococcus aureus is a human skin commensal resident. It may behave as an opportunistic pathogen following dysbiotic stimuli and contribute to the induction of local inflammatory disorders such as atopic dermatitis and psoriasis, and of systemic diseases like valvular- and endo-carditis, osteoarthritis, and pulmonary infections. Its leading role in the onset and progression of skin carcinogenesis, with serious consequences on people health, life-expectancy, and sanitary expenditure, has been recognized.

This bacterium is also quickly acquiring resistance to several antibiotics; in fact, its spread is representing a critical threat, whose contrast requires new, more targeted, and free from side effects prevention and treatment strategies.

In this study, the cell-free supernatants (CFSs) were produced by two selected lactic acid bacteria (LAB) in a standard meat-based medium and an animal derivatives-free broth; their efficacy in the containment of a methicillin (oxacillin)-resistant *S. aureus* (MRSA) strain was analyzed by in vitro assays.

CFSs role was assessed with respect to their capability to affect the MRSA viability, its metabolic status, aggregation, and biofilm formation. CFSs composition was also examined through high-resolution mass spectrometry and gas chromatography for the short-chain fatty acids and lactic acid content, and protein characterization.

The results obtained by these analyses demonstrate that beneficial bacteria CFSs represent a natural strategic prevention and curative instrument to counteract diseases related to microbial dysbiosis.

A machine learning approach to identify bacterial strains in microscope images.

Helena Todorov

The development and functioning of multi-species microbial communities is at the center of many studies, as the microbiome has been shown to play a role in many health-related mechanisms. Spatial behaviours and interactions can be studied through time-lapse microscope imaging, where cells can be followed in real time. However, only a small number of different bacterial strains can be studied together, since each strain needs to be tagged with a specific fluorophore and there is only a restricted number of fluorophores that can be easily deployed at the same time in live microscopy. Moreover, some bacteria cannot be easily tagged and thus remain difficult to identify by epifluorescence microscopy. To circumvent these issues, we aim at training machine-learning algorithms to recognize different strains from non-fluorescent (phase-contrast) images. We built a pipeline that allows to extract lineage related features on thousands of single cells in a fast and automated way. We used the resulting features to train a random forest classifier that is now able to identify strains in non-fluorescent time-lapse images. On an example of four soil-

derived isolates: *Pseudomonas putida*, *Pseudomonas veronii*, a *Lysobacter* and a *Rahnella* that we cultured on agarose-containing microscope growth patches to microcolonies, our classifier was able to successfully differentiate each strain in monoculture with an average accuracy superior to 90%. The classifier also shows very promising results when applied on images of co-cultures of the different strains, thus paving the way to studying bacterial strains without staining in large co-culture studies.

HEMATOLOGY

Treating Vaso-occlusive Crises in Sickle Cell Disease with Hemopexin

John Belcher

Anemia, hemolysis and vaso-occlusion are the hallmarks of sickle cell disease (SCD). The release of hemoglobin (Hb) and heme into the intravascular milieu can promote inflammatory responses with vasculopathy, leukocyte, platelet and endothelial cell activation, thrombosis, and even renal injury. Nature defends the vasculature from hemoglobin/heme by plasma haptoglobin and hemopexin, which tightly bind free hemoglobin and heme, respectively. Haptoglobin-hemoglobin and hemopexin-heme complexes bind to CD163 and CD91 receptors found primarily on macrophages and hepatocytes respectively and are taken up by receptor-mediated endocytosis. We examined serum haptoglobin and hemopexin levels and biomarkers of hemolysis in hemoglobin SS, SC and AA children in Brazil. A cross-sectional study was performed including 272 unrelated steady-state children with SCD; 179 with sickle cell anemia (HbSS) and 93 with hemoglobin SC disease (HbSC), all seen at the Foundation of Hematology and Hemotherapy of the Bahia state (HEMOBA), in Brazil. The study also included 28 healthy children (HbAA) selected from the Clinical Laboratory of the Pharmacy School (Federal University of Bahia). The AA controls were selected and matched to cases by age, gender, and African ethnic origin. All patients were in steady-state that was defined as an absence of any blood transfusion and acute events for a period of four months prior to blood sampling. Evaluating the haptoglobin and hemopexin levels, we found that SS and SC patients have significantly lower haptoglobin and hemopexin levels ($SS < SC < AA$) than AA controls. Similarly, SS and SC patients have lower hemoglobin ($SS < SC < AA$) than AA controls. Total and indirect bilirubin followed a similar pattern ($SS > SC > AA$). These data suggest more hemolysis in the following pattern: $SS > SC > AA$. Hemopexin was negatively correlated to LDH ($r = -0.509$, $p < 0.001$) and plasma heme ($r = -0.592$, $p < 0.001$). In preclinical studies, plasma-derived hemopexin inhibited heme-mediated cellular externalization of P-selectin and von Willebrand factor, and expression of IL-8, VCAM-1, and heme oxygenase-1 in cultured endothelial cells in a dose-responsive manner. In the Townes SCD mouse model, intravenous injection of free hemoglobin induced vascular stasis (vaso-occlusion) in nearly 40% of subcutaneous blood vessels visualized in a dorsal skin-fold chamber. Hemopexin administered intravenously prevented or relieved stasis in a dose-dependent manner. Hemopexin showed parallel activity in relieving vascular stasis induced by hypoxia-reoxygenation. Hemopexin had a half-life in wild-type mice, rats, and non-human primates of 80–102 h, whereas a reduced half-life of hemopexin in Townes SCD mice was observed due to ongoing hemolysis. These data have led to a Phase 1 clinical trial of hemopexin in adults with SCD, which is currently ongoing.

Structure of a sialo-oligosaccharide from glycophorin in carp red blood cell (RBC) membranes.

Dr. Takahiko Aoki

We isolated a high-purity carp glycophorin (GP) from carp erythrocyte membranes following extraction using the lithium diiodosalicylate (LIS)-phenol method and streptomycin treatment. This GP preparation was observed bacteriostatic activity against all tested bacteria, including two known fish pathogens. The oligosaccharide fraction of carp GP was separated into two components (P-1 and P-2) using a Glyco-Pak DEAE column. These P-1 and P-2 fractions were desalted using a GL-Pak Carbograph cartridge. The obtained preparation was retained for analysis by NMR and GC-MS. Using TLC and HPLC with an ED 40 electrochemical detector and a Carbo Pac PA10 column, these O-linked oligosaccharides (P-1 and P-2) were composed of glucose, galactose, fucose, N-acetylgalactosamine and N-glycolylneuraminic acid (NeuGc). Only the NeuGc form of sialic acid was detected in the carp glycophorin. The P-1 and P-2 contained one and two NeuGc residues, respectively, and the P-1 exhibited bacteriostatic activity. From obtained NMR (TOCSY, COSY, HSQC and H2BC) and GC-MS spectra, we determined that the structure of the bacteriostatic P-1 was NeuGc α 2 \rightarrow 6 (Fuc α 1 \rightarrow 4) (Glc α 1 \rightarrow 3) Gal β 1 \rightarrow 4GalNAc-ol. This O-linked oligosaccharide was unique for a vertebrate with respect to the hexosamine and hexose linkages and its non-chain structure.

The Critical Role of Complete Blood Count in the Management of Patients with COVID-19

Maryame Ahnach

Background: Since December 2019, the world has declared a global health crisis caused by the coronavirus disease (COVID-19) pandemic. The coronavirus can cause various clinical manifestations, but appears to have a direct impact on the hematopoietic system and blood cells. The hematologic analysis of quantitative and qualitative abnormalities plays a key role in the early diagnosis, severity prediction and follow-up of COVID-19 infection. We aimed to assess hematological change in COVID-19 patients admitted to the Cheikh Khalifa International Hospital in Casablanca and its association with the severity of the disease.

Methods: In this single-center, retrospective, observational study, we included all consecutive patients who were admitted in Cheikh Khalifa International University Hospital, Casablanca, Morocco, between February to April 2020, with a confirmed diagnosis of COVID-19 infection using SARS-CoV-2 viral nucleic acid via RT-PCR. All clinical and laboratory data of patients were collected and analyzed. The complete blood count was routinely measured on admission with blood smears control. The classification of the disease severity was in accordance with the clinical classification of the WHO interim guidance, and the management of patients were adapted to the national management guideline. Patients were separated into two groups: non-severe patients were those with mild or moderate forms of COVID-19, and severe patients were those admitted to the intensive care unit (ICU) who had one of the following signs-respiratory rate > 30 breaths/min; oxygen saturation < 93% on room air; acute respiratory distress syndrome (ARDS); or required mechanical ventilation. We used univariable and multivariable logistic regression to explore predictive hematologic factors of severity.

Results: We reported 134 patients with confirmed SARS-CoV-2 infection. The median age was 53 years (interquartile range [IQR], 36-64), and 73 (54.5%) were men. Eighty-nine non-severe patients (66.4%) were admitted to single bedrooms, and 45 (33.6%) were placed in

the ICU. Of the 134 patients, 61 (45.5%) had comorbidities, such as hypertension (n = 36; 26.9%), diabetes (n = 19; 14.2%), and coronary heart disease (n = 16; 11.9%). The most frequent symptoms were fever (n = 61; 45.5%), dry cough (n = 59; 44%), and dyspnea (n = 39; 29%). The hematological analysis found a normal median rate of hemoglobin (14g/dl) and platelet (266. 103/mm³). The most common change occurs in leukocyte lineage with increase of neutrophils count, eosinopenia (0.02 103/mm³) and significant lymphopenia less than 800/mm³ in the severe form (42,5%). The blood smears testing revealed morphological abnormalities in the white blood cells and platelet lines. In univariable and multivariable analysis, older men, comorbidities, higher neutrophile count, lymphopenia lower than 800/mm³, eosinopenia and neutrophils/lymphocytes ratio were significantly associated with severe forms of COVID-19.

A literature review confirms that the pathophysiology and inflammatory mechanism of the infection causes changes in white blood cells, but also abnormalities in red blood cells and platelets.

Conclusion: The blood cells perturbations are seen as a prognosis factors, careful analysis and interpretation of blood cell count allows not only to identify hematologic change but above a clinician to predict severity. Compared to specific inflammatory biomarker tests, the blood count remains a less expensive alternative, especially in countries with limited resources.

Profile of Anemic People in Hematology Outpatient Private Clinic

Jiviane Barretto

Anemia's prevalence in the world is around 30%, much higher than expected as acceptable by the World Health Organization. Due to the lack of official records on the epidemiological distribution of this disease, especially in private health sector, demonstrating its prevalence and verifying its distribution in terms of sex, age, severity, and etiology is very important. Thus, a descriptive analysis was performed, from the medical records of patients of a hematology outpatient clinic in the private sector in Brazil. More than 1400 patients were selected, 32% diagnosed with anemia, with a predominant age range between 40-49 years, and with women occupying almost 80% of the sample, in most cases being normocytic and mild anemia. More than 60% of the sample had iron deficiency anemia. The second most prevalent cause was anemia of inflammation. So, it was possible to conclude what the epidemiological profile of anemia was in the analyzed group and infer that, in most cases, anemia is a preventable disease, making it possible to decrease its prevalence.

Treating Vaso-occlusive Crises in Sickle Cell Disease with Hemopexin

John D. Belcher, PhD.

Anemia, hemolysis and vaso-occlusion are the hallmarks of sickle cell disease (SCD). The release of hemoglobin (Hb) and heme into the intravascular milieu can promote inflammatory responses with vasculopathy, leukocyte, platelet and endothelial cell activation, thrombosis, and even renal injury. Nature defends the vasculature from hemoglobin/heme by plasma haptoglobin and hemopexin, which tightly bind free hemoglobin and heme, respectively. Haptoglobin-hemoglobin and hemopexin-heme complexes bind to CD163 and CD91 receptors found primarily on macrophages and hepatocytes respectively and are taken up by receptor-mediated endocytosis. We

examined serum haptoglobin and hemopexin levels and biomarkers of hemolysis in hemoglobin SS, SC and AA children in Brazil. A cross-sectional study was performed including 272 unrelated steady-state children with SCD; 179 with sickle cell anemia (HbSS) and 93 with hemoglobin SC disease (HbSC), all seen at the Foundation of Hematology and Hemotherapy of the Bahia state (HEMOBA), in Brazil. The study also included 28 healthy children (HbAA) selected from the Clinical Laboratory of the Pharmacy School (Federal University of Bahia). The AA controls were selected and matched to cases by age, gender, and African ethnic origin. All patients were in steady-state that was defined as an absence of any blood transfusion and acute events for a period of four months prior to blood sampling. Evaluating the haptoglobin and hemopexin levels, we found that SS and SC patients have significantly lower haptoglobin and hemopexin levels (SS<SC<AA) than AA controls. Similarly, SS and SC patients have lower hemoglobin (SS<SC<AA) and increased reticulocyte counts and serum LDH (SS>SC>AA) than AA controls. Total and indirect bilirubin followed a similar pattern (SS>SC>AA). These data suggest more hemolysis in the following pattern: SS>SC>AA. Hemopexin was negatively correlated to LDH ($r = -0.509$, $p < 0.001$) and plasma heme ($r = -0.592$, $p < 0.001$). In preclinical studies, plasma-derived hemopexin inhibited heme-mediated cellular externalization of P-selectin and von Willebrand factor, and expression of IL-8, VCAM-1, and heme oxygenase-1 in cultured endothelial cells in a dose-responsive manner. In the Townes SCD mouse model, intravenous injection of free hemoglobin induced vascular stasis (vaso-occlusion) in nearly 40% of subcutaneous blood vessels visualized in a dorsal skin-fold chamber. Hemopexin administered intravenously prevented or relieved stasis in a dose-dependent manner. Hemopexin showed parallel activity in relieving vascular stasis induced by hypoxia-reoxygenation. Hemopexin had a half-life in wild-type mice, rats, and non-human primates of 80–102 h, whereas a reduced half-life of hemopexin in Townes SCD mice was observed due to ongoing hemolysis. These data have led to a Phase 1 clinical trial of hemopexin in adults with SCD, which is currently ongoing.

HEPATOLOGY

Seroconversion of HEV IgM to HEV IgG in Women Depending on Pregnancy And Disease Severity Status

Nargis Begum Javed

Background: HEV infection in pregnancy is common in developing countries, especially in India. HEV infection during pregnancy is associated with adverse maternal and fetal outcome.

Objective: To study seroconversion of HEV IgM to HEV IgG and viremia in the study population.

Methodology: Study population comprised of 76 pregnant and 58 non-pregnant women with HEV induced acute viral hepatitis (AVH) as well as 17 pregnant and 17 non-pregnant women with HEV induced fulminant hepatic failure (FHF). Five ml blood sample was collect from participants on enrolment, 7th, 15th, 30th, 60th and 90th day.

Results: At baseline, all participants were positive for anti-HEV IgM while anti-HEV IgG was positive in 25% and 11.8% pregnant women with AVH and FHF respectively, and in 63.8% and 35.3% non-pregnant women with AVH and FHF, respectively. On 90th day, anti-HEV IgM was positive in 6.6% pregnant women with AVH, 3.4% non-pregnant women with AVH and in 5.9% pregnant and non-pregnant women with FHF while all non-pregnant women

(AVH and FHF) were positive to anti-HEV IgG on 30th day, and all pregnant women (AVH and FHF) were positive to anti-HEV IgG on 60th day. HEV-RNA was detectable in the samples which had anti-HEV IgM titre >1.800 OD at 450 nm and HEV-RNA was not detectable when anti-HEV IgG titre >2.500 OD at 450 nm. HEV-RNA was not detected in all pregnant women on 90th day and in non-pregnant women with AVH and FHF on 30th day and 60th day, respectively.

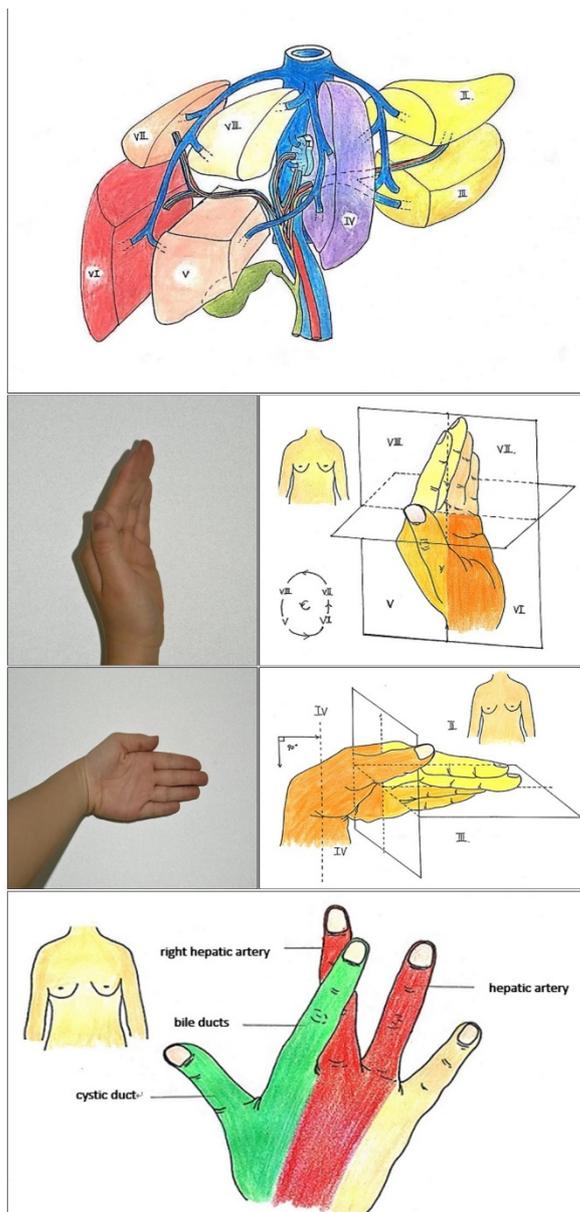
Conclusion: Seroconversion of HEV IgM to HEV IgG occurred earlier in non-pregnant women than pregnant women with AVH and FHF. Pregnancy was associated with delayed seroconversion and viral clearance.

Keywords: AVH, FHF, HEV, Pregnancy, Seroconversion, Viremia

Application of Hand-Foot Teaching Method in Hepatobiliary Surgery Anatomy

Jingrui Yang

We would like to describe our clinical and teaching experience on knowledge of liver segment and gallbladder triangle anatomy. Using the image teaching method, the liver anatomy knowledge is skillfully memorized through gesture changes, helping young



doctors to quickly grasp the position of each liver segment and bile duct. In the study of the right half of the liver, the left hand is compared to the right liver and the image memory of the upper and lower anterior segments of the right liver carried out. Put the left hand out. Take the fingertips as the side of the head, the wrist as the side of the foot, and the entire left hand as the right side of the liver. Then the vertical left hand is the right side of the liver when the patient is standing. Take the plane of the metacarpophalangeal joint as the section plane perpendicular to the vertical direction of the left hand. Take the plane of the vertical direction of the middle finger of the left hand as the longitudinal section, dividing the left hand into four parts. The right anterior lower part nearest to us is divided into a starting point, going counterclockwise, passing through each part exactly as the four parts of the right hemisphere, namely V, VI, VII and VIII. 1 As for the study of left liver, the left hand is stretched out like a knife, with the palm perpendicular to the forearm. At this time, the left hand is regarded as the left liver when the patient is standing. The

metacarpophalangeal joint is taken as the boundary, the palm part is regarded as the left medial lobe of the liver (section IV), the finger part as the left lateral lobe of the liver, the upper part of the finger part as the upper part of the left lateral lobe (section II), and the lower part of the finger part as the lower part of the left lateral lobe of the liver.

Finally, we would like to introduce the learning of the extrahepatic biliary tract and hepatic artery with the right hand. The common anatomical relationship between the extrahepatic biliary tract (gallbladder, hepatic duct, common bile duct) and the hepatic artery is difficult for beginners to establish three-dimensional concepts,² especially the right hepatic artery. In this part the right forearm and hand is straighten horizontally, fingers spread separate and the index finger raised and pressed against your middle finger. At this point, the right hand is equivalent to the patient lying flat, the thumb is the gallbladder, the index finger is the bile duct, the middle finger is the right hepatic artery, the ring finger is the left hepatic artery, the bile duct and the right hepatic artery cross obliquely, the right hepatic artery in the gallbladder triangle is oblique to the right gallbladder artery. The hepatic artery and the bile duct are roughly interrelated outside the liver and the portal vein is located in the back between them. (Fig. 1)

Fig 1. "Hands " figural teaching method in hepatic anatomy

This teaching method through the change of the hand gesture, aims to building of a profound three-dimensional structure, greatly improving learning efficiency.

Atherosclerosis and Chronic Viral Infection: What Can Be Learnt From Hepatitis C Virus?

Margaret F Bassendine *BSc, MBBS, FRCP, FRCP(E), DSc(Med), FoAP, FRSM, FRSB, FAALSD*

In 2020 Michael Houghton, Harvey Alter, and Charles Rice were awarded the Nobel Prize in Physiology or Medicine for their discovery of the hepatitis C virus (HCV). It is estimated that 71 million people globally are living with HCV & deaths among those chronically infected have reached > 500 000 annually.

In addition to liver-related deaths, HCV infection lowers cholesterol but, paradoxically, is associated with an increased risk of atherosclerosis. It has been estimated that the global burden of cardiovascular disease associated with HCV is responsible for 1.5 million disability-adjusted life-years, with the highest burden in low-income and middle-income countries (1). Potential mechanisms, including endothelial dysfunction and induction of autoimmunity, will be discussed.

In 2016, WHO set goals for the elimination of HCV by 2030. HCV clearance can now be achieved by direct acting antiviral (DAA) therapy. Emerging studies show, again

paradoxically, an increase in small dense LDL and carotid intima-media thickness after HCV clearance but a reduction in cardiovascular events.

HCV demonstrates that the causes of atherosclerosis are multifactorial. Viruses are part of a dynamic network of microorganisms that inhabit the body (collectively, the virome) and their role in atherosclerosis/inflammatory processes can now be examined using high-throughput sequencing technologies.

Activin B Promotes the Initiation and Progression of Liver Fibrosis

Guoli Dai, DVM, PhD

Background & Aims: Liver fibrosis is a pivotal pathology in multiple hepatic disease indications, profoundly characterizing disease severity and outcomes. The role of activin B, a TGF β superfamily cytokine, in liver health and disease is largely unknown. We aimed to investigate whether activin B modulates liver fibrogenesis.

Methods: Liver and serum activin B, along with its analog activin A, were analyzed in patients with liver fibrosis from different etiologies and in mouse acute and chronic liver injury models. Activin B, activin A, or both was immunologically neutralized in mice with progressive or established carbon tetrachloride (CCl₄)-induced liver fibrosis. The direct effects of activin B and A on hepatocytes and hepatic stellate cells (HSCs) were evaluated *in vitro*.

Results: As a result, hepatic and circulating activin B was increased in human patients with liver fibrosis caused by several liver diseases. In mice, hepatic and circulating activin B exhibited persistent elevation following the onset of several types of liver injury, whereas activin A displayed transient increases. The results revealed a close correlation of activin B with liver injury regardless of etiology and species. We found that neutralizing activin B largely prevented, as well as remarkably regressed, CCl₄-induced liver fibrosis, which was augmented by co-neutralizing activin A. Mechanistically, activin B directly promotes hepatocyte death, induces a profibrotic expression profile in HSCs, and stimulates HSCs to form a septa structure. In addition, activin B and A interdependently upregulated the transcription of profibrotic factors including connective tissue growth factor and TGF β 1 in injured livers.

Conclusions: We demonstrate that activin B, cooperating with activin A, directly acts on multiple liver cell populations, and drives the initiation and progression of liver fibrosis. Our finding inspires the development of a novel therapy of chronic liver diseases.

Treatment with A Protease Inhibitor with Induction Therapy with Natural Interferon-beta in Patients with HCV Genotype 1b Infection with viral inhibition linked to the restoration of innate and adaptive immune responses.

Yutaka Kishida

Background: Hepatitis C virus (HCV) has successful strategies to antagonize the host immune responses. A persistent HCV infection leads to chronic hepatitis and eventually causes cirrhosis and hepatocellular carcinoma. Spontaneous clearance of the HCV infection is associated with a prompt induction of innate immunity. A persistent HCV infection results from inefficient innate and adaptive immunities with exhausted virus-specific T-cell

responses. Host cytokines and innate immune responses play an important role in controlling a HCV infection. Innate immune responses modulate adaptive immune responses. These responses have recently been shown to play a role in the context of antiviral therapy for chronic HCV infection. Our previous study supports the concept that viral clearance early in the course of therapy is linked to the restoration of innate and adaptive immune responses. The restoration of innate immune responses has potential as a novel therapeutic strategy for chronic hepatitis C (CHC).

Methods: We compared the efficacy and safety of induction therapy (IT) with natural interferon-beta (n-IFN-beta) followed by pegylated-IFN-alpha/ribavirin (PR) alone (group A, n = 30) and IT with a protease inhibitor (PI) (Simeprevir or Vaniprevir)/PR (group B, n = 13) in CHC patients with genotype 1b and high viral loads.

Results: During IT with nIFN-beta, virologic response rates in group A and group B were 10% and 8% ($p = 0.6792$) at week 4, 30% and 16% ($p = 0.6989$) at week 12 and 47% and 20% ($p = 0.0887$) at week 24 respectively. During and after the treatment with PR alone or PI/PR, virologic response rates in groups A and B were 50% and 82% ($p = 0.01535$) at week 4, 53% and 91% ($p = 0.006745$) at week 8, 57% and 91% ($p = 0.001126$) at week 12. At the conclusion of the study, the results were 57% and 100% ($p < 0.001845$) at the end of the treatment and 57% and 80% ($p < 0.005166$) after treatment cessation.

Conclusion: IT with PI/PR linked to the restoration of innate immune response was tolerated well, and overcame virological breakthrough, enhanced early virologic responses, and resulted in a sustained virologic response in difficult-to-treat CHC patients. IT with PI/PR is beneficial for treating difficult-to-treat CHC patients. We also need to identify steps for augmenting immune responses.

HYPERTENSION

IMMUNOLOGY

Stimuli-responsive liposomes for drug delivery

Aayush Aayush

The non-viral mRNA delivery vector encoding the SARS-CoV-2 antibody has come into the limelight due to the expedited formulation, evaluation, and reliable production of lipid nanoparticles (LNPs) encapsulating the mRNA. Liposomes and LNPs can undergo receptor-mediated endocytosis and are generally made to release their cargo intracellularly. The LNPs encapsulating the drug cargo protect the cargo from being degraded/excreted prematurely and the host itself from the potentially toxic effects of the drug. This means that the LNP should have enough stability until it is endocytosed but then should lose that stability and release the drug after entering the cell. With ever-increasing advancements in nanomaterial design, synthesis, and formulation technologies, we have designed LNPs which can release cargo intracellularly upon a physical/chemical stimulus. In my talk, I will discuss one such example of a pH-responsive liposome designed to deliver Cerivastatin directly through inhalation of the liposome. The encapsulation of the drug not only reduced the direct toxicity on heart cells in vitro but also resulted in lower levels of its toxic lactone metabolite that plagues most statin-based drugs in vivo.

Fecal Microbiota of Humans Colonized by Protozoa Regulates the Intestinal Immune Response in Gnotobiotic Mice

Cecilia Ximenez Garcia

Background: The intestinal microbiota plays a fundamental role in the development and regulation of the intestinal immunity. Despite the close interactions between protists and bacteria in the gut, there is little knowledge about the influence of intestinal protozoa over the local balance between intestinal microbiota and immunity.

Methods: To know if protozoa-associated human gut microbiota modifies the regulation of the immune response in the gut, a humanized mice model was created by transferring human microbiota into germ-free mice by fecal microbiota transplant from people colonized with multiple intestinal protozoa, such as *Entamoeba dispar*, *Blastocystis hominis*, *Endolimax nana*, *Chilomastix mesnili*, *Iodamoeba butshlii* and *Entamoeba coli*, and from people without intestinal protozoa. Changes on immune regulation were evaluated by measuring intestinal cytokine production, counting lymphocyte populations in colon, and by evaluating the expression of marker genes of intestinal epithelium integrity and mucus production.

Results: The results showed a general downregulation of the immune response in the mice transferred with protozoa-positive fecal samples, characterized by a lower production of pro-inflammatory cytokines such as IFN- γ , IL-6 and IL-12, and changes in the architecture of the intestine, such as an increased production of colonic mucus, changes in the gene expression of the tight junction protein *tjp1*, and in the gene expression of the antimicrobial peptide *reg3g*.

Conclusion: The protozoa-associated fecal microbiota seems to downregulate the immune response in the gut.

Multispectral Imaging of Brightfield Multiplex Immunohistochemistry

Daniel Bauer, Larry Morrison, Rachel Beck, Morteza Waskasi, Mark Lefever, Esteban Robert, Mike Schurig, Brian Kelly

Background. Brightfield microscopy is the current gold standard for tissue-based cancer diagnoses and has long been the choice of pathologists. However, brightfield multiplex imaging historically has had limited ability to support multiplex assays due to 1) the broad spectral absorbance of conventional chromogens and 2) color cameras inability to distinguish more than three color channels. In this work, we combine novel narrowband covalently deposited chromogens (CDC) with matched narrow illumination channels to demonstrate that high-order multiplexing is possible in brightfield.

Methodology. Multiplex IHC was performed using assays with up to 8 narrowband CDCs (spectral widths <100nm) and hematoxylin nuclear counterstain on formalin-fixed paraffin-embedded (FFPE) tissue sections stained on a DISCOVERY ULTRA instrument with a custom protocol. High-order brightfield multiplexing was enabled by tuning narrowband LED illumination to the respective absorbance peaks of our internally developed CDCs. Multispectral images were acquired on a monochrome camera. Spectral unmixing was used to calculate protein abundances, which were then either pseudocolored to produce a visual display of the assay or quantitatively analyzed using digital pathology algorithms.

Results. Multiple tissues were tested on FFPE sections of lung, prostate, breast, and gastric tumors with assays up to 8-colors (7 IHC markers + counterstain). Spectral cross-talk between CDC signals was significantly reduced with spectral unmixing (SNR \approx 30). Biomarker concentrations were pseudo-colored to produce customizable visualizations of each assay.

Brightfield renditions of each assay were concordant with traditional visualization. Multiplex staining results were concordant with single stain DAB IHC of serial sections. Whole slide multispectral scanning of slides was achieved in ~10 minutes due largely to the system's short exposure times (average $\Delta t \sim 2$ ms) which facilitated high-speed multispectral image acquisition. Additionally, we have implemented multiple examples of combining H&E-based morphology with IHC staining on the same slide as a novel tool to understand the complexity of the tumor microenvironment.

Conclusion. Feasibility of brightfield IHC multiplexing was achieved by matching narrowband CDCs with specific light channels to enable detection of up to seven analytes (7 CDCs plus nuclear stain), approaching the capabilities of immunofluorescence. Our 8-color system is expandable to even higher-order multiplexing and boasts imaging speeds roughly comparable to that of a clinical brightfield scanner. This system presents an attractive technology to enable clinical multiplexing in the near term by combining the rich medical value of high-order multiplexing with the speed, pathologist familiarity, and broadly established clinical utility of brightfield microscopy.

Improvement of Effectiveness of Lymph Node as Endoecological Well-Being Factor in Aging

Gorchakov V.N., Nikolaychuk K.M., Gorchakova O.V.

Introduction: Lymphatic system is the subject of lymphology and immunology research. The integration of sciences offers new approaches to solution the problem of ensuring endoecological safety of the organism and increasing non-specific resistance, especially in relation to senile age.

Methods: The experiment was carried out on 160 white rats of Wistar with conditionally isolated groups: «young» (age 3-5 months) and «old» (age 1.5-2 years). Half of the animals took the original phytocomposition from medicinal plants of Siberia in a daily dose of 0.1-0.2 g/kg for a month. The subject of the study were lymph nodes of different localization. Histological, thermogravimetric, X-ray fluorescence analysis with synchrotron radiation, statistical methods were used.

Results: Aging is a negative process for the lymphatic system, leading to a decrease in drainage-detoxication and immune functions of lymph nodes in the lymphatic region. This is due to the change and destabilization of microelement exchange, hydration parameters and morphometric indicators of structural-functional zones lymph nodes. Ensuring lymph node operability is a condition of endoecological comfort in aging. This can be achieved using lymphotropic phytotechnology. In this situation, the lymphatic system is a tool for providing drainage and detoxification of the endoecological space. Phytotherapy has a structural-modifying effect on the structure of the lymph node, restoring the size of compartments. We established a direct relationship between compartments and immune response intensity across humoral and cellular types. Medicinal plants are donors of trace elements and fill the deficiency of trace elements during aging. There is a direct relationship between trace elements and enzymes involved in lymphoid cell proliferation. The lymphoproliferative effect (neolymphogenesis) as a result of phytotherapy was first noted. There is the formation of temporary compensatory lymphoid structures – lymphoid follicles outside and inside the lymph node. The noted effects of phytotherapy correct the

senile changes in lymphoid tissue when achieving the "dynamic age norm of health" in providing protection at the organ level (endoecology of the lymphatic region).

Conclusion: Lymphotropic phytotechnology is positioned as an opportunity to improve the quality of life and preserve health through the optimization of the structure and functions of the lymph node in the lymphatic region during aging.

INFECTIOUS DISEASES

Mathematical modeling on bacterial resistance to multiple antibiotics caused by spontaneous mutations

Eduardo Ibarguen

Bacterial population dynamics is characterized by four growth phases, in this work we focus on predicting the competitive interaction dynamics between sensitive strain and resistant strain to multiple antibiotics considering spontaneous mutations as the mechanism of resistance acquisition. Depending on the value of the basic offspring number of bacteria, the results reveal scenarios in which bacterial propagation is eliminated, controlled, persists only with resistant strains or with both of them.

Certainty of success: Three Critical Parameters in Coronavirus Vaccine Development

David C Kaslow

Vaccines for at least twenty major human viral pathogens have been licensed for use in humans. For many other major human viral pathogens, the absence of efficacious preventative vaccines is not for lack of effort. Two critical parameters, incubation period and broadly protective, relative immunogenicity, have previously been proposed to account, in part, for past successes in vaccine development, and to be useful in estimating the "certainty of success" for new vaccine development efforts. In this presentation the 5-day incubation period rule is reconsidered for the human coronaviruses, particularly SARS-CoV-2. A third, related critical parameter, infectious inoculum intensity, at an individual-level, and force of infection, at a population-level, is introduced for consideration. Analyses of this third parameter suggests that continued use of public health and social measures (PHSMs), when deploying vaccines, may lead to a virtuous cycle of vaccine effectiveness. Decreasing the force of infection and lengthening the incubation period, through continued use of PHSMs, may provide a greater opportunity for an anamnestic response, based on vaccine-induced immune memory, to protect against symptomatic infection.

Implementation of a Molecular Microbiology Laboratory in the Current Context in a Latin American Clinic

Cecilia Tapia

Advances in medicine have significantly prolonged the life expectancy of people, however, there is a growing challenge to control infectious diseases associated with health care. In order to manage this problem in a timely and comprehensive manner, surveillance is required to first detect and then perform interventions to prevent the spread of infections. The clinical microbiology laboratory has an important role in providing information to isolate patients and provide appropriate antimicrobial treatment. Based on the regulation of initially detecting and isolating patients coming from other hospital centers and those hospitalized in Critical Patient Units and other services, the incorporation of molecular

surveillance of resistance mechanisms is a tool that has made it possible to speed up this process and to learn about these mechanisms in order to reduce their transmission within the hospital. The implementation includes the diagnosis of Covid-19 and other viruses of medical importance.

The objectives of this presentation are to present the experience in the use of molecular surveillance in monitoring at admission and its importance in reducing transmission within the hospital and the rational use of antimicrobials and the impact of the implementation of the diagnosis of Covid and other viruses of epidemiological importance.

A Comprehensive Approach to Risk Reduction for Asian and Pacific Islander American Women With HIV/AIDS

Todd Sabato

As HIV incidence rises globally among underserved populations, Asian and Pacific Islander communities are increasingly affected. While often overlooked, Asian and Pacific Islander American women have shown significant increases in HIV diagnosis rates. The development of a multilevel and multi-strategy approach to HIV/AIDS education, prevention, and treatment among Asian and Pacific Islander females requires health care providers to identify personal and cultural barriers to prevention and treatment and implement culturally sensitive and specific measures. The purpose of this presentation is to illuminate barriers to HIV-related prevention, treatment, and care among Asian and Pacific Islander American females and provide practical application-based suggestions for providers, which may enhance Asian and Pacific Islander female inclusion in comprehensive HIV prevention.

Aedes mosquito transmitted diseases: Epidemiology and overview.

Ricardo Efren Searcy Pavia

Mosquito transmitted diseases (MTD) are endemic to tropical and subtropical regions of the world, where they are known public health threats given their potential of causing disability, reproductive harm and death. Over the last decade, Aedes mosquitoes and Aedes MTD have been observed to spread significantly causing new epidemics in regions like the Americas. Among the multiple factors explaining this expansion as the increased air travel and urbanization, climate change stands out for creating new suitable environmental and climatic conditions for vectors. According to climate change models, climatic suitability for Aedes MTD transmission is anticipated to expand in the northern hemisphere over the next few decades. Focused on dengue, zika and chikungunya; this talk will cover the most recent preventive, clinical and epidemiological research done in the field.

INTERNAL MEDICINE

Immunoglobulin G4-related Disease with Scant Tissue IgG4

Tetsuya Makiishi

A 56-year-old man was admitted for renal dysfunction and symmetrical swelling of submandibular glands. Laboratory and imaging findings were consistent with immunoglobulin G4-related disease (IgG4RD). Histological findings of the submandibular gland and the kidney were consistent with IgG4RD. However, the patient did not have elevated serum or tissue IgG4 concentrations. Oral prednisolone therapy, initially 50 mg/day and gradually tapered over 12 months, improved his laboratory abnormalities and

the swelling of his affected organs. These findings prompted our final diagnosis of IgG4RD. IgG4RD is a newly recognised disease with an unknown aetiology. This case suggests that IgG4 antibodies do not play a primary role in the aetiology of IgG4RD. Furthermore, clinicians should not exclude the diagnosis of IgG4RD in patients lacking elevated IgG4 levels in their affected tissues, particularly if they have other features of IgG4RD. Steroid therapy should be considered for such patients.

Percutaneous Coronary Interventions in Left Main Artery Lesions: Indications and Techniques

Homorodean Calin, MD, PhD

The incidence of left main coronary artery stenosis on coronary angiography is between 5-7%. Untreated left main stenosis carries a mortality risk of 20 to 50% by 3 years of follow-up. In patients with low coronary disease complexity scores, for which complete percutaneous revascularization is achievable, interventional strategy is a suitable alternative to cardiac bypass surgery. In randomised clinical trials, patients with more complex coronary disease continued to derive a benefit from surgery over stenting at long-term follow-up. However, in acute coronary syndromes especially in myocardial infarction, percutaneous revascularization often remains the only treatment option.

The outcomes after left main percutaneous interventions could be improved following stent optimization strategies, using intracoronary imaging guidance through intravascular ultrasound or optical coherence tomography. Intracoronary imaging also quantifies lesion severity, guides lesion preparation and facilitates stent selection and identifies acute complications as dissections, or intramural hematoma.

Currently, the preferred interventional technique at the level of left main bifurcation is provisional stenting. Nevertheless, when complex bifurcation lesions are present a double stent technique is needed. In this clinical situation, the double kissing crush technique has been shown to be associated with improved outcomes when compared to other strategies in clinical trials and meta-analyses. The outcomes after such complex interventions are largely dependent of the experience of the operator with different stenting techniques.

Bisoprolol transdermal patch improves orthostatic hypotension in patients with chronic heart failure and hypertension

Shunsuke Kiuchi

Increasing heart failure (HF) patients draw worldwide concern. In the current aging society, the incidence of HF preserved ejection fraction (HFpEF) has been increasing and hypertension is one of inducible causations of HFpEF. In addition, higher blood pressure (BP) is associated with a sudden onset of acute vascular insufficiency in HFpEF. Therefore, an optimal control of BP is essential in HF management, particularly in HFpEF. However, it is often not practically possible to increase the dosage of antihypertensive medications for an optimal control of BP. Antihypertensive medications often cause orthostatic hypotension (OH). Choosing a medication with the difference of the half-life of the medication and the onset of action in mind is one of these solution methods. We revealed bisoprolol transdermal patch improves OH in patients with chronic heart failure and hypertension, compared with bisoprolol fumarate tablet. Herein, we focus on the importance of a

management of BP in the HF treatment based on the clinical evidence, including our results.

Better Bone Health: Improving Recognition and Treatment of Osteoporosis

Sarah Knish Hall

Osteoporosis is a worldwide disease with an increasing incidence that affects a large number of older adults. Vertebral compression fractures are the most common type of osteoporotic fracture and can serve as a strong indicator of future fracture risk, but such vertebral compression fractures frequently remain clinically silent. Recognizing prevalent osteoporosis through identification of asymptomatic vertebral fractures found incidentally on imaging studies represents one avenue for improving bone health among populations. In this lecture we will review diagnosis and management of osteoporosis, with an emphasis on improving rates of diagnosis and treatment using health systems approaches.

COVID-19 Related Hypercoagulability

Luca Spiezia

Most patients affected by the novel coronavirus SARS-CoV-2 — responsible for the Coronavirus disease, COVID-19 — remain asymptomatic or develop mild symptoms. Only a small percentage of cases develop a severe disease that may lead to a fatal outcome. Since the early reports published in the literature by Wuhan colleagues, we have learned that patients hospitalized for acute COVID-19 infection have different clinical and laboratory pictures of coagulopathy. In particular, a marked increase in blood clotting capacity has been reported in most hospitalized patients – COVID-19-associated coagulopathy, CAC – which in turn increases the risk of developing thrombotic complications. The main pathophysiological mechanisms underlying this hypercoagulable state are inflammation, endothelial damage, hypofibrinolysis and hypoxemia. Traditional coagulation assays in patients with CAC show elevated levels of D-dimer (most severe cases), Factor VIII (FVIII) and Von Willebrand Factor (VWF). Prothrombin time (PT) and activated Partial Thromboplastin Time (aPTT) may be slightly prolonged in few cases. Fibrinogen levels may be both normal or increased, due to acute inflammation. Overall, traditional coagulation tests fail to fully characterize the nature and severity of COVID-19-associated hypercoagulability (CAH). Hence the need for functional coagulation assays (i.e. tromboelastometry/graphy, thrombin generation, platelet function test) and circulating extracellular vesicles to better understand these peculiar conditions. It would be very helpful to use these tests to identify patients at increased risk of developing thrombotic complications or with a worse prognosis as well as to ascertain the effectiveness of the anticoagulant treatment.

INFLUENZA/ BIOLOGY

LYMPHOMA

Immunization With the CSF-470 Vaccine Plus BCG and rhGM-CSF Induced in a Cutaneous Melanoma Patient a TCR α ≤ Repertoire Found at Vaccination Site and Tumor Infiltrating Lymphocytes That Persisted in Blood

Jose Mordoh

VACCIMEL vaccine is a mixture of four allogeneic irradiated melanoma cell lines plus BCG and rhGM-CSF (VACCIMEL) that has been assayed in cutaneous melanoma patients, in the adjuvant randomized Phase II study CASVAC-0401. Vaccinated patients had longer distant-metastases-free survival (DMFS) than patients treated with IFN α 2b. Five years after locking the data, an actualization was performed. The benefit in DMFS was maintained in the vaccinated group versus the IFN α 2b treated group ($p=0.035$), with a median DMFS of 96 months for VACCIMEL and 13 months for IFN α 2b. The favorable risk-benefit ratio was maintained. VACCIMEL induced an immune repertoire of T lymphocytes at the vaccination site, resulting in the expansion of Ag-boosted T-cell clones which persisted in blood by the end of the 2-yr vaccination. Twenty-four hours after vaccination, VACCIMEL induced a systemic response, with transitory increases in C reactive protein and IL-6. VACCIMEL plus BCG and GM-CSF is an effective treatment in adjuvancy for stages IIB, IIC and III cutaneous melanoma patients, and it is compatible with subsequent treatments with ICKi.

CAR-T cell therapy for B - cell lymphomas**Gerhard C Hildebrandt, MD, FACP**

Recent advances in medicine have significantly changed the prognosis of patients with B cell lymphoma. Historically, the prognosis of patients with highly aggressive and relapsed / refractory disease was very limited. However, the development of novel therapies engaging the immune system rather than relying solely on chemotherapy - induced cancer cell death, have proven very efficacious and have significantly changed how we are currently treating these patients and how they will be treated in the future. Major side effects of these treatments include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged hypogammaglobulinemia and cytopenia. The majority of these side effects is reversible with expedited treatment, and mortality of CAR-T cell therapy is low. We here review the current use of chimeric antigen receptor T cells (CAR-T) for large B cell lymphoma, follicular lymphoma and mantle cell lymphoma, demonstrating across all three groups significantly improved progression free survival and overall survival.

MEDICAL EDUCATION**Reducing Diagnostic Errors Worldwide Through Diagnostic Management Teams****Michael Laposata**

There are many mimics of child abuse that bring children to medical attention, including bruises and bleeding. Approximately 1 and 20 children evaluated for abuse in a large study involving nearly 3000 children were ultimately found to suffer from an underlying disorder that predisposed to bleeding rather than from intentional injury to the child. There are many common bleeding disorders that are often overlooked leading to an incorrect diagnosis of child abuse. These include van Willebrand disease, hemophilia A and hemophilia B and their carrier states, idiopathic thrombocytopenic purpura, and dozens more. The complexity associated with the diagnosis of a bleeding disorder requires appropriate and thorough testing and correct interpretation of the results. This information is often beyond the content knowledge of individuals who participate clinically in a child abuse program. The need for consultation on all questionable cases associated with

bleeding or bruising with an established expert who has substantial expertise in bleeding disorders is absolutely essential before determining that a bleeding or bruised child is the victim of an intentional injury. This presentation presents concepts and case examples of incorrect diagnoses and the consequences that resulted from each diagnostic error.

Could Application of Leader-Member Exchange Theory Have Saved a Residency Mentorship Program

Jessica Bunin

Mentorship offers numerous benefits including improved self-esteem, increased interest in research, and/or enhanced productivity. There are also pitfalls that can lead to failed mentor-protégé relationships such as personality conflicts, poor communication, differing goals, and lack of training for mentors and protégés. In this session, we describe a mentorship program that while initially successful was terminated due to perceptions of inequity and favoritism. We use leader-member exchange theory (LMX) to highlight deficits within the program to offer potential solutions and best practices to others instituting mentorship initiatives. The need for a mentorship program was identified as only 11.5% (n=26) of residents endorsed having a mentor. Twelve months after the initiation of a mentorship program, 96% of residents reported having a mentor. A majority of residents felt that mentor relationships were quite or extremely important, they were quite or extremely satisfied with the psychosocial support received, and they felt that mentors were quite to extremely important to their professional development. However, during the third year of the mentorship program complaints were filed based on perceived inequality causing leadership to redesign the mentorship program and ultimately dissolve it. LMX provides a lens to illuminate why complaints emerged and to offer steps to mitigate such challenges. LMX focuses on the importance of relationships, communication, and awareness of biases to optimize interactions between dyads such as a mentor and a protégé.

Grateful Client Philanthropy and Veterinary Medicine: Experiences at North Carolina State University

Dianne Dunning

The veterinary literature contains few publications or empirical research on the impact of grateful client philanthropy. To improve our understanding of the impact of philanthropy on veterinary medicine, we surveyed the faculty at NC State University College of Veterinary Medicine. This qualitative study involved an anonymous survey of NC State CVM faculty members administered and analyzed through an online survey software program, QualitrixXMTM. Over one-third of faculty responded to the survey. The majority of the respondents indicated that their personal interactions with clients led to gifts to their research or service and many indicated that they have received six or more gifts from their interactions with clients of the hospital. The top three examples of direct beneficial impacts from grateful client giving were research support, technological improvements and equipment upgrades, and professional development. The top three negative impacts of faculty interactions with a grateful client program were the perceived expectation to address the overwhelming needs of the donor, the faculty's concerns regarding the owner's higher expectations of service and time. It should be noted that the majority of respondents did not note any negative impacts. Overall, the faculty reported a positive impact with

grateful patient philanthropy. Continued development and understanding of the philanthropic process is recommended to maximize donor support for academic medical efforts. (214/250)

Effective Tangible Fixed Assets Management

Vladimir BUKVIČ, PhD

In this paper, the author investigates some conventional tools and criteria-indicators belonging to business analysis, by means of which firms should monitor and assess the effective use of their fixed assets. As fixed assets are an element of the business process, and among the most relevant and biggest resources in terms of value, the author asks how to handle fixed assets in the most economical way possible and how to manage them well. Within this context fall their rational use and optimal exploitation. These questions can be answered by means of indicators such as operating leverage (OL), the rate of return of total assets (ROA), depreciation as an average fixed cost (AFC), and overall equipment effectiveness (OEE). The answers are additionally clarified and supported by calculations of these criteria-indicators on the examples of several concrete cases from the real economic sector. Finally, the author suggests raising awareness among managers and educating them so they increase control over their exploitation in order to manage them properly and use them effectively.

Keywords: operating leverage, average fixed cost, return on assets (ROA), overall equipment effectiveness (OEE), fixed assets management

E-Health Telemonitoring Project in Patients with Dream Apnea Low Cpap Treatment with Low Fulfillment

lourdes Guerra

CPAP (Continuous Positive Pressure) is the treatment of choice in SAHS. Discontinuation or insufficient use may lead to a relapse of symptoms and a return of cardiovascular risks to unacceptable levels. It is estimated that between 30 and 60% of patients are non-adherent to CPAP treatment when evaluated one year after the indication of therapy. Although there are no data to accurately define the amount of sleep needed for each individual, CPAP treatment has been shown to be effective for those who stay longer than 3-4 hours/night for at least 70% of nights. In the Sleep Cohort of Vitoria, with 4274 patients treated with CPAP, the number of non-compliant is about 15%.

There are multiple possibilities for improving CPAP patient compliance, but they are humanly expensive and difficult to reproduce. New information technologies, such as telemonitoring, are now available that send data to a platform to alert the alarm signs and symptoms (leaks, airflow, pressure, IAH and leakage) and to promote the exchange of information, which means better management of resources and having real data on the situation on a day-to-day basis.

Determinants of Health: How the United States Measures Up

Patricia A. Gabow, MD. MACP

The health of individuals depends on an array of factors including their genetics, the availability and quality of healthcare, and a set of factors, labeled the social determinants of health (SDOH), which are income, education, behaviors, and environmental circumstances

including housing, food, toxic exposures, and community. These factors interact with each other and with race and determine many health outcomes including life expectancy. Among the high-income countries (HIC) there are considerable differences in the total expenditures for health and in the distribution of expenditures between healthcare and the SDOH. The United States is an outlier in its total expenditures, the distribution of those expenditures between healthcare and social care, and the outcomes achieved. The United States spends almost twice as much as other developed countries on healthcare for multiple reasons. Despite this expenditure, the American healthcare system has substantial shortcomings in coverage, access, and equity. Moreover, the life expectancy achieved by Americans is below that of other HIC in absolute years and also in comparison to its expenditures. This poorer life expectancy begins at birth and continues through many decades. This gap in life expectancy compared to other HIC with lower healthcare expenditures suggests a causative role of the under expenditure on the SDOH. This presentation will examine income, education, behaviors, and environmental contamination in the United States in comparison to other HICs and the impact of these variables on American's health. The presentation will conclude with some possible solutions to these issues by healthcare providers, healthcare institution, and the government in the United States.

Trust Transparency: And Why We Need Them Both

Stephen Child

The rideshare business "Uber" significantly and successfully disrupted the worldwide regulated taxi market.

New technology, fake news, iconoclasm and reduced health literacy are all leading to a rise in " alternative" healthcare delivery that potentially threatens the role of doctors and evidence-based medicine. Historically, regulation, ethical behavior and rigorous training have fostered trust in the profession which has delayed major disruption.....but will this last? What is happening to trust in doctors, what does this mean for the future of our profession and what can we do?

Topics in Study Design and Analysis for Multistage Clinical Proteomics Studies

Irene Suilan Zeng

Introduction: This presentation summarises the design chapter of clinical-proteomics (CP) studies in springer's book "Statistical analysis in proteomics study" with further developments based on the author's recent research in network analysis of integrated "omics".

Method: The author will provide suggestions on how to strengthen the robustness of its ethical and scientific attributes by including specific CP considerations in the current STROBE-Molecular Epidemiology guideline. It will start with the four "S" components of a clinical proteomic study, followed by a discussion on its clinical designs. The author will also briefly introduce methods for the sample size estimation in study design at the discovery/verification stages, emphasizing the systematic planning of a multistage CP study. The second part of the presentation will introduce an analytical framework of clinical proteomics data with four case studies.

Conclusion: The presentation aims to provide an overarching summary for audiences who are interested in using proteomics to identify protein markers for diagnosis, monitoring, and

prevention. The author hopes to encourage more researchers to use proteomics and omics technologies in clinical research.

World-wide, Cheaper, Higher Quality Healthcare Provider Using Blue Ocean and Idealized Designed Principles

Philip Slocum, D.O., FCCP, FACOI, FCCM, FACP

While there are many people and organizations who devote their lives and resources to the aid of those who are sick or injured, they can only be of help to a small number of the most disadvantaged and only for a limited time. Why do we not develop a cheap, higher quality, educational system that provides the appropriate healthcare providers for all regions of the world? This presentation uses principles of Blue Ocean Strategy and Idealized Design to suggest such a system is feasible. Knowing this is a topic of limited interest, the model will be presented first. This will be followed by a very brief historical background to understand how our higher and medical education systems developed. This helps us understand how we are trapped in old ways of thinking. We next explore modern modifications in higher education, technologies that potentially improve learning, and the educational theories in support of the new model.

Mind Mapping to Enhance Critical Thinking Skills in Physician Assistant Education: A Randomized Controlled Study

Cynthia Israel

Physician Assistant (PA) students need to assimilate and integrate voluminous information quickly and effectively to promote the critical thinking skills required to deliver competent care. Mind mapping is an innovative strategy used to facilitate students' recognition, recall essential information, and ensure depth in their understanding via making connections between pieces of information. In addition, the establishment of relationships between concepts expressed in mind maps promotes critical thinking skills.

Seventy-four PA students were randomly assigned to Standard Note Taking Group (SNTG) or Mind Mapping Group (MMG) to complete the pre-HSRT (Health Science Reasoning Test). MMG constructed mind maps for nine weeks. The SNTG followed their study method and did not make mind maps for nine weeks. Differences in the mean pre- and post-overall HSRT scores between the groups and within the groups were analyzed using independent and dependent t-test, respectively. There was no significant difference between pre-and post-overall critical thinking scores as measured by HSRT post nine weeks of intervention in both groups. In addition, there was no significant difference in the mean pre-HSRT overall critical thinking scores between the groups. However, there was a significant difference in the mean overall post-HSRT scores between the groups ($p=.026$). Hence, mind mapping is a viable active learning strategy to promote critical thinking in PA students.

Keywords: critical thinking, mind mapping, Health Science Reasoning Test

The Journey of medical education in Saudi Arabia: lessons learned during the COVID-19 pandemic

Khalid Bin Abdulrahman

Although the history of medical education in Saudi Arabia is relatively short, the first Saudi medical college was established in 1967. However, the speed of development in Saudi medical education is remarkable in quantity and quality. At the beginning of the emergence of medical education in the seventies, there were only four public medical colleges, and there was no private medical education.

Curricula in the 1970s to 1990s were traditional, teacher-centered, and subject-based. The basic medical courses were separated from the clinical rotations. Exams are based on subjective tools such as long essay questions, oral questions, etc. Nowadays, there are 29 public medical colleges and eight private colleges. Most colleges nowadays have adopted active learning educational strategies that make students proactive, self-learners, and learn cooperatively with their peers. Vertical and horizontal integration is a prominent feature in undergraduate medical education. Patient simulation types of equipment are used in clinical training and linking the courses with the medical service provided in the community. The Saudi Deans National Committee (SDNC) and the Saudi Society for Medical Education (SSME) had the leading role in adopting the national framework for graduate competencies and advancing the movement to improve the quality of outputs and adopt modern medical education strategies. This role was manifested during the COVID-19 pandemic, as they created a guide for medical schools that can be summarized in the most prominent lessons we learned from the pandemic, which are as follows: 1. The time has come to shift to high-fidelity simulation-based learning resources that can be used for teaching, learning, and assessment, 2. Virtual medical schools once sounded like a dream that may now turn into reality, where all member schools can share their best practices, 3. Preventive medicine, disease control, and public health education should be incorporated into all courses, particularly in clinical teaching, learning, and assessment, 4. Medical schools should invest in a technology-enhanced education system as it is the future, 5. Students, faculty, and supporting staff should be trained on how to deal with technology so that they can acclimatize themselves according to modern education.

MENTAL HEALTH

Increasing Mental Health Services by Transforming Pediatric Primary Care

Peter S. Jensen, MD

In this presentation, Peter S Jensen MD, former Associate Director for Child & Adolescent Research at the National Institute of Mental Health (NIMH), describes the underlying principles and specific training methods required for transforming pediatric mental health services. Using methods informed by basic behavior change and communication sciences, nearly 6000 primary care practitioners have completed the six-month practice transformation process across the US and Canada. The program has been widely acclaimed, is very user-friendly, and transforms pediatric practices such that mental health services for children are greatly increased and improved. During the presentation, Dr. Jensen describes the specific training methods and 15-year program results.

The Second Tidal Wave of Covid19: The Mental Health Impacts

Alyson Pompeo-Fagnoli

This presentation will focus on the "second tidal wave" of Covid19 treatment, or patient inflow with mental health diagnoses. Many of the Covid19 survivors are now showing lasting mental health impacts, as the mental health link regarding physical health and mental health of inpatient survivors has been well-established. This presentation will include information about the mental and physical health impacts of what is being coined as "long Covid," or the long-lasting impacts following a Covid19 infection. Recommendations for mental health clinicians and other medical professionals will be offered.

Experience in Online Therapy During the Covid-19 Pandemic and Its Influence on Events in the Group**Jelena Adamlje**

In the context of global events during the pandemic, experts in the field of mental health have recognized the necessity of offering alternative modes of providing support and treatment, and many of them have engaged in conducting online services/therapy for the first time. Herein I present my experience in conducting online group work from the very beginning of the pandemic and the changes and events that the virtual environment brought to light. The presented group therapy is performed as part of my training in group analysis (group analytic psychotherapy). The group, which had previously met face-to-face for two years, was able to adjust to the new setting and achieve progress despite certain difficulties and permanent longing for meeting in the live circle again.

This article presents the advantages of online therapy, like the availability of help and support during a period of increased patient needs and in achieving continuity of treatment as well as progress in therapy until face-to-face meetings become possible once more. On the other hand, it describes the challenges tied to the virtual setting, which requires adjustments from all therapy participants with regard to maintaining boundaries within the group, overcoming separation anxiety, technical and communication difficulties, and other unique factors that influence group therapy.

Systematic Review of Interventions for Depression for People Living with HIV in Africa**Sarah Lofgren, MD**

Depression worsens outcomes for people with HIV at every level of the HIV care cascade. Individuals with HIV and depression are less likely to engage in care, be retained in care, and even have higher mortality. The connection between depression and worse HIV outcomes is true globally, although the burden of HIV is highest in Africa. Depression interventions for individuals with HIV/AIDS in Africa are being increasingly evaluated. In 2018 I completed a systematic review. MEDLINE was searched using key terms: depression, Africa, and HIV, to identify depression interventions for HIV-infected adults in Africa. Perinatal women were excluded. Results were extracted, and relative change in depression scores for interventions and net effect were calculated. The MEDLINE search yielded 18 articles.

Six of seven studies evaluating feasibility were positive, and seven studies evaluating acceptability were also positive. Three studies investigated the effect of psychotherapy (% relative decrease of depressive symptoms for intervention: %net decrease compared to controls) (73%:39% decrease). Four studies investigated task-shifting of psychotherapy (47%:34% decrease). Three studies evaluated antidepressants (79%:39% decrease). Three

studies investigated task-shifting of antidepressant treatment (82%:65% decrease). An exercise intervention was evaluated (66%:49% decrease). One trial investigated minocycline with non-statistically significant results. Finally, three studies investigated other psychosocial interventions (44%:21% decrease). Overall, our results highlighted the need for large, randomized trials to establish efficacy and implementation studies. Since 2018 a group in South Africa has published a pilot study and randomized controlled trial evaluating task shifted cognitive behavioral therapy with promising results. A group in Kenya did similar work using interpersonal psychotherapy in women, also with good results. Other similar studies are underway, including my group's evaluation of group therapy in Uganda. Overall, there is exciting work evaluating depression interventions for Africans with HIV, which is greatly needed given the burdens of disease in this population.

MELANOMA

NEONATOLOGY

Neonatal Phototherapy Radiometers: Current Performance Characteristics and Future Requirements

Douglas Clarkson

A description is provided of technologies used to develop a neonatal 'body shape' device to determine the integrated phototherapy power in Watts delivered to its surface. Initial observations related to the use of discrete photodiodes though it was determined that these would introduce errors over non flat areas such as arms and legs. Further work on use of solar film elements to improve accuracy and function of such technology is described.

NEPHROLOGY

Peritoneal Ultrafiltration with Icodextrin Improves Functional Class in Patients with Congestive Heart Failure without End-Stage Kidney Disease – a Single-centre Report

Božidar Vujičić

Objectives: The efficacy of therapies of refractory CHF are frequently assessed through their effect on New York Heart Association (NYHA) classification. We reported the impact of peritoneal ultrafiltration (PUF) on functional status in refractory CHF patients without end-stage CKD.

Methods: This pilot-study involves four refractory CHF patients. Transversus abdominis plane (TAP) block, a regional ultrasound-guided local anaesthesia technique, was used for peritoneal catheter placement in all patients. A single 12-hour night-dwell of 2000 ml icodextrin daily was used to maintain PUF. We analysed body weight, CRP, NTproBNP, NYHA class, 24h diuresis, eGFR, number and days of hospitalization, at the start of PUF and after six months.

Statistics. Only basic descriptive statistics were calculated: means, standard deviations, differences between two points of measurement (N=4).

Results: Comparisons of baseline and six months measures show that analysed parameters were significantly better after employed procedure: 24h diuresis and PUF were higher, while body weight, was lower, and NYHA class went from 4 to 2. There are clear differences between two points of measurements, showing that on average: eGFR went up for 0.25 units, 24h diuresis went up for 637 units, PUF went up 400 units. Furthermore, NTproBNP went down 7.088,25 units, CRP went down 6.85 units, body weight was lower for 18.675 kg, number of hospitalisations changed from 6.25 times to 0.5 times, while days of hospitalization went down from of 83.5 to 3.0.

Conclusions: Peritoneal ultrafiltration should be an efficient therapeutic option in refractory CHF. Hospitalization rates were found to be significantly reduced, indicating a greater medical and economical advantage. Further studies are desirable to obtain specifications about PUF in HFpEF, HFmrEF and HFrEF patients. Even though there were only four patients in this pilot study, clear benefits of the employed method emphasize the importance of further investigation.

New Gab Chronic Kidney Diseases Classification

Jaime Arturo Jojoa

The KDIGO Chronic Kidney Disease (CKD) classification and New GAB CKD classification, identify the same ranges of kidney function; however, the New GAB classification, unlike the KDIGO, give us better details of albumin/creatinine ratio (ACR) and identifies the blood pressure level, therefore, it allows a wider and precise diagnosis and facilitate the clinical follow-up.

Comparative Effectiveness and Safety of Direct Oral Anticoagulants versus Warfarin in Patients with Chronic Kidney Disease Stage III and Atrial Fibrillation

Laurie-Anne Boivin-Proulx MD SM, Aurélie Lenglet BPharm PhD, Ziad Massy SM, Marc Dorais MSc, Sylvie Perreault BPharm PhD

Introduction: The effectiveness and safety of direct oral anticoagulants (DOACs) in atrial fibrillation (AF) patients with stage III chronic kidney disease (CKD) is still questioned. This study assessed the comparative effectiveness and safety of DOACs vs warfarin in stage III CKD AF patients.

Methods: A cohort of patients with inpatient or outpatient coding for AF who were newly prescribed an oral anticoagulant (OAC) was created using Quebec provincial administrative databases from 2011-2017. The primary effectiveness outcome was a composite of ischemic stroke, systemic embolism and death and the primary safety outcome was a composite of intracranial, gastrointestinal and major bleeding from other sites in the first year after OAC initiation. Treatment groups were compared using inverse-probability-of-treatment-weighting Cox proportional-hazards models at under-treatment analysis.

Results: 14,200 qualifying patients filled a claim for a new OAC prescription; 7,592 for warfarin 1,110 for rivaroxaban 20 mg, 2,084 for apixaban 5 mg and 1,674 for apixaban 2.5 mg. Rivaroxaban 20 mg was associated with a similar composite effectiveness (hazard ratio [HR] 0.84; 95% confidence intervals [CI] 0.62-1.12) and composite safety risk (HR 1.09; 95% CI 0.74-1.62) compared to warfarin (Figure 1). Apixaban 5 mg was associated with a lower composite effectiveness (HR 0.68; 95% CI 0.53-0.86), but similar composite safety risk (HR 0.89; 95% CI 0.64-1.22), whereas apixaban 2.5 mg was associated with a similar composite effectiveness (HR 0.97; 95% CI 0.78-1.21), but lower composite safety risk (HR 0.56; 95% CI 0.37-0.85).

Conclusions: In comparison to warfarin, rivaroxaban and apixaban appear to be effective and safe in stage III CKD patients with AF.

The Fatal Outcome of Aluminum and Citrate Interaction in Patients with End-Stage Renal Disease: A Lesson from 1985

Asad A. Bakir

Between April and September, 1985, we saw 4 patients with end-stage renal disease (ESRD), who presented with confusion, staccato speech or mutism, inattention, myoclonic jerks progressing quickly to generalized convulsions, coma and circulatory collapse, all refractory to treatment. They died within 3 weeks. Their ages were 53, 86, 63 and 70 years (68 \pm 14). One had received hemodialysis and another peritoneal dialysis for one month; the other two were not on dialysis. They had been taking 5 \pm 0.9 g/day of aluminum hydroxide, Al(OH)₃, as a phosphate binder, and 64 \pm 19 ml Shohl's solution (buffer of citric acid and sodium citrate) as an alkalinizing agent. The tests aiding the diagnosis were very high serum aluminum levels (sAL) of 14.1; 22.6; 28.9; and 42.2 micromoles/L, mean 26.9 \pm 11.8 (normal 0.11-0.26) and EEG tracings resembling those of the 1970's dialysis dementia from high aluminum content of the dialysis water. Dialysis, charcoal hemoperfusion desferrioxamine and vasopressors were not effective.

Of 34 patients with chronic kidney disease (CKD) seen in 1985, seven, Group 1, took neither Al(OH)₃ nor citrate (age 52 \pm 16; sAL 1.96 \pm 1.96); 5, Group 2, took only citrate (age 54 \pm 13; sAL 2.18 \pm 2.5); 12, Group 3, took Al(OH)₃ only (2.1 \pm 1.7 g/day; age 48 \pm 14; sAL 2.7 \pm 1.2); and 10, group 4, took Al(OH)₃, (3 \pm 1.6g/day) and citrate (54 \pm 21 ml/day; age 49 \pm 8; sAL 5.8 \pm 3.1).

sAL values correlated positively and significantly only with age, dose of aluminum hydroxide and the combined aluminum/citrate intake. The encephalopathic patients had much higher sAL than all other groups, including Group 4, were older, and had taken more Al(OH)₃.

In 5 healthy volunteers who took Al(OH)₃ and, after a 2-week washout, Al(OH)₃ and citrate, sAL and fractional excretion of aluminum increased significantly only with the combination of aluminum and citrate.

We concluded that the fatal hyperaluminemic encephalopathy was caused by the citrate - facilitated absorption of aluminum from the proximal small intestine, and recommended the abandonment of aluminum hydroxide as a phosphate binder and the use of non-aluminum containing binders. We subsequently saw no more cases of this fatal syndrome in CKD patients.

Aluminum links to the tricarbonyl groups of citric acid and forms a more soluble hexacoordinate complex. Citrate renders aluminum more soluble over a wide pH range, thus facilitating its absorption from the jejunum. Most importantly it also opens the jejunal epithelial cells tight junctions, thus enhancing the paracellular aluminum flux.

Latent tuberculosis infection and renal transplantation - Diagnosis and management

Sriram Krishnamoorthy

Background: Tuberculosis (TB) constitutes one of the most common infectious diseases in the world. TB is a severe impediment to the smooth progress of patients undergoing a renal transplant. Latent tuberculous Infection (LTBI) is a condition where the patient does not have a clinically demonstrable tubercular disease but shows a persistent immune response to tuberculous antigen. Patients undergoing renal allograft transplantations are immune-deficient and are predisposed to develop this condition. Various data suggest that up to 1.7 billion people worldwide are affected by LTBI.

Objectives: The purpose of this manuscript is to highlight the issues related to LTBI in renal transplantation and to stress the need for a standardised protocol for early diagnosis and appropriate treatment.

Methodology: The PubMed database was searched for studies and guidelines on the diagnosis and management of LTBI in renal transplantation. Allograft recipients with LTBI in the post-operative period were analysed.

Findings: Pathogenesis of LTBI in allograft recipients can occur either from the donor's kidney or from endogenous reactivation of latent infection or acquiring a new TB infection. Treatment for LTBI had been very diverse, with varied protocols. World Health Organization (WHO), 2018, has framed guidelines with definite protocols for managing patients with LTBI. Various meta-analyses and guidelines have recommended routine screening for LTBI in all renal allograft recipients.

Conclusions: LTBI is a potentially serious complication that, if diagnosed and treated appropriately, can significantly reduce the risk of allograft loss. A high index of awareness of this problem, an aggressive screening of the susceptible group and early appropriate treatment would to a greater extent prevent renal allograft damage due to tuberculous infection.

Keywords: Latent tuberculosis, renal transplantation, Tuberculin test, allograft, immune suppression.

Outcomes of Metabolic Resuscitation Using Ascorbic Acid

Jose Iglesias

Over the last 18 months the greatest impact that COVID-19 has had has been on utilization of intensive care units (ICUs), given as approximately 20% of hospitalized cases develop acute respiratory failure (ARF) requiring ICU admission.

Early experience with COVID-19-associated ARF reported inexplicably high mortality rates, with frequent prolonged durations of mechanical ventilation (MV), even from centers expert in such supportive care strategies. These reports led the authors to form a clinical expert panel called the Front-Line COVID-19 Critical Care Alliance (www.flccc.net). Based on the shared early impressions of "what was working and what wasn't working", the increasing medical journal publications and the rapidly accumulating personal clinical experiences with COVID-19 patients, a treatment protocol was created for the hospitalized patients based on our previous experience with a metabolic resuscitation protocol involving Glucocorticoids, high dose ascorbic acid and thiamine in patients with sepsis the core therapies of methylprednisolone, ascorbic acid, thiamine, heparin and non-antiviral co-interventions (MATH+) were formulated. This presentation reviews the scientific and clinical rationale behind MATH+ based on published in-vitro, pre-clinical, and clinical data in support of each medicine, with a special emphasis of studies supporting their use in the treatment of patients with viral syndromes and COVID-19 specifically.

Rational use and therapeutic drug monitoring of cannabidiol and immunosuppressants in kidney transplantation in Uruguay

Leticia Cuñetti

Chronic pain is a very frequent complication in kidney transplantation. Its treatment is limited by the nephro and cardiotoxicity of NSAIDs and the potential interaction of analgesic drugs with immunosuppressants.

WHO has been promoting the rational prescribing program since 1985. This program proposes a process of reasoned therapeutics. Rational prescribing involves applying a

systematization of reasoning by which the use of a medicinal product in a particular clinical situation is justified or ruled out.

There is a proven benefit in treating chronic pain with cannabinoids. Since 2013, a law was passed authorizing the prescription of cannabinoids for therapeutic use. This resulted in many patients demanding the use of cannabinoids in their treatment.

Many of these patients with limiting chronic pain were undertreated by the toxicity of various analgesics. These patients did not understand our refusal to associate this new group of drugs. We also understood that some were associating illegal products from the uncontrolled market, which put them at too high a risk.

Analyzing the rationality of cannabinoid prescription in our patients, our main concern was the potential interactions between cannabinoids and immunosuppressive drugs.

CBD is extensively metabolized in the body by hepatic hydroxylation and oxidation involving CYP3A4 and CYP2C19 isoenzymes (Phase I metabolism) but it can also undergo direct conjugation by Phase II enzymes.

Cyclosporine (CYA) is extensively metabolized in the liver and in the intestine by CYP3A4, which determines potential pharmacokinetic interactions with drugs that are metabolized by the same pathway or that are capable of inducing or inhibiting this enzyme.

Mycophenolate is absorbed and transformed into mycophenolic acid (MPA), its active metabolite, by the action of carboxylesterases located in the enterocyte and liver.

The other point that worried us was that we didn't have quality controlled products in our country at that time, so we imported them. The problem arose when we did not access the preparations that associated THC. The benefit in the treatment of chronic pain was proven with THC or 1:1 solutions of THC and CBD.

Due to cardiovascular safety and accessibility to quality-controlled products; we decided to do a therapeutic test with CBD for the treatment of chronic pain in our transplant patients

We are interested in communicating our experience on the use of CBD for the treatment of chronic pain in renal transplant patients, the benefits found, risks and the monitoring of adverse effects and its potential drug interactions.

Ferric Maltol in the treatment of Anemia of Chronic Kidney Disease (CKD)

Nelson Kopyt

Anemia, a common feature of CKD, becomes more prevalent as kidney function declines. It is partly related to the decreasing production of erythropoietin which plays a central role in the regulation of erythropoiesis. The development of erythropoiesis stimulating agents (ESAs) substantially improved the management of anemia in patients with CKD reducing anemia-related symptoms and the need for regular blood transfusions. In addition, CKD patients are frequently in negative iron balance, indicated by a decrease in serum ferritin and transferrin saturation (TSAT) below 16%. For efficient erythropoiesis to occur an adequate iron supply that matches the iron needs of the erythroid marrow is key. When a diagnosis of iron deficiency anemia (IDA) is made, oral or Intravenous (IV) iron-therapies are used to address the anemia of CKD before considering ESAs to achieve a goal hemoglobin (Hgb) of 10 to 11 g/dL.

Until recently the current treatment options for IDA had limitations. The iron in oral ferrous (Fe²⁺) compounds, readily available and widely used, tend to be poorly and variably

absorbed. They also form reactive hydroxyl radicals that may lead to mucosal irritation and damage associated with potentially severe gastrointestinal (GI) adverse events such as nausea, epigastric discomfort, and constipation limiting tolerance and reducing adherence. Ferric (Fe³⁺) salts are also available for treatment of IDA; however, the Ferric (Fe³⁺) ion must also be dissociated from the salt for absorption and the dissociated ferric iron is reduced to ferrous iron in the acidic duodenal environment and is associated with increased risk of GI adverse events, thus offering little advantage over ferrous salts regarding tolerability.

Ferric maltol is a complex of ferric iron and maltol (3-hydroxy-2-methyl-4-pyrone), a naturally occurring sugar derivative found in many food products, which is stable at physiologic pH. The complex remains strongly chelated until the point of absorption when the greater affinity of iron for the iron transport receptor on the surface of luminal enterocytes promotes dissociation from maltol. This results in no free iron in the gut to generate hydroxyl radicals, minimizing the risk of GI toxicity. The uptake of iron from ferric maltol is saturable and dependent on the expression of iron transport receptors, meeting physiologic needs while avoiding iron overload. In the AEGIS-CKD study, a randomized, double-blind, placebo-controlled study in patients with stage 3 or 4 CKD and IDA, oral ferric maltol achieved a statistically significant and clinically meaningful increase in hemoglobin and all iron indices from baseline to week 16 compared with placebo. Long-term treatment during the open-label extension showed that continuation of oral ferric maltol maintained the achieved Hgb above 10 g/dL for up to 52 weeks, the threshold value commonly considered as the threshold for initiation of ESA therapy in CKD 3 / 4 patients. In summary, a drug such as ferric maltol that can replace and restore iron, that is orally administered, and that patients can tolerate provides a clinically relevant treatment option for patients with moderate to severe CKD and anemia due to iron deficiency.

Acute Kidney Injury: What Does Urine Have to Do with It?

Susan Dirkes

This session will describe the syndrome of AKI, its causes, the influence of sepsis in AKI, and the prevention of AKI. The significant mortality of the sequelae of AKI will be emphasized with regard to outcomes, mortality and quality of life. Sepsis, being the largest cause of AKI as a disease of the microcirculation will be examined. Special attention will be made to our existing biomarkers such as urea nitrogen and creatinine, late indicators of AKI, and why they are not real-time indicators of kidney injury. New biomarkers that occur in the urine or serum within 3-12 hours after kidney insult will be discussed as alternative biomarkers such as NGAL, IL-18, TIMP-2, KIM-1 and others. In addition, glomerular filtration rate, reflected in urine output will be discussed as a real-time biomarker in AKI and as an effective tool to assess for AKI. The evidence supporting accurate and frequent urine output monitoring with regard to earlier detection of AKI with new tools will be examined and will be presented as well as discussion of why utilization of new technology that measures urine hourly may improve outcomes in patients with AKI.

Peritoneal Ultrafiltration with Icodextrin Improves Functional Class in Patients with Congestive Heart Failure without End-Stage Kidney Disease – a Single-centre Report

Vujičić B, Benko K, Markić D, Protić A, Španjol J, Rački S, Ružić A

Introduction: Congestive heart failure (CHF) refractory to pharmacological therapy is a growing medical problem. Renal sodium and water retention remains a key event in the pathogenesis of the disease progression and episodes of severe cardiac decompensation, being also the leading cause of high hospitalization rates and an important risk factor for worsening kidney function and chronic kidney disease (CKD). Peritoneal ultrafiltration (PUF) has emerged as an efficient therapeutic modality for management of fluid overload in CHF. Due to a specific structure of densely vascularized peritoneum, it takes advantage of the fact that, after filling peritoneal cavity with an osmotically active fluid (icodextrin), ultrafiltration of water is achieved. Continuous slow character of PUF does not cause significant blood volume fluctuations and facilitates hemodynamic stability. The efficacy of therapies of CHF are frequently assessed through their effect on New York Heart Association (NYHA) classification. In this pilot-study, we reported the impact of PUF on functional status in CHF patients without end-stage CKD.

Methods and Patients: It is important that this is the first cohort of patients treated with this method in Croatia. This pilot-study involves four patients, who could be classified as either HFpEF (N=3) or HFmrEF (N=1), and who received PUF due to refractory CHF. All patients were in stage 3A-4 CKD. Transversus abdominis plane (TAP) block, a regional ultrasound-guided local anesthesia technique, was used for peritoneal catheter placement in all patients. A single 12 hours night-dwell of 2000 ml icodextrin daily was used to maintain PUF. We analyzed body weight, CRP, NTproBNP, NYHA class, 24h diuresis, eGFR, number and days of hospitalization, at the start of PUF and after six months.

Statistics: Since N=4, only basic descriptive statistics were calculated: means, standard deviations, differences between two points of measurement.

Results: Comparisons of baseline and six months measures show that analysed parameters were significantly better after employed procedure: 24h diuresis and PUF were higher, while body weight, was lower, and NYHA class went from 4 to 2. There are clear differences between two points of measurements, showing that on average: eGFR went up for 0.25 units, 24h diuresis went up for 637 units, PUF went up 400 units. Furthermore, NTproBNP went down 7.088,25 units, CRP went down 6.85 units, body weight was lower for 18.675 kg, number of hospitalisations changed from 6.25 times to 0.5 times, while days of hospitalization went down from of 83.5 to 3.0. Even though results were obtained on only four patients, their clinical importance is obvious.

Conclusions: PUF offers various benefits in HF therapy, but there are also substantial differences. Hospitalization rates were found to be significantly reduced, indicating a greater medical and economical advantage. While PUF can now be regarded as an option of advanced HF therapy, further studies are desirable to obtain specifications about PUF in HFpEF, HFmrEF and HFrEF patients. Even though there were only four patients in this pilot study, clear benefits of the employed method emphasize the importance of further investigation.

Autosomal Dominant Polycystic kidney disease: The 450-Year Journey

Nelson Kopyt

ADPKD is the most common inherited kidney disease and the 4th most common cause of end stage kidney disease (ESKD) with half progressing to ESKD by age 60. The first documented case was King Stephan Bathory of Poland in 1586 after a 9-day illness slipped into a coma and died with an autopsy revealing very large cyst laden kidneys. The

relationship of “Cystic degeneration of the kidney” with kidney failure was first described by Royer in 1841. Lejars, in his 1888 doctoral thesis, first used the term “polycystic kidney disease” and stressed that the disease involves both kidneys being anatomical as well as associated with notable symptoms. Dr Steiner, in 1899 first noted the genetic basis for the disease with an autosomal dominant penetrance resulting in the name changing to ADPKD. Epidemiological studies in the early 1900’s revealed the high variability in the phenotypic expression of ADPKD, even within the same family.

Over the past 35 years we have learned a great deal regarding the pathogenesis and natural history of ADPKD beginning with the discovery that increased intracellular cAMP in the renal tubular epithelial cells (RTEC) stimulated cyst formation. A series of eloquent studies revealed the intricate linkage between the PKD1 and PKD2 mutations (identified in the 1990’s) affecting polycystin 1 & 2 function resulted in further increasing intracellular cAMP concentration in addition to that seen with the PKD1 & PKD2 mutations. This germ line mutation set the stage for cyst formation; however, it became apparent that a second modulator was required for cyst development and growth. Vasopressin was found to fulfill this role in binding to the V2 receptor of the RTEC causing a further increase in intracellular cAMP resulting in cell proliferation and fluid secretion leading to progressive cyst formation and growth over the lifespan of these affected individuals with ultimate destruction of the kidneys over 40 to 60 years and eventually ESKD in half of these patients with the genotype by the age of 60 as seen with King Bathory 450 years ago. Translational research with this information progressed from pre-clinical to clinical trials demonstrating that a selective V2 receptor antagonist, tolvaptan, could significantly impact on decreasing the growth of the kidneys and the progression of kidney disease in those ADPKD patients who are at risk of rapid progression.

Over the past 20 years studies have allowed us to identify biomarkers that predicted increased risk of rapid progression with the most validated being the relationship of height adjusted total kidney volume to age. This allows us to stratify our patients with ADPKD regarding rate of progression and now afford a treatment to slow down the progression of the disease culminating a 450-year journey.

NEUROLOGY & NEUROSCIENCE

Olfactory Dysfunction after Brain Injury and its Related Quality of Life

Mazlina Mazlan

Olfactory dysfunction after traumatic brain injury is not uncommon, with an estimated prevalence of 13%. The site of impact may play a role in the occurrence of olfactory dysfunction, especially trauma to the orbitofrontal region. The presence of post-traumatic anosmia (total loss of smell), hyposmia or phantosmia were shown to greatly affect quality of life (QoL) of brain injury survivors. We examined a group of Malaysian brain injury survivors to determine the influence of olfactory dysfunction on their QoL. The negative impacts include various aspects, from reduced food enjoyment, hazard avoidance, poor personal hygiene, and social isolation. Fear of exposure to hazardous substances was most commonly reported, while social relationship was the least affected. The severity of olfactory dysfunction and functional impairment were main factors influencing QoL. Diagnosing post-traumatic olfactory dysfunction using an objective testing with multiple

odours can be challenging, especially in a multi-cultural population in Malaysia. Thus, we use the cultural adapted Malaysian version of Sniffin' Sticks smell identification test for evaluation of the olfactory function.

Seizure outcomes of posterior reversible encephalopathy syndrome and correlations with electroencephalographic changes

Zhiyi Sha

Posterior reversible encephalopathy syndrome (PRES) is a well-recognized entity characterized by a combination of clinical and neuroimaging findings. Typical neurological symptoms include headache, AMS, seizures, visual abnormalities, nausea, vomiting, and focal neurological deficits. Most patients who had acute/subacute focal lesions from PRES can have full recovery and do not develop epilepsy. Though uncommon, epilepsy can develop following PRES in adults and children. Epilepsy and neurological sequelae are more common in Children with PRES

Initial Studies on the direct and modulatory effects of nitric oxide on an identified central *Helix aspersa* neuron.

Nicholas Wright

Ever since the late-eighties when Endothelium-derived Relaxing Factor was found to be the gas nitric oxide (NO), production has been observed in virtually all animal groups, plants, diatoms, slime molds and bacteria. The fact that this messenger was a gas and therefore didn't obey the established rules of chemical transmission made it even more intriguing. NO is typically produced on demand by the enzyme Nitric Oxide Synthase (NOS) although there are at least 7 potential enzymatic sources. NOS is typically activated by increased intracellular calcium and guanylate cyclase, a principal target, is activated by forming a covalent bond with the generated NO which in itself is novel. This results in the production of the secondary messenger cyclic guanosine monophosphate (cGMP) and subsequent interactions with targets such as Protein Kinase G. However, NO has also been shown to affect 3,000 plus proteins by covalently reacting with cysteine residues in a process known as nitrosylation which is both reversible and specific. Nitrosylation can affect apoptosis, DNA methylation and transcription among others. NO has also been linked to the nitrogen cycle and the "metabolic budget" of a cell; its half-life being dependent on a cell's redox status.

NOS has been demonstrated in various mollusc brains including *Helix aspersa*. Initial results show NO can be generated in the region around neuron F1 in the right parietal ganglion of the snail *Helix aspersa* and that NO directly hyperpolarizes this neuron when synaptically isolated. This is duplicated by the application of 8-bromo-cyclic guanosine monophosphate (8-bromo-cGMP). Application of the NO-donors sodium nitroprusside (SNP) and S-nitroso-N-acetyl-D,L-penicillamine (SNAP) cause significant hyperpolarization (50 μ M SNAP; 31.2mV) while 2millimolar 8-bromo-cGMP produced a mean hyperpolarization of 29.6mV. Additionally, pre-exposure to NO-donors or 8-bromo-cGMP appears to significantly reduce or even eliminate the normal hyperpolarizing K⁺-mediated response to dopamine (DA) by this neuron. Pretreatment with 50micromolar SNAP halves the response to 0.5micromolar

DA (16.5 to 8.6mV); 200micromolar abolishes it totally. One millimolar 8-bromo-cGMP reduces it 62% (16.5 to 5mV). This presentation reviews the actions of NO generally and specifically on the Helix aspersa neuron F1.

Association of Blood Pressure and Cognition after Stroke

Deborah A. Levine, MD, MPH

Cognitive dysfunction is a common effect of stroke. Cognitive dysfunction increases the mortality, morbidity, and healthcare costs of stroke survivors, and decreases their quality of life. Identifying modifiable risk factors that lessen cognitive dysfunction after stroke is critical. The association between blood pressure and cognition after stroke is unclear. We present the results of a study of the relationships between systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure with cognition, each measured 90 days after stroke.

Characterization of the Mutation Spectrum in A Cohort of Portuguese Patients with Frontotemporal Dementia: A Single Center Experience

Maria Rosário Almeida, Miguel Tábuas-Pereira, Inês Baldeiras, Maria Carmo Macário, Isabel Santana

Heterozygous mutations in the progranulin (GRN) gene are one of the major genetic defects of Frontotemporal dementia (FTD). The vast majority are loss-of-function mutations, leading to GRN haploinsufficiency, resulting in a reduction of serum GRN levels, even in unaffected mutation carriers. However, the distribution of these mutations along the gene varies in different geographically populations. In this study, we describe the mutation analysis of GRN gene in more than 200 FTD patients followed at the Dementia Clinics of the Coimbra University Hospital between 2012 and 2022. Serum GRN level was assessed by a commercial ELISA kit and the genetic analysis of was performed by Sanger sequencing and/or NGS-gene panel on an Illumina MiSeq sequencer. According to the ACMG/AMP 2015 guidelines, seven different likely pathogenic or pathogenic GRN variants were identified in the patient's cohort, allowing at-risk relatives being tested, in the context of genetic counseling. In a total, 40 individuals (32 patients and 8 family members) harbored pathogenic variants, all of them located in exons 8, 9 and 10 of the GRN gene. Of note, the pathogenic variant c.900_901dupGT; p.Ser301Cysfs*61, only reported thus far in FTD Portuguese patients, is the most common variant, identified in 50% of the carriers. Interestingly, we identified previously this later variant in homozygosity in a patient with neuronal ceroid lipofuscinosis, segregating in a family with neuropathologic confirmed FTD. Thus, our results expanded the mutation spectrum and the GRN-related clinical phenotype, since it unveils novel pathogenic variants, highlighting the specific genetic background of our FTD population. These additional evidences have been important for genetic counseling and clinical management.

Cerebral Microvascular Injury: A Potentially Treatable Endophenotype of Traumatic Brain Injury-Induced Neurodegeneration

Danielle K. Sandsmark

Traumatic brain injury (TBI) is one of the most common human afflictions, contributing to long-term disability in survivors. While initially conceptualized as a primary insult and subsequent recovery/stabilization in the weeks-months following injury, emerging data indicate that functional improvement or deterioration can occur years after TBI. Recent epidemiological data has revealed that TBI, even in its mild form, is a risk factor for late-life neurodegenerative disorders. Because TBI is an incredibly heterogeneous disorder encompassing numerous pathobiological processes, a better understanding of the specific processes that contribute to neurodegeneration are needed to develop mechanistically appropriate therapies. Traumatic microvascular injury is a common, but relatively understudied, TBI endophenotype that has been described across the TBI severity spectrum. More recently, the role of vascular dysfunction in several neurodegenerative conditions has been appreciated. We will discuss the development of biomarkers to identify TBI-associated microvascular dysfunction and explore the potential of those biomarkers to employ vascular-directed therapies in appropriate TBI survivors in the next generation of TBI clinical trials to ameliorate TBI-associated neurodegeneration.

The aging mind: neuroplasticity in response to cognitive training

Vivian Brockwell

With increasing age, the human brain exhibits shrinkage in volume, white matter damage and decreased connectivity among regions. Nevertheless, cognition in older adults functions relatively well. How can this be? Park and Reuter-Lorenz (2009) argue that the brain shows functional resilience and compensation scaffolds. These are somewhat inefficient pathways that are honed from additional compensatory activity in brain regions that are not typically recruited by young adults. The Dallas Lifespan Brain study is a twelve-year longitudinal study of adults aged 20 to 90 that was designed to test the Scaffolding Theory of Aging and Cognition model (STAC). Evidence will be presented that provides support for STAC, but there are also data that better fit models of cognitive maintenance than models of compensation. Who is most likely to compensate for brain deficits by increasing brain activity will be discussed and conditions under which compensation is less likely to occur will also be presented. Challenges faced by neuroscientists in understanding the mechanisms that account for human cognitive aging will be presented in this free-ranging talk that will be accessible to both undergraduate majors, as well as of interest to neuroscientists who study cognitive aging.

The Effect of Nanostructuring of Semi-Conductor or Polymer Materials in Neural Cell Cultures: Implications for Neural Implant Design

Gaëlle Piret, Fannie Darlot, Jean-Marie Mayaudon, Vijayalakshmi Rajendran, Lionel Rousseau, Maria-Thereza Perez, Christelle N. Prinz

Nanowires can be used in a broad range of bio-applications among which are neural implants for brain computer interface or neuroprostheses. We have shown that neurons from the Central Nervous System thrive when cultured on vertical arrays of semi-conductor nanowires (NWs), whereas the growth of glial cells on such arrays is limited compared to when cultured on flat substrates. However, semi-conductor nanowires present challenges in

terms of integration in neural implants, such as their integration in a flexible substrate and their resistance to corrosion. We have analyzed the interaction of neuronal cells with NWs made from insulator polymers that are usually used for neural implants. For this purpose, we performed retinal and cortical cell cultures on SU8 and parylene-C polymer NWs. Four μm long SU-8 NWs positively influenced cell adhesion and neurite network formation compared to 1 μm long SU-8 NWs and flat SU-8 substrates. However, flat parylene-C was found to be the best polymer. Although we anticipate that parylene-C NWs might improve cell behavior, it has not yet been possible to obtain parylene-C NWs longer than 2 μm . Taken together, these results suggest that arrays of nanowires are promising nanomaterials for designing neural interfaces and that the type of material and shape/dimensions of such nanomaterials play an important role.

Malignant Peripheral Nerve Sheath Tumor - How Imaging Can Help

Guilherme Girardi May

The malignant peripheral nerve sheath tumors (MPNST) are tumors originating from peripheral nerve sheath cells, which can originate de novo or even arise from pre-existing tumors, such as neurofibromas, ganglioneuromas or Schwannomas¹. These tumors represent approximately 5 - 10% of soft tissue sarcomas, with no recognized gender predilection². Among the risk factors for the development of these neoplasms are previous exposure to radiation³ and type 1 neurofibromatosis, in which patients have a 10% lifetime risk of developing an MPNST, as well as usually presenting them earlier when compared to sporadic cases⁴. These patients often present with a rapidly growing mass that can cause local pain or focal neurological symptoms, with the proximal portion of the extremities being the most frequently affected sites². The aim of this presentation is to review the imaging characteristics of MPNSTs, focusing on their rhabdomyoblastic differentiation (malignant triton tumors) and the role of imaging methods in differentiating benign from malignant peripheral nerve sheath tumors.

Initial studies on the direct and modulatory effects of nitric oxide on an identified central *Helix aspersa* neuron

Nicholas J.D.Wright.

Ever since the late-eighties when Endothelium-derived Relaxing Factor was found to be the gas nitric oxide (NO), production has been observed in virtually all animal groups, plants, diatoms, slime molds and bacteria. The fact that this messenger was a gas and therefore didn't obey the established rules of chemical transmission made it even more intriguing. NO is typically produced on demand by the enzyme Nitric Oxide Synthase (NOS) although there are at least 7 potential enzymatic sources. NOS is typically activated by increased intracellular calcium and guanylate cyclase, a principal target, is activated by forming a covalent bond with the generated NO which in itself is novel. This results in the production of the secondary messenger cyclic guanosine monophosphate (cGMP) and subsequent interactions with targets such as Protein Kinase G. However, NO has also been shown to affect 3,000 plus proteins by covalently reacting with cysteine residues in a process known as nitrosylation which is both reversible and specific. Nitrosylation can affect apoptosis,

DNA methylation and transcription among others. NO has also been linked to the nitrogen cycle and the “metabolic budget” of a cell; its half-life being dependent on a cell’s redox status.

NOS has been demonstrated in various mollusc brains including *Helix aspersa*. Initial results show NO can be generated in the region around neuron F1 in the right parietal ganglion of the snail *Helix aspersa* and that NO directly hyperpolarizes this neuron when synaptically isolated. This is duplicated by the application of 8-bromo-cyclic guanosine monophosphate (8-bromo-cGMP). Application of the NO-donors sodium nitroprusside (SNP) and S-nitroso-N-acetyl-D,L-penicillamine (SNAP) cause significant hyperpolarization (50 μ M SNAP; 31.2mV) while 2millimolar 8-bromo-cGMP produced a mean hyperpolarization of 29.6mV. Additionally, pre-exposure to NO-donors or 8-bromo-cGMP appears to significantly reduce or even eliminate the normal hyperpolarizing K⁺-mediated response to dopamine (DA) by this neuron. Pretreatment with 50micromolar SNAP halves the response to 0.5micromolar DA (16.5 to 8.6mV); 200micromolar abolishes it totally. One millimolar 8-bromo-cGMP reduces it 62% (16.5 to 5mV). This presentation reviews the actions of NO generally and specifically on the *Helix aspersa* neuron F1.

The Role of Tau Strains in Phenotypic Variability in Alzheimer’s Disease

Androuin A, Grznarova K, Stimmer L, Abada YS, Duyckaerts C, Potier MC, Haïk S, Delatour B, Boluda S.

Clinical phenotypic heterogeneity of Alzheimer’s disease (AD) is well established. Rapidly progressive subtype of AD (rpAD) has a specific phenotype (unusual symptoms, shorter disease duration and faster cognitive decline than classic AD (cAD)) suggesting a different potential tau strain.

We have investigated tau protein characteristics through different approaches: biochemistry (sucrose gradient sedimentation) (n=5 cAD , n=5 rpAD , n=2 CTRL cases), « in vitro » (HEK biosensor cell system) (n=2 cAD , n=2 rpAD , n=2 CTRL) and « in vivo » (hippocampal injections in tau P301S Tg mice) (n=8 cAD , n=8 rpAD , n=8 CTRL) studies.

We have observed a higher seeding activity of Tau-cAD compared with Tau-rpAD as seen in the "in vitro" and "in vivo" experiments. cAD brain homogenate induced higher amount of tau pathology than rpAD extracts when applied intracerebrally in tau-P301S mice or on tau P301S biosensor HEK cells. Tau in rpAD subjects is formed by less dense particles, probably corresponding to the presence of higher amount of oligomeric forms, as seen with sucrose gradient sedimentation.

These observations could be consistent with the existence of different tau conformers leading to distinct diseases.

Hint1: A Key Regulator of Nmdar Function, Pain and Inherited Neuropathy

Carston R. Wagner, Cristina Peterson, Maxwell Dillenburg, Rachit Shah

The interactions between the mu-opioid (MOR) and N-methyl-D-aspartate receptor (NMDAR) constitute an area of intense investigation due to their contributions to maladaptive neuroplasticity. Through the use of medicinal chemistry, biochemistry and neuropharmacology studies, our team has recently demonstrated that Histidine Triad Nucleotide Binding Protein 1 (HINT1) is a key mediator of the cross-regulation of the μ -

opioid receptor (MOR) and the glutamatergic N-Methyl-D-Aspartate Receptor (NMDAR). The ability of MOR activation to reduce pain is highly dependent on its interaction with NMDAR. We have found that HINT1 directs the association of MOR with NMDAR. Upon binding with morphine and activation of analgesia, Zn is mobilized and binds to the HINT1 active site, resulting in Protein Kinase C gamma (PKC γ) recruitment. NMDAR phosphorylation by PKC γ results in activation of the channel and Calmodulin-Dependent Kinase II (CaMKII) suppression of MOR. Consistent with these observations, HINT1 knock-out mice exhibited enhanced analgesia and resistance to tolerance with no apparent adverse side-effects.

Through kinetic, mutagenic and x-ray crystallography studies, our group has delineated key features of the catalytic mechanism and potential biochemical role of human HINT1. These studies have enabled the rational design of inhibitors of hHINT1. We have demonstrated that the dosing of mice with one of these inhibitors, 5'-tryptamine guanosine carbamate (TpGc), can significantly enhance morphine analgesia, reverse morphine tolerance and reduce neuropathic pain. In addition, we have also recently demonstrated that TpGc can abolish chemotherapeutic induced neuropathic pain, as well as block the antagonist effect of the mu-opioid receptor on NMDAR activation in the spinal cord. In addition, based on recent familial genetic analyses, HINT1 mutations have been found to be responsible for inherited peripheral neuropathy (IPN). Through detailed mutational, kinetic and structural studies we have provided a biochemical framework for understanding the potential perturbation of the associated mutations on HINT1 function. Taken together, our results demonstrate the unique regulatory role of HINT1 on MOR and NMDAR, as well as reveal it to be a potential new non-opioid target for the development of pain therapeutics and IPN. The results of ongoing mechanistic and chemical probe development studies will be discussed.

Charcot's Neuroarthropathy – early recognition is essential for optimal outcomes.

Dr. Shan Bergin

Charcot's Neuroarthropathy (Charcot's) is a debilitating condition that is most prevalent amongst those with diabetes and associated sensory loss. Most recently described as an inflammatory process, Charcot's can result in significant foot deformity which then acts as a precursor to ulceration, infection, and possible amputation. Early signs and symptoms of Charcot's, which include unilateral heat, swelling and erythema, are often mistaken for other pathologies such as gout, deep vein thrombosis or cellulitis. Misdiagnosis results in treatment delays, further increasing the chance of major disruption to bones and joints in the foot thereby reducing the likelihood of a positive clinical outcome. Early identification and management through immobilisation are essential to preserve foot architecture and safe mobilisation, and to prevent the patient from experiencing future ulceration and related complications. This presentation will describe the known pathophysiology of Charcot's, its clinical presentation, and current evidence-based management strategies used to minimise the impacts of this potentially catastrophic process.

Combined DMH1 and Neural Stem Cells treatment improved ischemic stroke outcome

Lei Chen, Binoy Joseph, Kathryn Saatman, Guoqiang Yu

Stroke is a leading cause of disability and mortality in the adult population worldwide, while neural stem cells (NSC) therapy shows promise for stroke patients. Smad1, the downstream

of bone morphogenetic (BMP) signaling, has been implicated in the stroke pathology and the activation, proliferation, and differentiation of NSCs. Therefore, we investigate whether a strategy combining pharmaceutical inhibition of Smad1 with NSCs transplantation provides better outcomes than either approach alone. Young adult C57B6 mice received sham surgery or 1h middle cerebral occlusion-induced ischemia, and the latter were randomly assigned into 4 groups: 1. Daily i.p. injection of vehicle solution for 10days (control group); 2. Injection of DMH1 (Smad1 inhibitor, 5mg/kg) (10d); 3. Injection of vehicle solution (10d) + intra-arterial NSCs (isolated from the embryonic cortex of E18 eGFP (+) mice); and 4. Injection of DMH1 solution (10d) + NSCs delivery. On day3 post-stroke, 106 eGFP(+) NSCs in single-cell suspension were injected through the ipsilateral carotid artery to mice in groups 3 and 4. The stroke volume, motor function, and survival of NSCs were examined at 10days, 30days, and 3months post-stroke. Our results showed that inhibition of Smad1 signaling with DMH1 or transplant of NSCs mitigate brain injury; DMH1 treatment enhanced NSCs' survival and neuronal differentiation in the stroke area; however, we did not observe synergic protective effects. Taken together, our results suggest Smad1 inhibition and NSCs therapy's translational regimen for stroke.

Keywords: Smad1, neural stem cell therapy, ischemic stroke, mouse model

Polycomb Repressive Complex 2 (PRC2) in Neurodevelopmental Disorders

Naiara Aquizu-Lopez

Increasing evidence implicates Polycomb Repressive Complex 2 (PRC2) in genetic neurodevelopmental disorders. However, the underlying pathological mechanisms remain unknown. The main biological function of PRC2 is to maintain transcriptional repression of genes that determine cellular identities during development. Recent discoveries indicate that the incorporation of alternate subunits generates functionally specialized versions of PRC2. For example, the presence of EZH1 or EZH2 as the catalytic subunit, generates two versions of PRC2 with different catalytic strength and chromatin condensation ability. The major goal of our work is to understand the role of PRC2-EZH2 and PRC2-EZH1 in neural development and disease. Using the chick embryo as a model organism, our previous work showed that EZH2 is required for self-renewal and proliferation of neural progenitor cells during early neural tube development. In contrast, our recent work uncovers that EZH1 is necessary and sufficient for neuronal differentiation induction. Interestingly, we have identified genetic variants in EZH1 as the cause of a novel neurodevelopmental disorders characterized by intellectual disability and dysmorphic faces. Using pluripotent stem cells and their differentiation to cortical neurons in monolayer and organoid cultures, we show that EZH1 variants cause defects in neurogenesis timing. Together, our work demonstrates that EZH1 and EZH2 have non-redundant, but complementary roles in neural development that may be impacted by the pathogenic variants that lead to intellectual disability in EZH2 associated Weaver syndrome and EZH1 associated neurodevelopmental diseases we have just identified.

Fibroblast Growth Factor 13 in Brain Development and Diseases

Xu Zhang

Fibroblast growth factor 13 (FGF13), a non-secretory protein of the FGF family, is expressed in cerebral cortical neurons during development. FGF13 acts intracellularly as a

microtubule-stabilizing protein required for the axon development and neuronal migration in the cerebral cortex. FGF13 is enriched in axonal growth cones and interacts directly with microtubules to stabilize microtubules. FGF13-deficient mice exhibit neuronal migration defects and weakened learning and memory. Recently, we find a single-nucleotide polymorphism (SNP) in the 5'-untranslated region (5'-UTR) of FGF13 mRNA (NM_001139500.1:c.-32C>G) in 3 male children suffering from severe intellectual disability. This SNP reduces the translation of FGF13. The induced neurons from the iPSCs carrying patient SNP reduce the neuronal polarization and increase the axon branching. Mice carrying the homologous point mutation in 5'-UTR of *Fgf13* show impaired cortical development and weakened learning and memory. Furthermore, this SNP reduces the interaction between FGF13 5'-UTR and polypyrimidine-tract-binding protein 2, which initiates FGF13 translation in neurons. Thus, the 5'-UTR SNP of FGF13 found in patients reduces the FGF13 translation, and causes cognition deficits.

Kasia Kozłowska

Update about Functional Neurological (Conversion) Disorder in Children and Adolescents

Functional neurological disorder (FND) is a multi-network brain disorder that encompasses a broad range of neurological symptoms. Children and adolescents with FND present in a broad range of clinical settings: general practice, accident and emergency, general paediatrics, and neurology services. A growing body of paediatric research suggests that stress-related increases in arousal—a state of activation and dysregulation—are a key element of the neurobiology of FND in childhood. This presentation provides a brief update pertaining to research findings in paediatric FND, underlines key messages from that research, and discusses how research findings are being integrated into paediatric best practice. Finally, the presentation highlights those interventions for paediatric FND involve a biopsychosocial, stepped care approach and those outcomes—in specialised programs—are excellent.

A Multi-Metric Registration Framework for the Alignment of Multimodal Longitudinal Brain Images in Pediatric Oncology

Eros Montin

Survival of pediatric patients with a brain tumor has increased over the past 20 years, and increasing evidence of iatrogenic toxicities has been reported. In follow-ups, images are acquired at different time points where substantial changes of brain morphology occur, due to childhood physiological development and treatment effects. To address the image registration complexity, we propose two multi-metric approaches (Mplus, Mdot), combining mutual information (MI) and normalized gradient field filter (NGF). The registration performance of the proposed metrics was assessed on a simulated dataset (Brainweb) and compared with those obtained by MI and NGF separately, using mean magnitude and mean angular errors. The most promising metric (Mplus) was then selected and tested on a retrospective dataset comprising 45 pediatric patients who had received focal RT for brain tumors were recruited for DTI exams and neurocognitive tests (23 males and 22 females, median age at RT 6.2 years, median age at evaluations 11.1 years). The quality of the realignment was scored by a radiation oncologist using a perceived misalignment metric (PM). All patients but one was assessed as $PM \leq 2$ (good alignment), but the remaining one, severely affected by hydrocephalus and pneumocephalus at the first MRI acquisition,

scored PM = 5 (unacceptable). The workflow allowed us to identify in a different article 10 ROIs where RT dose and DTI metrics were significantly associated with cognitive tests results ($p < 0.05$), implying a possible cognitive or neuropsychological iatrogenic damage that can be decreased by avoiding those areas in the treatment plan. The framework will be made available to the scientific community in 2022 via the Cloud MR portal (<http://cloudmrhub.com>).

Engram in the medial orbitofrontal cortex as an elemental representation of binge alcohol drinking

Gilles E Martin

Binge alcohol drinking, generally defined as a drinking pattern that rapidly brings blood alcohol levels to 0.08 percent or higher, is most prevalent in late adolescents and young adults. Crossing the binge threshold increases the risk of acute harm, such as blackouts and overdoses, and is commonly believed to be a gateway to alcohol dependence. To understand the impact of binge drinking on brain function, we focused our research on the nucleus accumbens, a forebrain region thought to mediate the rewarding properties of all drugs of abuse, including alcohol. Our research supports the contention that binge alcohol drinking controls alcohol consumption by regulating the excitability of medium spiny neurons (MSNs), the sole neuronal population that sends downstream projections controlling behavior. MSNs receive glutamatergic projections from multiple forebrain and limbic regions such as the prefrontal cortex (PFCx) and basolateral amygdala (BLA), respectively. While the PFCx is responsible for evaluating long-term consequences and planning and is instrumental in retrieving drug-associated memories, the BLA encodes emotions that shape impulsive behavior and the response to associative learning. We recently showed that binge alcohol drinking is instrumental in helping MSNs prioritize emotional information from the BLA over cognitive information from the PFCx, possibly explaining the loss of control associated with binge drinking. We also found that binge drinking impacts MSNs glutamatergic synaptic transmission through the control of dopamine released by cholinergic interneurons. Taken together, our research demonstrates that binge alcohol drinking modulates the accumbens output through its complex interwoven action on glutamatergic, cholinergic and dopaminergic synaptic transmission. Importantly, we also found that optogenetic manipulations of accumbens glutamatergic and cholinergic synaptic transmission alter binge alcohol drinking.

Species-Specific Functional Features of Main Neuron Types in The Human and Rodent Neocortex

Karri Lamsa

There are substantial species differences in the properties of mammalian neurons, yet theories on human brain circuit activity, information processing and disease mechanisms are based heavily on results obtained from rodents and other experimental animals. Recent human neuron studies, utilizing living brain tissue resected in brain surgery, show that human neocortex has various microcircuit-level functional specializations not present in rodent, the most common experimental animal of biomedical research. Many of the species-specific features are associated with neural signaling speed and accuracy, and neuronal computation. My talk will summarize recent findings on the functional microcircuit specialization in the human neocortex, compared to rodent. I will review recent

experimental data on human excitatory glutamatergic principal cells and inhibitory GABAergic interneurons of the supragranular neocortex. I speculate that many species-specific neuronal features may contribute both to the greater cognitive capacity of humans as well as our susceptibility to neurodegenerative and neuropsychiatric disorders. This necessitates direct experimental investigation of human neurons despite the challenges in obtaining healthy tissue.

OTOF-Related Auditory Neuropathy Spectrum Disorder

G.A. Tavartkiladze, M.R. Lalayants, O.L. Shatokchina, N.M. Galeeva, T.G. Markova, O.P. Ryzhkova, A.V. Polyakov

Objective: Auditory neuropathy spectrum disorder (ANSD) is an electrophysiological label, that incorporates patients with hearing loss of different etiologies and pathogenesis, but united based on the presence of pre-neural cochlear responses such as otoacoustic emission (OAE) and cochlear microphonics (CM) and absent or grossly abnormal neural responses – auditory brain stem responses (ABRs) are usually absent. The ANSD etiology and pathophysiological mechanism of hearing loss predispose clinical features and cochlear implantation outcomes: patients with auditory synaptopathy have much better rehabilitation outcomes than patients with auditory neuropathy type of ANSD. The most common genetic cause of ANSD are *OTOF* gene mutations. Mutations in the *OTOF* gene encoding otoferlin result in a disrupted function of the ribbon synapses of inner hair cells, which predispose synaptopathy type of ANSD.

The aim of this study was to estimate the prevalence of *OTOF* mutations in Russian children with ANSD and evaluate electrophysiological and clinical features of *OTOF*-related ANSD.

Methods: 46 children with ANSD underwent two-step genetic testing: first step – *GJB2* gene testing to exclude *GJB2*-related hearing loss; second step – Next Generation Sequencing (NGS) to explore another 30 hearing loss genes (including *OTOF* gene) and/or exome sequencing. Electrophysiological testing in this study, besides standard audiological tests, included registration of electrically evoked auditory brainstem responses (eABR) and intracochlear electrocochleography (ECoG), which were performed after cochlear implantation.

Results: NGS-testing revealed *OTOF*-related ANSD in 10 out of 46 tested cases (22%). All 10 children with the *OTOF*-related ANSD passed hearing screening. OAE were present till the last testing at the age of 12 years in the oldest child. ABR were not detectable at 100 dB nHL, ASSR were measurable bilaterally at all frequencies in all cases, but they did not correlate with behavioral thresholds indicating severe hearing loss. After cochlear implantation auditory nerve action potentials to electric stimulation were detected within normal range, and eABRs were recordable in all 5 tested cases of *OTOF*-related ANSD. Clear CMs in *OTOF*-related ANSD were obtained at all tested frequencies during intracochlear ECoG.

Summary: Genetic testing of children with ANSD, first of all *OTOF* testing, enables to reveal hearing loss etiology at least in 22% of cases. and provide the optimal rehabilitation approach, including cochlear implantation, as early as possible. Electrophysiological testing (especially eABR) support pathophysiological mechanism of *OTOF*-related ANSD (synaptopathy) and enables to predict good rehabilitation outcomes after cochlear implantation.

Keywords: auditory neuropathy spectrum disorder, *OTOF*, eABR, electrocochleography

Regulation of Neuronal Morphogenesis by 14-3-3epsilon (Ywhae) via the Microtubule Binding Protein, Doublecortin

Kazuhito Toyooka

Mutations in activity-dependent neuroprotective protein (ADNP) are among the most common causes of autism spectrum disorder (ASD) and are associated with ADNP syndrome, in which ASD is one of the most prominent symptoms. Adnp regulates a number of cell events during the development of the cerebral cortex, including neuronal morphology and functional connectivity. As there is no treatment for patients with ADNP syndrome, it is imperative to investigate ADNP's role during development. The disruption of Adnp in the developing cortex led to multiple deficits in neuronal morphology, dendritic spine formation, neural connectivity, and neural activity. Furthermore, we demonstrated that Adnp is phosphorylated by PKC and transported and/or retained in the cytoplasm by a 14-3-3 protein during neuronal differentiation in the cortex. Ultimately, this shuttling/retention mechanism has caught our attention as well as is clinically relevant, because the most severe cases of ADNP syndrome are caused by mutations that result in ADNP remaining in the nucleus or cytoplasm. Furthermore, Adnp regulates the distribution of microtubule binding protein, MAP6, to microtubules within the cytoplasm. These studies will provide fundamental and transformative insights into the mechanisms that underlie ADNP syndrome and offer new perspectives for its treatment.

Superior Colliculus: Fast Detection of Danger and Defensive Behaviors in Norm and Pathology

Ludise Malkova

Threatening stimuli require fast detection and response from an organism. Based on studies in rodents, patients with "blindsight", and fMRI in control subjects, rapid detection of threatening stimuli may rely on a fast (subcortical) pathway. The proposed pathway includes the superior colliculus (SC), pulvinar, and amygdala. While documented in rodents, this pathway in primates was proposed only through MRI-based approaches. We injected retrograde tracers into the amygdala and anterograde tracers into SC and found regions of colocalization of these signals within the pulvinar in macaques (Elorette et al., 2018), most notably in the medial portions of the medial, oral and inferior pulvinar. Thus, our anatomical study filled the gap between the human/primate imaging studies and the rodent data and confirmed the hypothesis that pulvinar connects SC with the amygdala.

SC, a midbrain structure, consists of superficial layers, subserving visual processing, and deep/intermediate layers (DLSC), subserving multimodal integration. Integration of sensory information about environmental stimuli allows for rapid reflex-like responses to potential threats. DLSC functions in a larger network (periaqueductal gray, amygdala, and hypothalamus), well characterized in rodents, referred to as the "brain aversion system." Activation of this network evokes defensive behaviors (freezing, cowering, escape) and increased sympathetic arousal. Stimulation of the DLSC in rodents evokes both orienting (approach) and defensive responses, dependent on distinct output projections. In non-human primates (NHP), DLSC role was documented only in orienting behaviors (eye movements). We found (Desjardin et al., 2013) that activation of DLSC by intracerebral infusions of the GABA-A receptor antagonist, bicuculline methiodide, resulted in defensive

behaviors (cowering, escape, vocalizations), similar to those observed in rodents. We were the first to demonstrate that DLSC is an important substrate for defense-like behavior in the NHP, making it a likely substrate for this type of behavior in humans. Under normal conditions, this system serves as a rapid detection and response mechanism for avoiding sudden and threatening stimuli. When disinhibited, the defense-like responses emerge, resembling symptoms seen in post-traumatic stress disorder (PTSD). Indeed, studies in human patients with PTSD documented an overactivation of the SC under subconscious threat (Lanius et al., 2016).

Drosophila Melanogaster as a Model to Study the Effects of Drugs of Abuse on Brain Morphology and on Specific Neuronal Populations

Norma Andrea Velazquez-Ulloa

Alcohol and tobacco are consumed by millions of people worldwide, many of which become addicted to these drugs and many of whom die from complications associated with tobacco or alcohol abuse. *Drosophila melanogaster* is a model organism that has been successfully established in the last 30 years for the study of the genetic and molecular mechanisms of drugs of abuse, including alcohol, nicotine, cocaine and amphetamines. Most studies to date have focused on acute effects of the drugs. However, some studies have also looked at developmental effects of ethanol and nicotine. These studies have shown that known effects of alcohol and nicotine, the addictive compound in tobacco, are recapitulated in the *Drosophila* model. For example, flies exposed to these drugs have decreased survival, increased development time, and decreased weight. Moreover, these studies have also shown that developmental exposure to these drugs changes the acute response to these drugs in the adult organisms. Both exposure to ethanol or nicotine during development decrease the sensitivity to ethanol sedation in adult flies. In addition, developmental drug exposure resulted in morphological changes in the central nervous system, including changes in brain size and in specific neuronal populations. In particular, these studies have shown that insulin and dopamine neurons are altered. More work is needed to continue characterizing the neurological effects of ethanol and nicotine after developmental exposure. *Drosophila melanogaster*, with its fast generation time and documented similarities in some of the effects of these drugs in mammalian systems, is a complementary model to continue learning about how these drugs change the nervous system and how those changes impact behaviors later in life. In addition, the state-of-the-art molecular tools available to *Drosophila* researchers, make it a great model to elucidate genetics and molecular mechanisms that may uncover new targets for treatments of the effects of drugs of abuse during development.

Leveraging cancer elements to treat neurological disorders

DaZhi Liu, PhD.

Compelling evidence shows oncogenes/kinases that have been widely studied in cancers can be leveraged to treat neurological disorders including traumatic brain injury (TBI). Taking tumor suppressor miR-125 in TBI as the case, we hypothesized that miR-125 mimic improves outcomes after TBI, because miR-125 decreases multiple target oncogenes/kinases.

Using moderate lateral fluid percussion TBI model, our data show that miR-125 mimic (2.4 mg/kg, wrapped by PEG-liposomes, i.v.) blocks leukocyte infiltration, reduces cognitive

deficits, and decreases neuronal death in hippocampus after TBI. Our miR-125 targetome studies show that a set of miR-125 target genes (Mknk2, Alk3, Neu1, others) are responsible for the therapeutic efficacy of miR-125b mimic on TBI.

In summary, this study shows that miR-125 mimic improves TBI outcome via decreasing miR-125 target oncogenes/kinases (Mknk2, Alk3, Neu1). This study will contribute to the literature of oncogenes/kinases pathophysiology in the TBI field. The combined use of i.v. miR-125 mimic and liposomes to treat TBI in rats is novel, and can be translated to treat human TBI.

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Real-Time In Vivo Imaging of Interactions of Phagocytes with Disseminating Cryptococcus Neoformans in the Brain Vasculature

Meiqing Shi

Cryptococcus neoformans is an encapsulated pathogenic fungus, accounting for 180,000 deaths worldwide annually. The infection starts in the lung and the yeast cells can disseminate to the bloodstream, particularly in HIV patients due to impaired cellular immunity. Once the organisms enter the blood, they can invade the brain across the blood-brain barrier, causing fatal meningoencephalitis. The role of phagocytes during the invasion of C. neoformans into the brain remains incompletely understood. Here, with the use of intravital microscopy, we study the dynamic interactions of neutrophils and monocytes with disseminating C. neoformans in the brain vasculature of infected mice. We observed that neutrophils migrate to the arrested C. neoformans in the luminal surface of brain vasculature. Following interactions with C. neoformans, neutrophils were seen to internalize the organism and then circulate back into the bloodstream, resulting in a direct removal of the organism from the endothelial surface before its transmigration into the brain parenchyma. Complement C3 was critically involved in the recognition of C. neoformans by neutrophils and subsequent clearance of the organism from the brain. We also observed a substantial recruitment of monocytes, predominantly Ly6Clow monocytes in the brain vasculature during infection. The recruitment depends primarily on the interaction of VCAM1 expressed on the brain endothelium with VLA4 expressed on Ly6Clow monocytes. Furthermore, TNFR signaling is essential for the recruitment through enhancing VLA4 expression on Ly6Clow monocytes. Interestingly, the recruited Ly6Clow monocytes internalized C. neoformans and carried the organism while crawling on and adhering to the luminal wall of brain vasculature and migrating to the brain parenchyma. These data are the first to characterize directly the dynamic interactions of leukocytes with a microbe in the brain of a living animal and demonstrate a different role of neutrophils and monocytes during brain invasion of C. neoformans.

Species-Specific Functional Features of Main Neuron Types In The Human And Rodent Neocortex

Karri Lamsa

There are substantial species differences in the properties of mammalian neurons, yet theories on human brain circuit activity, information processing and disease mechanisms are based heavily on results obtained from rodents and other experimental animals. Recent human neuron studies, utilizing living brain tissue resected in brain surgery, show that human neocortex has various microcircuit-level functional specializations not present in rodent, the most common experimental animal of biomedical research. Many of the species-specific features are associated with neural signaling speed and accuracy, and neuronal computation. My talk will summarize recent findings on the functional microcircuit specialization in the human neocortex, compared to rodent. I will review recent experimental data on human excitatory glutamatergic principal cells and inhibitory GABAergic interneurons of the supragranular neocortex. I speculate that many species-specific neuronal features may contribute both to the greater cognitive capacity of humans as well as our susceptibility to neurodegenerative and neuropsychiatric disorders. This necessitates direct experimental investigation of human neurons despite the challenges in obtaining healthy tissue.

Central Nervous System Immunity; The Enigmatic Role of B cells and Antibody in Multiple Sclerosis Pathology

Gregory P Owens, PhD

Adaptive immune responses against self-antigens underlie multiple human neurologic diseases including multiple sclerosis, neuromyelitis optica, and paraneoplastic disorders of the CNS. Although B cells are infrequent in CSF under normal physiologic conditions, there is a recruitment and expansion of B cells within the CNS of autoimmune and infectious disorders that can be recovered and analyzed. In multiple sclerosis (MS) the most visible manifestation of humoral immunity is the presence of persistent CSF oligoclonal immunoglobulin G (IgG) bands. This is accompanied by elevated numbers of clonally expanded B cells and plasma blasts in CSF, meninges, and brain tissue. B cell receptor sequencing has further established clonal relationships between CSF IgG oligoclonal bands and CSF B cell clones, and between CSF, meningeal and MS lesion B cell infiltrates. Despite the successful treatment of disease with B cell depleting therapies, the trigger of CNS clonal expansion and the putative role of B cells in disease pathology remains enigmatic. To better understand the intrathecal B cell response in MS, we have utilized single cell B cell sequencing to construct recombinant monoclonal IgG1 antibodies (rAbs) from expanded CSF plasma blast clones. A subset of MS rAbs bind to white matter tracts and to discrete surface domains along oligodendrocyte (OG) processes and myelinated axons indicating a possible role in CNS demyelination; indeed, myelin-specific rAbs cause rapid oligodendrocyte cell death and myelin loss when applied to mouse cerebellar explant cultures or when injected with human complement into mouse brain. Demyelinating lesions are accompanied by terminal complement deposition and infiltration of CD68+ phagocytes. Pathogenic myelin-specific rAbs are also being used to investigate mechanisms of myelin repair to better understand the failure of remyelination in MS. We hypothesize that antibodies to myelin antigens offer a defined pathogenic mechanism for lesion formation in multiple sclerosis consistent with the histochemical description of Type II MS lesions.

Neuroinvasive forms of infectious diseases caused by Yersinia

Andrey Dmitrovskiy

Introduction: In a broad sense, the term Yersinioses can represent all diseases caused by representatives of the genus Yersinia.

However, historically, epidemiologically, pathogenetically and clinically, the Plague (a disease caused by *Y.pestis*) stands apart from the rest of the group. Therefore, in our understanding, under the term Yersinioses, it is necessary to consider diseases caused by "other" Yersinia, as more well-known, having their own names, for example, - Pseudotuberculosis (*Y.pseudotuberculosis*), or Yersiniosis (*Y.enterocolitica*), and "new", "rare" diseases caused by *Y.kristensenii*, *Y.frederiksenii*, etc. Therefore, in the future we will operate with the terms – Plague (*Y.pestis*) and Yersinioses (*Y.pseudotuberculosis* and *Y.enterocolitica*).

Material and methods: Under our supervision, 110 cases of Plague (*Y.pestis*) have passed in different years in Vietnam and Kazakhstan, in addition, clinical materials have been retrospectively studied in 400 cases in Vietnam. Also, 110 patients with Pseudotuberculosis (*Y.pseudotuberculosis*) and 103 with Yersiniosis (*Y.enterocolitica*) were under our supervision. All cases were confirmed by the bacteriological diagnosis - isolation of culture.

Discussion: The secondary meningoencephalitic form of plague develops in 1.7% and proceeds in the form of two variants - meningitis and encephalitis. Meningitis developed more often after the primary generalized form from 10 to 34 days of illness, which is preceded by fever up to 39-40 ° C, an increase in the phenomena of shock, an increase in leukocytosis (up to $30-35 \times 10^9 / L$), more higher in the dead. The course of the disease is long-term undulating, the maximum temperature is fixed in parallel with meningitis, lasting from 2 weeks to 1 month and having a mixed neutrophil-lymphocytic character. Among the patients, women aged 20-39 years predominate, while "meningism" develops in men in adolescence (14-17 years).

Encephalitic variant developed only in men aged 16-42 years after bubonic and other primary forms during 2 (8-9 days) and 3 (12-16 days) waves (in the form of persistent paresis and paralysis, disorders of cranial nerves and tendon reflexes), which can lead patients to death in the first two weeks or cause for a long time (up to a month or more) persistent pathology.

The pathogen can be detected both in bubons and in the liquor and blood: In two patients with Pseudotuberculosis (1.8%) and 2 with Yersiniosis (1.9%), the disease proceeded in a neuroinvasive form. All patients with meningitis were young people aged 16-17 years, the disease began acutely with chills and fever 38.6 – 39.6, headache appeared and increased. Upon admission on the 4th – 8th day of the disease, hyperemia of the pharynx, general intoxication, systolic murmur on the upper part of the heart, liver enlargement and meningeal symptoms were detected. There can be vomiting, sore throat, polyadenitis, convulsive syndrome.

The fever persisted for 4-9 days. Meningeal symptoms were manifested in the form of rigidity of the occipital muscles and Kernig's symptom. Encephalitic symptoms – in the form

of a slight paresis of the facial nerve, weakening of the convergence of the eyeballs, torpidity of tendon reflexes. In the liquor there were increased protein – 0.33-0.66 ppm, Pandi reaction + - ++; leukocytes – 213-613; neutrophils – 14-52%; lymphocytes – 48-86%; sugar 50 mg / 100 ml.

Meiningeal symptoms disappeared by the 10th-14th day of the disease. Peripheral blood was without significant abnormalities.

The diagnosis was confirmed by the isolation of the pathogen from feces (11 day of illness) and urine (12 day of illness) and an increase in the titer of antibodies in autoagglutination reaction.

Conclusion: Thus, damage to the central nervous system can develop both in Plague and in other Yersinioses, with approximately the same frequency (1.7 – 1.9%), which requires testing for these infections in patients with meningoencephalitis in appropriate conditions.

Neuroscience and the Future of the Chemical and Biological Weapons Non-Proliferation Regime: A Key Role for the Medical Community

Malcolm Dando

At the Spiez 'Convergence' Conference held in late 2021 at the Swiss Federal Institute for Nuclear, Chemical and Biological Protection one contribution demonstrated how an artificial intelligence system designed to generate novel drugs for the treatment of neurological diseases could easily be manipulated to generate thousands of novel chemical nerve agents - many of which were much more toxic than known nerve agents. This was dramatic bad news, but fitted easily within the usual understanding of dangerous dual-use research being related to the development of new chemical and biological agents. However, it was far from a worst-case scenario because, as a paper by US strategic analysts at the turn of the century pointed out, advances in the life sciences would lead to a paradigm change in which weaponeers could be able to switch their attention from modifying known agents to developing novel agents to attack the ever-increasing number of potential targets being revealed within the physiology of living organisms. A classic example of this process, of course, is the new State-level funded brain research projects devoted to elucidating the neuronal circuits underlying our behaviour. Set against such scientific advances the CBW non-proliferation regime is in a state of crisis, with the Chemical Weapons Convention being unable to halt the use of chemical weapons in warfare and assassinations and the Biological and Toxin Weapons Convention remaining in its 20years state of stagnation. However, biological security requires the application of various tools and mechanisms at different levels and one hopeful sign is the interest amongst States Parties to these Conventions in providing ethical guidance related to the Non-Proliferation Regime as in the 2015 Hague Ethical Guidelines for chemists and the more recent Tianjin Ethical Guidelines for life and associated scientists. It is suggested that the medical community, with its much longer concerns and activities in support of the CBW Non-Proliferation Regime, could play an important part in the adoption in Codes of Conduct derived from these ethical guidelines amongst their chemical, life and associated scientific colleagues through advocating their implementation along with the biological

security education necessary to underpin this important support for the prevention of chemical and biological weapons.

Nanoparticles Designed and Optimized for Intranasal Administration of Gene Therapy of Huntington's Disease

J. Sanchez-Ramos, PhD, MD

Background: Lowering HTT gene expression in patients with Huntington's Disease (HD) currently requires chronic administration of anti-sense oligonucleotides (ASO) or small interfering RNA (siRNA) into the cerebrospinal fluid (CSF) by intrathecal infusions or direct intracerebral injections. Ongoing clinical studies have demonstrated that intrathecal administration of anti-HTT ASO is well-tolerated for at least several years. However, repetitive long-term intrathecal infusions can result in range of complications and may not be acceptable for a lifetime of treatment.

Approach: In developing a nose-to-brain nanocarrier system for gene therapy, we prepared a series of nanoparticle (NP) formulations that used chitosan or other matrix materials for encapsulating anti-HTT siRNA. The NPs were designed to package the maximum amount of siRNA (an "enrichment" procedure) while at the same time protecting the payload from degradation "en route" to the target.

Results: Optimization experiments identified key factors to improve production of effective nanocarriers of anti-HTT siRNA. We identified four enriched chitosan-based formulations of NPs that protected the payload in transit while not impeding release of the siRNA in the target brain tissue. All four formulations were effective in lowering HTT mRNA expression by at least 50% in the YAC128 mouse model (HD).

Conclusion: Intranasal administration of nanoparticles carrying siRNA is a promising therapeutic alternative for safe and effective lowering of mutant HTT expression.

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Glucose-induced neurotoxicity is dependent on MMP-13 activity in the epidermis

Rieger S, Waldron AL, Schroder PA, Bourgon KL, Bolduc JK, Miller JL, Pellegrini AD, Dubois AL, Blaszkiewicz M, Townsend KL

Diabetic peripheral neuropathy (DPN) affects approximately 300 million people worldwide. This progressive condition of axon degeneration manifests in sensory nerve endings innervating the epidermis, leading to symptoms such as pain, paresthesia (tingling), and numbness in the hands and feet of patients. More severe DPN is characterized by the formation of foot ulcers, which can eventually lead to limb amputations. The causes leading to DPN have largely remained unknown. We created a zebrafish model to investigate the underlying mechanisms in vivo. According to these findings, activation of Matrix-Metalloproteinase 13 (MMP-13) in the epidermis is a primary cause of neuropathy. MMP-13 is activated by the formation of reactive oxygen species in the epidermis and causes axon damage due to increased extracellular matrix (ECM) degradation, affecting unmyelinated sensory nerve endings embedded within the ECM. We also show that inhibiting MMP-13 pharmacologically prevents glucose neurotoxicity in zebrafish and a type II diabetic mouse model. These findings suggest that MMP-13 is a new candidate target for DPN treatment.

Neuroinflammation – Friend or Foe in Ischemic Stroke?

Gabriela Vlădoiu (Catană)

In Ischemic Stroke (IS), inflammation plays a pivotal role exerting both beneficial and detrimental effects. In fact, activation of resident cells, such as microglia, astrocytes, and endothelial cells is neuroprotective and promotes brain regeneration and recovery, whilst the recruitment of immune cells expressing inflammatory mediators and leading to blood-brain barrier (BBB) disruption is responsible for neuronal death, brain edema, and hemorrhagic transformation. As early diagnostic accuracy of brain computed tomography scan is only about 85%, many studies in the last few years attempted at investigating the prognostic ability of inflammatory biomarkers toward IS diagnosis as well as response to treatment and prognosis. However, an individual biomarker validated for clinical use has not been identified yet. The main pro-inflammatory cytokines involved in the pathophysiology of ischemic stroke are: IL-6, IL-1 and tumor necrosis factor (TNF-alpha and TNF-beta). These markers are highly evident in the high traumatic central nervous system (CNS), giving rise to collateral damage. Following the acute phase of CNS trauma, the IL-1 and IL-6 drive a low-level and chronic inflammatory response, leading to cognitive impairments and reduced neuronal plasticity. Anti-inflammatory strategies are providing promising tools for regulating the inflammatory processes that take place during the acute phase of stroke, which predominantly produce deleterious effects. While several therapeutic strategies have been successful in both experimental models of ischemia and clinical trials, the translation from bench-to-bedside is still missing. Perhaps a better understanding of the inflammatory mechanisms involved during ischemic stroke would increase the knowledge of possible therapeutic targets to be modulated to fight against the disease and its complications.

Keywords: neuroinflammation, stroke, interleukins.

Seizures and electroencephalography findings in 61 patients with fetal alcohol spectrum disorders

Susana Boronat

Fetal alcohol spectrum disorders (FASD) cause neurodevelopmental abnormalities. However, publications about epilepsy and electroencephalographic features are scarce. In this study, we prospectively performed electroencephalography (EEG) and brain magnetic resonance (MR) imaging in 61 patients with diagnosis of FASD. One patient had multiple febrile seizures with normal EEGs. Fourteen children showed EEG anomalies, including slow background activity and interictal epileptiform discharges, focal and/or generalized, and 3 of them had epilepsy. In one patient, seizures were first detected during the EEG recording and one case had an encephalopathy with electrical status epilepticus during slow sleep (ESES). Focal interictal discharges in our patients did not imply the presence of underlying visible focal brain lesions in the neuroimaging studies, such as cortical dysplasia or polymicrogyria, however they had nonspecific brain MR abnormalities, including corpus callosum hypoplasia, vermis hypoplasia or cavum septum pellucidum. The latter was significantly more frequent in the group with EEG abnormal findings ($p < 0.01$).

The effect of nanostructuring of semi-conductor or polymer materials in neural cell cultures: implications for neural implant design

Gaëlle Piret, Fannie Darlot, Jean-Marie Mayaudon, Vijayalakshmi Rajendran, Lionel Rousseau, Maria-Thereza Perez, Christelle N. Prinz

Nanowires can be used in a broad range of bio-applications among which are neural implants for brain computer interface or neuroprostheses. We have shown that neurons from the Central Nervous System thrive when cultured on vertical arrays of semi-conductor nanowires (NWs), whereas the growth of glial cells on such arrays is limited compared to when cultured on flat substrates. However, semi-conductor nanowires present challenges in terms of integration in neural implants, such as their integration in a flexible substrate and their resistance to corrosion. We have analyzed the interaction of neuronal cells with NWs made from insulator polymers that are usually used for neural implants. For this purpose, we performed retinal and cortical cell cultures on SU8 and parylene-C polymer NWs. Four μm long SU-8 NWs positively influenced cell adhesion and neurite network formation compared to 1 μm long SU-8 NWs and flat SU-8 substrates. However, flat parylene-C was found to be the best polymer. Although we anticipate that parylene-C NWs might improve cell behavior, it has not yet been possible to obtain parylene-C NWs longer than 2 μm . Taken together, these results suggest that arrays of nanowires are promising nanomaterials for designing neural interfaces and that the type of material and shape/dimensions of such nanomaterials play an important role.

Physical Activity and Neurology for the Older Population – From a Sports Scientist Perspective

David Sullivan

Physical activity is an elixir of mental and physical health benefits. Even though the benefits of physical activity are strongly recommended for the maintenance of health and wellness, there is a substantial proportion of the population old and young not fulfilling the recommended guidelines. In this presentation I am going to highlight some of the findings of 2 studies and the relationship between other strength training programs with brain health. First, the effects of the growing strong program on neurotransmitter (serotonin, dopamine, epinephrine, and norepinephrine) and depression (Korean version of the short form of Geriatric Depression Scale) of older females. The data from this study shows significant differences between the control and exercise group for all the neurotransmitters with a large effect on epinephrine and norepinephrine. With both groups starting with a normal score in the depression scale the control group score increased from 5.2 to 6.7, which shows an increase in depression whereas the strength training group decreased but not significantly. Second, the effects strength training has on homocysteine, total cholesterol, triglyceride, erythrocyte sedimentation rate (ESR), blood pressure, heart rate

and senior functional fitness test (SFT) for the elderly daily life. This study the data shows significant interaction effect for the homocysteine, with significant main effects for the ESR, total cholesterol, and triglyceride. In the second half of the presentation, I will focus on providing some of the latest research linking the effect that strength training has on brain health related factors, such as cognitive function, neurotransmitters, hippocampus volume, endorphins, etc. Finally, I will present some of the latest research on how novel technologies, such as VR/AR are being used to stimulate the enjoyment of exercise and to address the challenges faced due to ageing with the development of digital therapeutics.

Focal thinning of the ganglion cell-inner plexiform layer mostly related to visual function and disability in patients with multiple sclerosis

Ce Shi, MD, Hong Jiang, MD, Ph.D., Giovana Rosa Gameiro, Jeffrey Hernandez, Yi Liu, MD, Ph.D., Silvia Delgado, MD, Jianhua Wang, MD, PhD

Objective: Thinning of peripapillary retinal nerve fiber layer (pRNFL) and combined ganglion cell and inner plexiform layer (GCIPL) as measured by optical coherence tomography (OCT) are reported in multiple sclerosis (MS) patients. However, the commonly used average thickness of these imaging markers may not be sensitive enough to detect the subtle changes that could be used to monitor disease progression and therapeutic efficacy. The goal of this project was to map the thickness of the intraretinal layers in detailed partitions to determine the most relevant OCT measures to visual function and physical disability in MS.

Design: Cross-sectional study.

Participants: Thirty relapsing-remitting MS (RRMS) patients without history of optic neuritis, and 38 age- and gender-matched healthy controls were recruited.

Methods: Both eyes of each subject were imaged using UHR-OCT to obtain volumetric data centered on the fovea. The thickness maps of six intraretinal layers were analyzed to determine the topographic thickness alterations. The association between OCT measures, low contrast visual acuity (LCVA) and Expanded Disability Status Scale (EDSS) were assessed.

Results: The changes in the intraretinal layer thickness were visualized in the MS group. The macular RNFL showed thinning mainly in the outer nasal sector, and the GCIPL showed horseshoe-like thinning, profoundly at the nasal sector. The GCIPL thickness in the nasal quadrant (GCIPL-N) had the most differentiation power in detecting retinal neurodegeneration, which highly related to LCVA and EDSS.

Conclusions: The GCIPL-N was highly sensitive and associated with visual function and physical disability. Focal thinning of GCIPL-N were mostly related to visual function and disability in patients with multiple sclerosis, which can be potentially developed as a more sensitive biomarker for detecting subtle neurodegeneration.

Immortalized adult rodent Schwann cells as useful tools to study peripheral nerve degeneration and regeneration

Kazunori Sango

Schwann cells play an essential role in the functional maintenance of the peripheral nervous system, and their abnormalities can trigger various kinds of intractable neuropathies and impairment of axonal regeneration after injury. We have established spontaneously immortalized Schwann cell lines IMS32 and IFRS1 from adult ICR mice and Fischer344 rats, respectively. These cell lines retain the characteristic features of Schwann cells, such as spindle-shaped morphology with expression of glial cell markers, and synthesis and secretion of neurotrophic factors (e.g., nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF)). IMS32 cells have been utilized for exploring the action mechanisms of neuroprotective molecules (e.g., ciliary neurotrophic factor (CNTF), sonic hedgehog, and oxidized galectin-1) and the pathogenic factors of diabetic neuropathy (e.g., polyol pathway hyperactivity, glycation, and oxidative stress). IFRS1 cells possess the capability of myelinating neurites in co-culture with adult rat dorsal root ganglion neurons and NGF-primed PC12 cells, and these co-culture models have been utilized for exploring the action mechanisms of myelination-promoting molecules (e.g., GDNF, CNTF, soluble neuregulin-1 type III, and extendin-4) and the pathogenesis of amiodarone-induced demyelinating neuropathy. These Schwann cell lines are useful tools to study axonal degeneration and regeneration and establish novel therapeutic approaches toward neurological manifestations in patients with relevant diseases.

Automated computer-assisted detection method for cerebral aneurysms in time-of-flight magnetic resonance angiography based on deep learning

Chen Geng

Screening for aneurysms in the asymptomatic stage of aneurysms can reduce the possibility of subarachnoid hemorrhage and other fatal consequences. At present, time-of-flight magnetic resonance angiography is the most commonly used non-invasive screening method for aneurysms. Convolutional neural networks have been applied to the detection of aneurysms, and three-dimensional features have been found to play an important role in the detection.

In our study, we proposed an improved 3D U-Net embedding the 3D SENet module, and proposed a complete set of automatic aneurysm detection methods, including automatic extraction of cerebral artery regions and aneurysm detection based on the deep neural network. A total of 231 magnetic resonance angiography image data are used in this study, among which 132 are training sets, 34 are internal test sets and 65 are external test sets. The presented method obtained 97.89 (0.88% sensitivity in the five-fold cross-validation and obtained 91.0% sensitivity with 2.48 false positive/case in the detection of the external test sets. The study proved the feasibility of 3D U-Net in the task of aneurysm detection and the effect of channel attention mechanism on the network performance in this task.

Central poststroke pain, comorbidity, and associated symptoms in animal and human models

Andrew Huang

The objective of the present review paper was to comprehensively introduce the pain symptom and comorbidities of depression, anxiety, and learning and memory dysfunctions in the central poststroke pain (CPSP) of human and animal models. CPSP is a disease in which the lesion or dysfunction of the spinothalamocortical circuits is due to thalamic stroke hemorrhage. According to previous literature, CPSP patients experience impaired explicit and implicit learning and memory in addition to the pain symptom. Moreover, there are associated depression and anxiety comorbidities for CPSP. However, the data from some clinical studies were not supportive of the notion that CPSP patients also experienced induced comorbid depression and anxiety. On the other hand, the motor function test was likely to be inconsistent in terms of the results of human and animal models. The review paper provides some implications for further development of animal models for examinations of CPSP comorbidities of depression, anxiety, learning and memory dysfunction, and motor functions, aside from the central pain symptom. In human models, some conflicting data related to comorbid depression, anxiety, explicit and implicit learning memory, and motor dysfunctions should be re-elucidated in further studies.

Use of High-Dose Omega-3 Fatty Acids to Treat Severe Brain Trauma.**Barry Sears, Ph.D.**

Severe brain trauma is characterized by significant secondary inflammatory damage. The prognosis for successful recovery of patients with an initial Glasgow Coma Scale of less than seven is poor. High-dose omega-3 fatty acid concentrates (16 grams of EPA and DHA per day) has been used as an oral supplement can treat severe brain trauma in such patients. These cases will be discussed. It is hypothesized that the molecular mechanisms may be mediated by the increased production of specialized pro-resolution mediators (SPMs) derived from EPA and DHA. The mechanisms by which SPMs may reduce neuro-inflammation will also be discussed.

DNA Integrity and Huntington's Disease

Aris Polyzos, Jung Hyun Yoo, Ana Cheong, Zachary Nagel, Cynthia McMurray

Although the cause of Huntington's Disease (HD) has been established (a mutation in the Huntingtin gene), the pathways that lead from this to the death of neurons are still a field of study. This could be due to the numerous and varied effects that are part but not directly cause neuronal degradation in HD. An effective preventative therapeutic target to allow us to fully cure or prevent the disease still remains forthcoming. We have studied the genetic integrity of brain cells in mouse models of HD and have recorded increased levels of damage in the DNA of neurons that are associated with disease. These occur concurrently with altered brain metabolism and production of cellular DNA damaging agents (reactive oxygen species generated in the mitochondria) and alterations in the DNA repair capacity of diseased cells. Our findings are exploring the relevance of DNA integrity in the brain and during disease and could uncover pathways relevant to neuroprotective therapeutics.

NURSING & HEALTHCARE MANAGEMENT

Clinical Quality Registries: A New National Approach to Reporting on Adherence to Evidence Based Care and Longitudinal Outcomes

Bernadette Aliprandi Costa

The Australian Commission on Safety and Quality in Health Care (the Commission) has revised the Framework for Australian clinical quality registries (the Framework) in consideration of requirements for health service organisations working in partnership with the Commonwealth, states and territories to meet their obligations under the National Health Reform Agreement (Addendum 2020-2025) to implement arrangements for a nationally unified and locally controlled health system which 'improves access to, and the use of data to support service delivery and improved patient outcomes.'

Clinical Quality Registries (CQRs) provide the mechanism by which to report on the safety and appropriateness of health care which is considered an important part of healthcare safety and quality improvement; a patient and consumer right[1]; an essential professional requirement[2] and health data custodian obligation[3]. Health information aggregated via agreement with data custodians for quality improvement informs compliance with National Safety and Quality Health Service Standards[4], adherence to evidence-based care guidelines and standards and clinician/patient decision making.

The revised Framework provides the quality standard and national arrangements for clinical quality registries as the mechanism by which clinicians, health service organisations and jurisdictions working in partnership, can authorise and secure health record-level data, within high-priority clinical domains, to measure, monitor and report on the appropriateness and effectiveness of health care.

Treating our Trans Patients: Lessons from community-driven survey and community-care program**Brayden A. Misiolek**

A trans-led community care organization, with support from researchers at the University of Michigan, piloted a US-based survey, Finding Our Strength. The mixed-methods survey explores the burden of minority stress upon transgender/nonbinary/gender diverse adults, measuring self-reported worry about discrimination in various settings (including healthcare) and coping behaviors. Key themes include recognizing the significance of stress within the transgender/gender diverse population across multiple realms of a patient's daily life and the important role healthcare plays in supporting wellness outcomes. Better understanding the anticipatory worries and coping responses equip practitioners to deliver more culturally responsive care.

This oral presentation leverages programmatic insights of a trans-led community care organization along with research themes calling for engagement with trans populations to improve gender-affirming care. As community-based participatory research is quickly growing in recognition in the US, this survey piloted a distinct methodology in which every stage of the research process was led by the community, employing a range of qualitative interviews, peer-review sessions, and focus group testing. The trans/gender diverse community defined survey objectives, designed the questionnaire, facilitated feedback and review sessions, implemented the survey, analyzed data, determined key themes, and disseminated findings through multiple avenues. A traveling, interactive, art-meets-exhibit

was produced from the dataset. Results were used to create continuous education for healthcare professionals and ally training for significant others and loved ones. Findings were used to enhance services and programs for the trans/gender diverse population.

Objectives:

Learners can expect to:

Better understand trans/gender diverse patient worries and coping responses within healthcare settings.

Recognize the unique position pharmacists/clinicians have within transgender and nonbinary healthcare and the importance of culturally responsive care.

Understand the benefits of community-driven and community-participatory research.

How to Choose the Proper Dressing for Chronic Wounds

Tanja Planinsek Rucigaj, MD, PhD

Chronic wounds are a very important health, social and economic problem. In treatment of wounds, it is necessary to know the characteristic healing mechanism of wound, so that we can choose the right treatment. There are many wound dressings at our disposal today, depending of their characteristic we can choose the right one which in short time and with low costs will lead us to healing of the wound. There are a myriad of wound dressings and one not familiar with different groups and names of dressings will have a lot of problems in choosing the proper dressing which will be beneficial to promoting wound healing. Dressings for the treatment and care of chronic wounds we divide into three big groups: passive or non-occlusive, interactive or semi and occlusive dressings, and active or biologic dressings. The phases of wound healing have been divided into three phases after haemostasis: inflammatory phase, the proliferative phase and maturational phase. Tissue debridement, controlling infection and inflammation, moisture balance and care for wound edges are parts of wound bed preparation. So simple dressing is sufficient to stimulate autolytic debridement, control moisture balance and encourage healing in different phases of wound healing. Between hydrogels, dressings with supplements, alginates, hydrocolloids, fibres, foams, hydrocappilar dressings, silicone dressings, acrylates, therapeutical dressings, dressings with collagens, hydrobalance cellulose dressings, antiseptics, films and meshes we choose according to the phase of wound bed and moisture from wounds by Falanga's classifications of wound bed.

Civil society, third sector and healthcare: the case of social cooperatives in Italy

Giulia Galera

This paper explores the role played by social cooperatives in the transformations of the Italian welfare systems, particularly in the provision of social-health services.

Following a brief historical analysis of the emergence of social cooperatives in Italy, attention is paid to their integration in the welfare system up to the recent Covid-19 pandemic, which has shed new light on the greater resilience of a "proximity", community-based versus a highly hospitalized health system. Recent debates highlight the need to actively engage all key concerned actors in relevant decision making about the planning

and management of welfare services. These include on the one hand of public and private welfare providers and of health professionals; social workers; recipients; volunteers, on the other hand.

The presentation consists of two parts. Based on an exploratory case study analysis, the first part will focus on the pioneer experience of social cooperatives; the second part will assess the viability of a social-health integrated system, based on a genuinely collaborative interaction between social enterprises and public administrations. In this direction, attention will be paid to the opportunities offered by the recent Third Sector reform, which provides for a innovative regulatory framework – the so called "shared administration" channel- in the planning of activities of general interest.

Healthcare Informatics Schemata: A Paradigm Shift over Time

Scott Erdley

The healthcare informatics schemata, "A paradigm shift over time©" (Sackett & Erdley), is a graphic model visualizing the development and progression of informatics in health over time. Depicting the early 1950s through today, the model portrays past and current information technology trends, from computers as resource through computational ubiquity, and the movement to social media, e-health, mobility, big data, AI and VR/AR. The discrepancy between "real" and "proposed" world suggests a gap, involving issues such as value, interoperability and ontology, requiring attention, development and ultimately adoption hinging on a universal standards framework. Additionally previous significant models of health informatics will be reviewed, and using these as a framework for critiquing and adapting the schemata to the present and future.

Dult Degenerative Lumbar Spondylolisthesis: Nonoperative Treatment

Edward Soriano

Non-Surgical Management of Degenerative Lumbar Spondylolisthesis: Degenerative spondylolisthesis is associated with multiple pain generators causing low back and leg pain. Biopsychosocial comorbidities should be recognized and treated appropriately. Physical therapy may be effective and should be the first line of treatment. Spinal injections can assist in confirming and treating the source of low back and leg pain. Spinal cord stimulation may provide relief in properly selected patients. The management of degenerative spondylolisthesis requires a comprehensive team approach to assess and treat all possible pain generators and underlying biopsychosocial factors.

The role of apology and forgiveness in second victims after a medical error.

Carla Martos

In the healthcare field, we know patient safety incidents are unfortunate events that occur. Two groups are affected by these incidents: Patients become first victims and the professionals involved turn into second victims. All of them need adequate support. The main objective of this study is to determine if forgiveness can play a significant role in the aftermath of a medical error. Specifically, the study explores the need for forgiveness of professionals after a patient safety incident, using a quantitative methodology. We also

include a qualitative approach to the need for forgiveness in professionals who have experienced a patient safety incident. Results indicated that forgiveness contributes to professionals' wellbeing. Knowing if the patients have forgiven helps professionals in their recovery process as second victims. These findings suggest that developing interventions, where forgiveness is facilitated between first and second victims, Contribute To Both Parties' Welfare.

Keywords: Patient Safety Incident, Second Victim, Apology, Forgiveness, Medical Complaint, Mental Health.

Evidence Based Longevity

Jose Barreto

We are experiencing an exponential growth of research and interest in longevity. Currently about 12% of the world's population is over 60 years old and this percentage will continue to increase in the coming decades. Aging is a known risk factor for most chronic conditions and disabilities and advances in this new field will improve the quality of life of the world's population. At the same time, this growing field is attracting many unproven claims, therapies and products claiming to have anti-aging or positive longevity effects. In this presentation, you will learn about different evidence-based interventions and lifestyle factors that can help you and your patients increase healthspan and potentially lifespan.

NUTRITION

Interaction between arsenic and high-fat diet on lipometabolic and endocrine alterations of adipose tissue associated with metabolic syndrome

Andrea Diaz Villasenor

White adipose tissue (WAT) dysfunction can develop in response to high caloric intake and/or endocrine disrupting chemicals (EDCs), among other factors. Arsenic is an EDC and its exposure through drinking water is a public health concern for many countries. Arsenic is a risk factor for type 2 diabetes and cardiovascular disease. However, little is known about its effects on WAT fatty acid metabolism and endocrine functionality, and even less in combination with high-fat diet.

Thus, the impact of chronic exposure to environmentally relevant arsenic doses was evaluated in an in vivo model of mice fed control or high-fat diet and in an in vitro model of 3T3-L1 adipocytes co-exposed to high doses of palmitic acid.

Different aspects of fatty acid metabolism were evaluated in visceral and subcutaneous mouse fat depots. The combination of arsenic and high-fat diet affected the most, mainly in retroperitoneal visceral adipose tissue (rVAT). However, selective WAT insulin resistance occurred in epididymal visceral adipose tissue (eVAT). Both fat depots impairment by the combination of arsenic and high-fat diet, contributed to the exacerbation of systemic insulin resistance phenotype and weight gain.

Leptin and adiponectin synthesis and secretion were also evaluated in mature 3T3-L1 adipocytes exposed to high doses of palmitate (simulating excess fat intake), to arsenic or to both throughout two different stages of adipogenesis.

The secretion of leptin and adiponectin decreased by arsenic alone or in combination with palmitate due to an impairment at the transcriptional level for leptin and at the intracellular protein amount level for adiponectin, with changes in the multimers proportion secretion.

Adiponectin was more affected when exposure started at the beginning of the cell differentiation, whereas the effects on leptin were higher when exposure started once adipocytes were mature.

Arsenic exposure in combination with an elevated amount of fat impairs different aspects of fatty acid adipose metabolism and synthesis and secretion of leptin and adiponectin.

Early-Life Manipulation of Gut Microbiome and Prevention of Breast Cancer

Chantal Matar

Early-life microbiota disruption or dysbiosis and its long-term consequences is considered as a major public health issue. Microbiota perturbations is sufficient to drive lasting metabolic changes and permanent endocrine alterations and potentially favor oncogenesis. Even after microbiota recovery, phenotypic changes such as remains with long-term effects on developmental programming. The Gut-Breast axis is important in regulating tumor growth and inflammation. Puberty is a critical period more responsive to stressors than in adulthood during which the mammary gland will be formed and exocrine glands could acquire pre-carcinogenic lesions if a stressor is present. Acute immune stress during puberty, when mammary tissue is undergoing extensive modeling, may result in epigenetic changes and specifically influence pubertal breast development and breast cancer risk in adulthood. Moreover, some epigenetic changes could be microbiota-dependent and affect the expression of many genes that predispose to long-term physiological programming at organs distant from the intestine.

Therefore, we investigated in animal models whether dietary approaches counteract inflammation-induced dysbiosis and epigenetic deregulation, during critical period of life, and predisposition to breast cancer later in life. We have shown that not only diet will improve diversity and richness of gut microbiota but also will prevent epigenetic and functional deregulation at the mammary level as well as counteracting impaired development of the pubescent mammary gland. In addition, diet will prevent the establishment of mammary carcinoma in adult mice and prevent the formation of cancer stem cells as well. This study provided novel evidence-based data highlighting the potential of dietary interventions to correct dysbiosis at puberty in prevention of breast cancer in adulthood.

Immunomolecular contribution of *Chenopodium quinoa* to Nutrition precision for the immunotherapy against hepatocarcinoma

Laparra JM, Martínez A, Rueda MA, Garcia-Tejedor A.

Chenopodium quinoa seeds constitute a good source of serine-type protease inhibitors (SETIs), which display innate immune and metabolic effects ameliorating the hepatocarcinoma (HCC) severity in mice. Innate immunity in the tumor microenvironment plays a pivotal role in HCC progression. Macrophages can play opposing roles in regulating the tumor microenvironment, according to its different phenotype subtypes, worsening or improving, tissue homeostasis and cell proliferation. Here, innate immune 'Toll-like' receptor (TLR)-4 activation has been identified as a key determinant of HCC progression. SETIs were mostly responsible for the effects showing biological correlation with TLR4

signaling. The elucidation of functional and structural features showed that bioactive SETIs appear as protein homomeric complexes where proteins carry a glucoside prosthetic group, and exhibit partial resistance to gastrointestinal enzymes and, therefore, low bio-availability rates. Studies on high-fat diet (HFD) fed mice have shown that inclusion of flour from *C. quinoa* exerts beneficial immune and metabolic effects within the gut–liver axis. The effects were evaluated in different preclinical models: (i) wild type animals, (ii) those displaying inherited disturbances in glucose homeostasis, (iii) displaying dietary iron-mediated impairment of the innate immune TLR4/TRAM/TRIF pathway, (iv) presence/absence of intestinal lymphoid cells as determinants of lipid uptake and homeostasis. Inclusion of *C. quinoa* into bread formulations enabled targeting different risk factors for hepatocarcinoma (HCC) development, among other, FASN/NRLP3, insulin resistance, hepatic fat accumulation and innate immunity. Feeding SETIs to HCC-developing mice favored a better control of the hepatic lipid distribution of mono and poly-unsaturated (PUFA) fatty acids, improving the hepatocellular susceptibility to ferroptosis processes. SETIs play relevant roles in the phenotypic conversion and pro-inflammatory functional polarization of hepatic infiltrated macrophages towards a stabilized intrahepatic macrophage M1-like phenotype (CD68+CX3CR1+CD74+).

Are Body Composition Valid Tool in Clinical Practice and In General Medicine?

Angela Andreoli M.D.; PhD

There is an increasing interest in the study of body composition fat-free and fat mass, body cell mass and fluids, (FFM, FM, BCM, TBW, ICW, ECW) to monitor conditions and delay in development of chronic diseases.

The assessment of nutritional status has major relevance at both the individual level, as is the case for clinical practice, in general medicine and among populations, as used in epidemiologic and public health research, to determine the presence of increased risk for nutrition-related conditions. The emergence of these evidence demonstrates the need of standard assessment of nutritional status based on body weight changes, playing an important role in several clinical setting, such as in quantitative measurement of tissues and their fluctuations in body composition, in survival rate, in pathologic condition and illnesses. Since body mass index has been shown to be an imprecise measurement of fat-free and fat mass, body cell mass and fluids, provides no information if weight changes occur as a result of a decrease in fat-free mass or an increase in fat mass or fluids or ratio. Non-invasive body composition methods can now be used to monitor fat-free and fat mass with weight gain and loss, and during aging. FFM loss or a low phase angle is related to mortality in patients with chronic diseases, cancer (including obesity and cancer patients), and elderly patients.

In numerous clinical situations, such as chronic diseases, and sarcopenicobesity the measurement of body composition with available methods, (dual-X ray absorptiometry, computerized tomography and bioelectrical impedance analysis), could be used tools to prevent or follow disease status.

Kids Cooking Schools Promote Nutrition and Culinary Knowledge Among Children in North Dakota (U.S.A.)

Julie Garden-Robinson, Ph.D., R.D., L.R.D.

The goal of the Kids Cooking School is to improve food preparation skills and enhance nutritional intake of healthful foods to reduce risk of obesity and chronic disease among

children and their families. The original program was piloted as a four-day cooking camp in four communities at an American Indian Reservation site during two consecutive summers. The topics included measuring, knife safety and kitchen equipment, reading Nutrition Facts labels, balancing a plate with MyPlate, traditional foods, basic gardening skills, and food preservation. Each lesson has specific objectives, “energizers” (physical activities), worksheets, associated recipes, a parent newsletter and evaluation tools specific to the lessons. Children showed significant improvements in food and nutrition knowledge and culinary skills.

During the pandemic, the schools have expanded throughout our state and have been offered through live Zoom calls and/or Facebook Live events. Each lesson is two to three hours in length, and the instructors can select the lesson activities that fit within their time constraints and setting. On average, each child participated in 10 to 12 hours of hands-on education during several sessions, with Zoom check-ins and self-guided activities with parents’ assistance. Each child received a “cooking kit” consisting of a lunch bag, measuring cups and spoons, can opener, spatula, cutting board, apron, workbook, cookbook, and other items.

External funding provided food supplies, printed materials and the cooking equipment kit so children could participate without costs. Despite widespread pandemic challenges, Extension agents from 11 counties reached more than 400 children in multisession (10- to 15-hour) cooking schools. Collaborators included parents, community volunteers, dietetic interns, public health nutritionists, community kitchens, with funding from several commodity groups and associations. The cooking kit included the cookbook, workbook, an apron, measuring cups/spoons, a can opener and other kitchen tools in a reusable insulated lunchbag.

According to the children’s self-assessment, 78% were eating more fruit, 66% were eating more vegetables, and 59% were eating more whole grains. About 87% planned to cook more at home, 91% felt confident following the basics of food safety, 95% knew how to use their kitchen tools received in the class and 90% felt confident using kitchen equipment. According to quotes from kids, “This is the BEST thing in the entire world!” and “Cooking school is fun – I learned so much!” According to parents, 78% of children were offering help at home and 73% were more confident using kitchen tools and appliances.

Latest Findings on Inulin as Inflammation Modulating Agent

Federica Farabegoli, PhD

Inulin is a natural polysaccharide used for storing energy by some plants; in human nutrition it is classified as a soluble fiber, with demonstrated prebiotic activity. Prebiotic compounds can reduce the intestinal and systemic inflammatory state through modulation of the microflora and their metabolites; moreover, extensive research is shedding light on the role of macrophages in the interaction between the gut microbiota and many chronic inflammatory diseases.

In our study we assessed the anti-inflammatory properties of this compound on an in vitro cell culture system, and investigated on its immuno-modulatory mechanism by means of Omic technologies; our purpose is to go further and identify new molecular markers of gene expression of the induced anti-inflammatory phenotype. Therefore, a murine macrophage (RAW 264.7) cell model, stimulated by lipopolysaccharide, was subjected to comprehensive transcriptomic, proteomic and gene pathway analyses. The transcriptomic

analysis identified the differentially expressed genes (DEGs), while the proteomic analysis found the differentially expressed proteins (DEPs) after inulin treatment. Gene Ontology functional annotation and Kyoto Encyclopedia of Genes and Genomes pathway analysis were performed on these DEGs and DEPs. The results of the comprehensive analyses of transcripts and proteins are being implemented, and will bring to light the jointly regulated DEGs and DEPs in the inflammatory pathways.

Genes and proteins, and their related dysregulated pathways identified in this study, may be promising targets for research on the immune-modulation of dietary fibers. This study provides large-scale omics data that can be used to formulate new strategies for the design of functional ingredients, foods and nutraceutical products, paving the way towards effective personalized nutrition strategies for improving consumers' health.

Reporting Cosmetic Adverse Events to the US Food and Drug Administration

Linda M. Katz, MD, MPH

The Center for Food Safety and Applied Nutrition (CFSAN), one of the centers of the Food and Drug Administration (FDA), is responsible for overseeing the safety of the foods, dietary supplements, and cosmetic products in the United States and collects adverse event reports (AERs) involving FDA/CFSAN-regulated products as part of its mission to protect public health. The CFSAN Adverse Event Reporting System (CAERS) provides a venue, for consumers, health care professionals or industry, to report adverse events (AEs) and product complaints (PCs) pertaining to FDA-regulated foods, dietary supplements, and cosmetic products. AE reports are monitored to assess trends, follow clusters, and analyze data in order to determine if regulatory action is warranted or additional research is needed to further assess safety of specific products or ingredients. This presentation will describe the process, some of the limitations of the data, and provide further information on how to obtain publicly available data.

The Effects of Vitamin D3 Supplementation on Muscle Physical Performance and Vitamin Status in a Physically Active Population: A Randomized, Placebo-Controlled Blind Intervention Study

Ransone JW, Markin-Dufford KD, Bilborough JC.

Objectives: This study aimed to determine if an eight-week supplementation of 50,000 IU of VitD3 will reverse deficiency in a physically active population. **Patients or Other Participants:** A total of 29 physically active collegiate subjects (age =23.21±1.52 yrs, weight =70.66±14.23 kg, height=171.18±9.03 cm) volunteered to participate in the study. **Intervention(s):** Before completing pre-testing, performance measures and beginning supplementation, venous blood samples to assess baseline serum 25(OH)D levels were collected from the cubital vein. **Main Outcome Measures:** Serum 25(OH)D levels and muscle performance metrics (bench press, vertical jump, and 40m sprint) were analyzed to determine differences between pre-test and post-test data of both the control and treatment groups, respectively. **Results:** A repeated measures ANOVA showed a significant increase in serum 25(OH)D levels after supplementation ($p < .001$) with a more noticeable increase in the treatment group. These analyses indicate no significant difference between

the two treatment groups (VitD3 vs. placebo) at pre-treatment measurement. Post-treatment serum 25(OH)D status increased at a greater magnitude for Vitamin D (VitD) compared to the placebo group, which showed a relatively small change in serum 25(OH)D levels. Before D3 supplementation, 19 of 29 total subjects (66%) had serum 25(OH)D concentrations considered to be deficient (<32 ng/ml). Conclusions: Total serum 25(OH)D concentration significantly increased and eliminated pathological deficiency in the supplementation group after eight weeks of supplementation with 50,000 IU of VitD3. Muscle performance metrics increased over the treatment period but were not significantly increased between treatment and control.

The role of different types of dietary lipids on the gut-liver axis in alcohol-associated liver disease

Irina A. Kirpich, Ph.D., MPH

Background and Goal: The interplay among the diet, intestinal homeostasis, and microbiome plays a critical role in the development and progression of alcohol-associated liver disease (ALD). Recent work from our group and others demonstrated deleterious effects of dietary n6 PUFAs, primarily linoleic acid, on EtOH-mediated alterations in the gut-liver axis in mice. We also showed that decrease in tissue n6/n3 PUFA ratio via endogenous conversion of n6 to n3 PUFAs in transgenic mice attenuated ALD. In the current study: i) we investigated potential mechanisms contributing to beneficial effects of a decreased n6/n3 PUFA ratio on ALD. Specifically, we examined whether lowering n6/n3-PUFA ratio would rescue EtOH-mediated downregulation of hepatic Wnt signaling, a pathway important for liver homeostasis and regeneration; and ii) we explored the impact of a decreased n6/n3 PUFA ratio on EtOH-mediated intestinal alterations and changes in the gut microbiome. Methods: Male Wild type (WT) and fat-1 transgenic mice (that directly desaturate n6 to n3 PUFAs in all tissues) were provided an EtOH-supplemented diet for 6 weeks followed by a single LPS insult at the end of the protocol. Liver injury, steatosis, inflammatory responses and Wnt pathway expression were evaluated. Ileum RNAseq, fecal microbiota composition and metabolic activity were analyzed. Results: EtOH+LPS challenged fat-1 mice had less severe liver damage than WT littermates as evidenced by reduced plasma ALT levels, hepatic steatosis, liver tissue neutrophil infiltration, and pro-inflammatory cytokine expression. WT mice had a greater downregulation of Axin2, a key gene in the Wnt pathway, than fat-1 mice in response to EtOH+LPS. Further, there were significant differences between WT and fat-1 EtOH+LPS treated mice in the expression of five additional genes linked to the Wnt signaling pathway, including Apc, Fosl1/Fra-1, Mapk8/Jnk-1, Porcn, and Nkd1. Next, compared to WT, fat-1 mice exhibited an improvement in the intestinal epithelial architecture and lamina propria inflammation caused by EtOH+LPS challenge. Intestinal RNAseq analysis revealed that numerous pro-inflammatory genes were decreased, while several anti-inflammatory and anti-microbial genes were elevated in fat-1 vs. WT EtOH+LPS challenged mice. Pathways involved in degradation of ATP, a potent immune cell activator, were also up-regulated in fat-1 mice accompanied by a decrease in several fecal purine and pyrimidine metabolites (e.g.,

xanthine, hypoxanthine). Fecal microbiome analysis showed that several Lachnospiraceae, Ruminococcaeae, and Bacteroidales OTUs were enriched in fat-1 vs. WT mice following EtOH challenge. The Porphyromonadaceae:Barnesiella ratio was elevated in EtOH+LPS treated fat-1 but not WT mice. Conclusion: Our data suggest that n6 and n3 PUFAs play an important role in the interplay between liver injury, intestinal homeostasis, and gut microbiota in ALD

Application of Different Activities of Plant Extracts in Preservation of Animal Products

Vladimir S. Kurćubić, DVM, Ph.D.

The use of plant extracts as natural additives is a newer approach, developed intensively, for the prevention of microorganisms reproduction or protection of food from oxidative rancidity. There is a great interest in the meat industry for the use of phytochemicals as bioactive components, with potential health benefits. We illustrate their application in food matrices. Fermented dry sausages (FDS) enriched with bioactive phenol and flavonoid compounds from the ethanol herb extract of *Kitaibelia vitifolia* without nitrite added, with improved shelf-life, safety, and provide health benefits to consumers as well. The primary aim was to select the most suitable effective concentration of extract to be added, on the basis of the oxidative and microbiological stability of FDS during storage under aerobic or anaerobic packs. *K. vitifolia* extract exerted a powerful AO effect. *K. vitifolia* extract (10% w/v, effective concentration of 12.5 g/kg of meat dough) revealed the strongest activity of 5 contemporary methods for AO activity examination. The highest susceptibility to the extract of sausages was exhibited by *E. coli* (MIC = 15.625 µg/mL), in both groups fortified with various concentration of *K. vitifolia* extract.

The goal of application of *K. vitifolia* ethanol extract for decontamination of beef surface was to evaluate AM effects, when applied in spray to *E. coli* (inoculum containing 10.000 cfu - to 100 µL of inoculum injected into 10 places of the intacted, uncut sample surface of beef, 1 mL total). The inoculated samples were randomly divided into 3 experimental groups (EG), with 20 samples in each. Control samples were not subjected to any treatment. All samples from EG II were treated with water, applied as a spray during 5 s. All samples from the EG III were treated with 0.3% extract of *K. vitifolia*, applied for 5 s as a spray. Between the values obtained from samples of control (I) and EG II and III, there are significant differences ($p < 0.05$). The difference in a stronger reduction of the number of *E. coli* after the effect of *K. vitifolia* extract when applied as a spray (EG III), compared to the reduction after the "washing" of beef (EG II) was not statistically significant.

Probiotic microorganisms: definition, challenges, food applications and their dark side

Antonio Bevilacqua

The definition of probiotics dates to 2001 when the Commission WHO/FAO defined them as "Live microorganisms which, when administered in adequate amounts, confer a health

benefit to the host". This definition was slight modified in 2014, but the three keywords (live microorganism, amount, health benefit) are still pillars to correctly define probiotics.

The current definition of probiotics must also consider their regulatory framework in different Countries (QPS status, GRAS, definition in Asia etc.).

Market trends suggest the increasing awareness and interest of consumers towards probiotics amongst consumers, stakeholders and policy-makers; moreover, functional food niche, including foods and beverages supplemented with probiotics, is the only segment of food chain experiencing an increasing trend in the last decade.

Apart from probiotic use as supplements, the most important and promising use is in food, although there are some challenges to face with, including their viability throughout food processing and shelf life, impact on sensory scores and on the physico-chemical properties of matrices, viability and bioavailability in the gut.

Moreover, there is also a dark side of probiotics including antibiotic-resistance and translocation across host.

Thus, this communication is a report on the current knowledge of probiotics, including the following topics:

- a) Definition and regulatory framework
- b) Effects with a short meta-analysis of the health benefits demonstrated through clinical trials
- c) Short overview of antibiotic-resistance on probiotics
- d) Challenges to face with for an effective application of probiotics in food.

From apps to intermittent fasting: Weight management in adolescents clinical controversy or opportunity?

Alaina Vidmar, MD

There continues to be a steady increase in the prevalence of obesity in adolescents. Current treatment recommendations in pediatrics are costly, labor intensive and difficult to implement on a large scale. The creation of innovative and personalized treatment strategies that target the whole adolescent, including diet, activity and behavioral skills training are essential. Dr. Vidmar's lab is interested in three components of the treatment of obesity in adolescents: 1) Cognitive Phenotyping: The relationships between food addiction, executive function, and mood in adolescence are not well-understood. Her lab aims to categorize these cognitive phenotypes of adolescents with obesity seeking treatment to better understand the overlap and how these phenotypes impact treatment engagement and response. 2) Intervention Delivery Modalities: Her lab aims to utilize app-based interventions to deliver targeted treatment in their real life setting to determine which delivery method is most cost effective at promoting sustained behavior change and weight control. 3) Prescriptive Dietary Interventions: There is a growing interest in the use of time limited eating in obesity management and little is known about its use in adolescents. Dr. Vidmar just completed a pilot study to substantiate the feasibility, acceptability and effectiveness of time limited eating coupled with continuous glucose monitoring in

adolescents with obesity and is now expanding this dietary approach into youth with type 2 diabetes.

Are body composition valid tool in clinical practice and in general medicine?

Angela Andreoli M.D.; PhD

There is an increasing interest in the study of body composition fat-free and fat mass, body cell mass and fluids, (FFM, FM, BCM, TBW, ICW, ECW) to monitor conditions and delay in development of chronic diseases.

The assessment of nutritional status has major relevance at both the individual level, as is the case for clinical practice, in general medicine and among populations, as used in epidemiologic and public health research, to determine the presence of increased risk for nutrition-related conditions. The emergence of these evidence demonstrates the need of standard assessment of nutritional status based on body weight changes, playing an important role in several clinical setting, such as in quantitative measurement of tissues and their fluctuations in body composition, in survival rate, in pathologic condition and illnesses. Since body mass index has been shown to be an imprecise measurement of fat-free and fat mass, body cell mass and fluids, provides no information if weight changes occur as a result of a decrease in fat-free mass or an increase in fat mass or fluids or ratio. Non-invasive body composition methods can now be used to monitor fat-free and fat mass with weight gain and loss, and during aging. FFM loss or a low phase angle is related to mortality in patients with chronic diseases, cancer (including obesity and cancer patients), and elderly patients.

In numerous clinical situations, such as chronic diseases, and sarcopenicobesity the measurement of body composition with available methods, (dual-X ray absorptiometry, computerized tomography and bioelectrical impedance analysis), could be used tools to prevent or follow disease status.

ONCOLOGY

Plexin-A2 enables the proliferation and the development of tumors from glioblastoma derived cells

Shira Toledano

The semaphorin guidance factors receptor plexin-A2 transduces sema6A and sema6B signals and may mediate, along with plexin-A4, the anti-angiogenic effects of sema6A. When associated with neuropilins plexin-A2 also transduces the anti-angiogenic signals of sema3B. Here we show that inhibition of plexin-A2 expression in glioblastoma derived cells that express wild type p53 such as U87MG and A172 cells, or in primary human endothelial cells, strongly inhibits cell proliferation. Inhibition of plexin-A2 expression in U87MG cells also results in strong inhibition of their tumor forming ability. Knock-out of the plexin-A2 gene in U87MG cells using CRISPR/Cas9 inhibits cell proliferation which is rescued following plexin-A2 re-expression, or expression of a truncated plexin-A2 lacking its extracellular domain. Inhibition of plexin-A2 expression results in cell cycle arrest at the G2/M stage, and is accompanied by changes in cytoskeletal organization, cell flattening, and enhanced expression of senescence associated β -galactosidase. It is also associated with reduced AKT phosphorylation and enhanced phosphorylation of p38MAPK. We find that the pro-proliferative effects of plexin-A2 are mediated by FARP2 and FYN because mutations in the FARP2 binding domain or in the FYN phosphorylation sites of the plexin-A2 intracellular domain inhibit the rescue of cell proliferation upon expression of the

mutated intracellular domain in the knock-out cells. Our results suggest that plexin-A2 may represent a novel target for the development of anti-tumorigenic therapeutics

The Use of Immunotherapy for the Treatment of Refractory Forms of Hodgkin Lymphoma in Real Clinical Practice

Inna Kamaeva

Background. The incidence of Hodgkin's lymphoma is growing worldwide; it is one of the most frequent lymphomas. The frequency is 2.2 per 100,000 of population in Russia, so Hodgkin's lymphoma is one of the most common malignant neoplasms among young people, most often at the age of 16-35 years old. Considering the spread of Hodgkin's lymphoma, the problem of its effective treatment remains relevant. About 70-90% of patients have a long period of remission after a standard chemotherapy or radiotherapy. However, 10% of patients with progressive disease do not respond to the therapy, and 30% of patients have a relapse. Application of anti-PD-1 inhibitors opens new possibilities for the treatment of recurrent/refractory Hodgkin's lymphoma.

Methods. The study included 9 adults with Hodgkin's lymphoma who underwent more than 3 lines of chemotherapy in the Department of Oncohematology since 2006. All of the patients were in various age groups, had different tumor stages, different initially therapies and outcomes. But they had something in common. After the 2nd line of chemotherapy they had a relapse or a refractory form of the disease. The aim of this study was to demonstrate the results of immunotherapy in real clinical practice.

Results. The most frequent chemotherapy regimen in the 1st line was BEACOPP because of the prevalence of lymphoma. As for chemotherapy in the 2nd line, it was DHAP, MINE, GDP-21. Some of patients had a stable disease, but within 6 months they had a progression. All cases were interpreted as refractory to a standard regimen of chemotherapy, and continuing of treatment with immunotherapy, exactly nivolumab 3 mg/kg every two weeks, was recommended to patients. A good response to therapy was achieved in most patients (77.7%), without any adverse events. The median duration of treatment was 16 weeks. Interruptions in drug administration were registered in 1 patient; the duration of the delay was 3 weeks.

Conclusions. So, this clinical study confirms the validity of immunotherapy for refractory forms of this type of lymphoma after 3 or more lines of chemotherapy, including patients with comorbidity and a long history of the disease. In addition, the clinical experience we have gained allows us to conclude that earlier administration of PD-1 inhibitors in patients diagnosed with refractory Hodgkin's lymphoma enables a possible option of autologous stem cell transplantation to achieve a long-term response.

Antitumoral Effects of Attenuated *Listeria Monocytogenes* in a Genetically Engineered Mouse Model of Melanoma

Marianna Vitiello

Melanoma is one of the most aggressive cancers. Several approaches have been introduced for melanoma patients' treatment in the last decade, but none of them represents a definitive melanoma cure. *Listeria monocytogenes*, in its attenuated form, is broadly used as cancer vaccine and is already under evaluation in phase I-III clinical trial for cancers such as cervical, pancreatic and prostate.

We have recently demonstrated that *Listeria monocytogenes* is very efficient for treatment of melanoma in a mouse model. Indeed, we have shown that in vitro *Listeria monocytogenes* causes ROS production and, in turn, apoptotic killing of a wide variety of melanoma cells, irrespectively of their stage, mutational status, sensitivity to BRAF inhibitors or degree of stemness. We also show that *Listeria* causes a strong decrease in the size and volume of primary melanoma tumors, as well as a reduction of the metastatic burden, when administered in the therapeutic setting to Braf/Pten genetically engineered mice. It exploits its role by the potentiation of immune response of the organism against the infected tumor. Moreover, we are currently potentiating *Listeria* efficacy for melanoma treatment by the expression of tumor associated antigens and by the conjugation of drug molecules on *Listeria monocytogenes* wall. The first strategy increases the immune system response against tumor cells and will allow an immune response also in case of tumor relapse. Conversely, in the second strategy there is a synergic effect of the *Listeria* and of the anticancer drug. Finally, we are also trying to use *Listeria* as a 2nd line treatment for melanoma that are resistant to BRAF inhibitors. This option is very important since sometimes target therapy is the only way to treat melanoma patients. However, as it is known, they inevitably show signs of acquired resistance in few months. *Listeria*, used as 2nd line treatment, offers an opportunity to treat these types of melanomas, where no other options of therapy exist.

Overcoming Resistance to Immune Checkpoint Inhibitors with Oncolytic Viruses

Jason Chesney, Smita Ranjan, Ryan Bycroft

Immune checkpoint inhibitors (ICIs) that block the T cell suppressing activity of immune checkpoint proteins including CTLA-4, PD-1/PD-L1 and LAG-3 have revolutionized the practice of oncology and are translating into marked increases in progression-free survival (PFS) as well as overall survival (OS) in multiple cancer types. Unfortunately, intrinsic and acquired resistance to ICIs is common in the majority of cancer patients. Multiple strategies to overcome ICI resistance have been proposed including promoting T cell priming and infiltration and inhibiting T cell exhaustion and the immunosuppressive microenvironment. Oncolytic viruses that selectively replicate within and lyse cancer cells cause antigen release and activate innate immune responses which, in turn, may lead to both T cell priming and infiltration. Accordingly, the combined administration of ICIs with oncolytic viruses may overcome resistance and increase PFS and OS in multiple cancer types. The first oncolytic virus to receive FDA-approval, talimogene laherparepvec (TVEC), is an attenuated herpes simplex virus, type 1, engineered to express granulocyte-macrophage colony stimulating factor which stimulates the generation of antigen-presenting dendritic cells and T cell priming. In randomized clinical trials, this first-in-class oncolytic virus was found to increase the efficacies of ICIs that target CTLA-4 (ipilimumab) and PD1 (pembrolizumab) and a recent phase 2 clinical trial reported that TVEC can overcome resistance to pembrolizumab in melanoma patients. Based on these data, intratumoral injection of TVEC may prove to have utility to overcome resistance to ICIs and thus warrants further investigation.

Ceramide Metabolism Alterations In Melanoma: From Basic Mechanisms To Immunotherapy In Advanced Melanoma Patients

Bruno Ségui

Cutaneous Melanoma represents the main cause of death among malignant skin neoplasms. Immune checkpoint inhibitors (ICI), such as anti-PD-1 or anti-CTLA-4 blocking antibodies, are successful only in a subset of metastatic melanoma patients due to primary or adaptive resistance mechanisms. Abnormal lipid profiles are often associated with an altered metabolic phenotype in tumor cells, which is a hallmark of cancer. We recently provided evidence that sphingomyelin synthase 1 (SMS1) is frequently downregulated in various solid cancers, more particularly in melanoma. Low SMS1 expression was associated with ceramide metabolism reprogramming and a worse prognosis in metastatic melanoma patients (Bilal et al., *Front Pharmacol.* 2019). We also identified ceramide metabolism dysregulation [i.e., downregulation of neutral sphingomyelinase 2 (nSMase2) and upregulation of sphingosine kinase 1 (SK1)] in immune escape and resistance to ICI in mouse melanoma models. Reprogramming ceramide metabolism by re-expressing nSMase2 or downregulating SK1 in melanoma cell lines enhances the CD8 T cell-dependent immune response and overcomes the resistance to ICI. Mechanistically, whereas nSMase2 expression increases the small extracellular vesicle immunogenicity, SK1 downregulation reduces the production of key immunosuppressive molecules such as PGE2 and TGF β , thus limiting tumor-infiltrating regulatory T lymphocyte content (Montfort et al., *Cancer Immunol Res* 2021; Imbert et al., *Nat Commun.*, 2020). Interestingly, TNF, which impairs the anti-melanoma immune response (Bertrand et al., *Cancer Res.* 2015) and confers resistance to ICI in mice (Bertrand et al., *Nat Commun.* 2017) and possibly in patients (Montfort et al., *Clin. Cancer Res.* 2021), modulates ceramide metabolism in melanoma cell lines. Ongoing experiments aim at evaluating whether TNF-induced ceramide metabolism changes contribute to melanoma progression and resistance to ICI not only in mice but also in advanced melanoma patients enrolled in prospective clinical trials.

Outreach to Primary Care Patients in Lung Cancer Screening: A Randomized Controlled Trial**Ronald Myers**

Current guidelines recommend annual lung cancer screening (LCS), but rates are low. The current study evaluated strategies to increase LCS.

This study was a randomized controlled trial designed to evaluate the effects of patient outreach and shared decision making (SDM) about LCS among patients in four primary care practices. Patients aged 50-80 years of age at high risk for lung cancer were randomized to Outreach Contact plus Decision Counseling (OC-DC, n = 314), Outreach Contact alone (OC, n = 314), or usual care (UC, n = 1,748).

LCS was significantly higher in the OC/OC-DC group versus UC controls (5.5% vs. 1.8%; hazard ratio, HR = 3.28; 95% confidence interval, CI: 1.98 to 5.41; p = 0.001). LCS was higher in the OC-DC group than in the OC group, although not significantly so (7% vs. 4%, respectively; HR = 1.75; 95% CI: 0.86 to 3.55; p = 0.123). LCS referral/scheduling was also significantly higher in the OC/OC-DC group compared to controls (11% v. 5%; odds ratio, OR = 2.02; p = 0.001). We observed a similar trend for appointment-keeping, but the effect was not statistically significant (86% v. 76%; OR = 1.93; p = 0.351).

Outreach contacts significantly increased LCS among primary care patients. Research is needed to assess the additional value of SDM on screening uptake.

The Challenges of Treating Hodgkin Lymphoma in a Developing Country: Results from the Brazilian Hodgkin Lymphoma Registry

Rafael Dezen Gaiolla

Introduction: Hodgkin lymphoma (HL) is a B-cell malignancy that predominantly affects young adults with a higher incidence at ages 15 to 35 years. HL's peculiar histological features and biological behaviour make it highly responsive to chemotherapy and radiation. In fact, in the last decades, relevant clinical trials conducted by cooperative groups in Europe and North America have demonstrated that HL is a highly curable disease, with cures rates that exceed 90%, especially in early-stage disease. However, in developing countries, the scenario is more challenging. Although data are scarce and usually comes from small population-based and retrospective studies, the reported outcomes are significantly lower than those observed in developed countries, especially for advanced-stage disease. In 2009, the Brazilian Hodgkin Lymphoma Registry was created to collect data on clinical presentation, socioeconomic status (SES), treatment modalities, and outcomes in a prospective cohort of HL patients. Brazilian Centers that treat HL are invited to participate voluntarily. Data on patients consecutively treated from 2007 are being collected and inserted into an online platform. Results: 20 medical centres from 7 states are currently participating. Eighteen are public institutions, and 2 are private hospitals. As of September 2021, a total of 1700 patients have been included. This analysis is based on the first 674 patients with classical HL. The median time from symptoms to diagnosis was six months, and from diagnosis until the beginning of treatment was 21 days—most patients presented with advanced-stage disease (65%) and B symptoms (69%). Treatment outcomes for early-stage disease were similar to those observed in developed countries. However, for advanced-stage disease, results were 5% to 10% inferior compared to those reported in US and European cohorts. Regarding socioeconomic status (SES), 33% of the patients were lower SES. Compared to higher SES patients, this population was older, had a worse performance status, and presented with more advanced-stage disease and poor prognostic factors. Lower SES remained independently associated with poorer survival. Infections and treatment toxicity accounted for 81% of deaths during treatment. Discussion and Conclusion: These results provide a reliable portrait of the HL population in Brazil. The higher frequency of advanced-stage disease and poorer outcomes may be explained by differences in SES and problems with full access to public healthcare. The present findings suggest that the health system in Brazil is still unable to provide a timely diagnosis for many patients with HL but is reasonably efficient in responding once the diagnosis is established. Improvements are needed to provide quick access to primary healthcare and to allow the health system to promptly identify and forward patients with complex diseases to the following levels of care.

Unraveling the Biology of BRAFV600E Isoforms in Melanoma

Laura Polisenio, PhD

BRAFV600E is the most frequent mutation in melanoma. Two BRAFV600E protein isoforms, ref and X1, coexist in melanoma cells, but their specificities are unknown. Through the expression of the two isoforms, one by one, in multiple in vitro and in vivo systems, we aim at deciphering their individual contribute to melanomagenesis.

We expressed BRAFV600E-ref and X1 separately in a collection of yeast strains deleted for non-essential genes and evaluated the fitness alteration of each deleted yeast strain. Interaction network and gene enrichment (GE) analyses of the isoform-specific functional interactors highlighted BRAFV600E-ref as specifically involved in autophagy, while BRAFV600E-X1 in de novo fatty acid synthesis. These observations, confirmed by further analyses in yeast, are currently under investigation in melanoma patients, by interrogation of appropriate repositories.

We are creating human melanoma cell lines that inducibly express only one of the two isoforms at the time. The strategy we have devised is based on sh-mediated silencing of endogenous BRAF isoforms, coupled with expression of exogenous BRAFV600E-ref or BRAFV600E-X1, by means of CRISPR/Cas9-mediated insertion of the desired coding sequence in the AAVS1 genomic locus.

Finally, we are developing zebrafish melanoma models that overexpress each BRAFV600E isoform individually. Once injected at 1-cell stage with plasmids that encode for BRAFV600E-ref or BRAFV600E-X1, under the control of melanocyte lineage-specific mitfa promoter, fish of the p53^{-/-} line show distinctive features. Specifically, the ref variant causes earlier nevi appearance, earlier melanoma onset and higher incidence. Currently, we are analyzing tumor samples collected so far, to identify histological differences. We are also developing stable transgenic lines for each BRAFV600E isoform. In this way, we can corroborate the results obtained on mosaic and perform drug screenings.

Our model system can contribute to identify new molecular factors involved in BRAFV600E-driven malignant transformation and in response/resistance to BRAF inhibitors, paving the way to more informed combinatorial therapeutic strategies, designed according to the BRAFV600E-ref/X1 ratio present in each melanoma patient.

Endocrine Resistance in Breast Cancer - A Cancer Systems Biology Perspective.

Robert Clarke, PhD, DSc

Breast tumors that express detectable levels of estrogen receptor-alpha (ESR1; ER) represent over 70% of all newly diagnosed breast cancers. Drugs that target ER action by either competing for binding with endogenous 17 β -estradiol (antiestrogens) or reducing its biosynthesis (aromatase inhibitors) have a significant overall survival benefit. Nonetheless, many ER⁺ breast cancer eventually recur. Recurrent disease is almost inevitably fatal. Over the years, many individual genes, gene mutations and signaling pathways have been proposed as explanations of the acquired endocrine resistance phenotype. However, the overall survival rate for ER⁺ breast cancers treated with an endocrine monotherapy has improved only modestly since the introduction of Tamoxifen in 1972. A new paradigm is needed to interrogate the resistance phenotype and to understand better how to intervene to improve patient survival. We have developed an overall modular network framework that allows us to take an integrative approach to understand endocrine resistance. Using both mathematical and computational modeling of omics and other data from patients, animal models, and cell lines we have begun to develop an integrative systems-based understanding of how ER⁺ breast cancer cells acquire an endocrine resistant phenotype.

Superior Mesenteric Artery-First Approach in Radical Antegrade Modular Pancreatosplenectomy for Borderline Resectable Pancreatic Cancer: A Technique to Obtain Negative Tangential Margins

Yasunari Kawabata

Introduction: Achievement of complete tumor removal with tumor-free margins (R0) along with adequate lymph node clearance is difficult in patients with borderline resectable pancreatic cancer (BRPC). To reduce residual tumor resection (R1 or R2) in performing a pancreatectomy for left-sided pancreatic cancer, we devised radical antegrade modular pancreatectomy (RAMPS) using superior mesenteric artery (SMA)-first approach.

Surgical technique

RAMPS with SMA-first approach: The basic principle of this artery-first approach is early dissection of the SMA from behind the body of the pancreas as one of the first steps of the operation, to be sure of resectability with R0 resection before reaching the point of no return.

Surgical procedure starts with a staging laparoscopy, followed by a laparotomy with an upper midline incision. The retroperitoneum is opened at the left side of the duodenojejunal flexure, and the pancreas is mobilized together with the SMA so that the anterior surface of the aorta, inferior vena cava, and left renal vein are completely exposed in an effort to secure the posterior surgical margin. An inter-aortocaval lymph node dissection is routinely performed. After division of the gastrocolic ligament, and then, the middle colic artery (MCA) is identified, and the SMA is also identified safely by dissecting the anterior surface of the transverse mesocolon along the MCA. On the posterior aspect of the body of the pancreas, the left semicircle lymph nodes dissection between the pancreas and the SMA is carried out from the origin of the MCA up to the origin of the SMA. Although a complete dissection of the nerve plexus around the SMA (PLsma) can be done, we should preserve the nerve plexus at the left aspect of the SMA as much as possible under the strict guidance of frozen section analysis. If the tumor infiltrates the MCA and transverse mesocolon, the involved part should be removed at this time. After confirming cancer-free margins on the anterior and left aspect of the SMA, the portal venous system is freed from the posterior aspect of the head of the pancreas.

The next step is directed toward the superior border of the pancreas. A lymphadenectomy with skeletonization of the hepatic arteries, left gastric artery, splenic artery (SPA), and the celiac trunk is performed. The hanging tape passed along the anterior surface of the SMA around the body of the pancreas. This pancreas-hanging maneuver with tape allows elevation of the pancreas away from the SMA to obtain a wide view of the anterior surface of the SMA. Once the oncologic aspects around the SMA are assessed sufficiently and resectability with R0 resection is confirmed, the origin of the SPA and gastrosplenic ligament are divided, and the SMA-first approach in the RAMPS procedure is completed.

Laparoscopic approach of this procedure can also be performed in patients with left-sided pancreatic cancer.

Conclusions: RAMPS utilizing SMA-first approach would facilitate a high rate of negative tangential margins around the major vessels and complete tumor resection in pancreatic body and tail cancer including borderline resectable cases.

Blood Glutamate Scavengers Increased Pro-Apoptotic Signaling and Reduced Metastatic Melanoma Growing In-Vivo**Angela Ruban**

Background: In the past few years, an ever-increasing body of data has suggested that glutamate (Glu) plays a crucial role in the growth of glioma cells, their invasiveness and ability to destroy neighboring brain tissue. The ability of glioma to secrete Glu into the tumor microenvironment has prompted the question of whether this feature is common to other types of cancer like melanoma. It has been shown that transgenic mice, which conditionally express mGluR1 in melanocytes, secrete Glu and produce melanomas at a frequency of 100% 52 weeks after transgene activation. Furthermore, it is possible that more advanced tumors in stage III and IV metastases have a higher frequency of mGluR1 expression and that ectopic mGluR1 is more frequent in more advanced stages of the disease. In such case, the inhibition or reduction of extracellular brain glutamate could be very effective in the management of brain metastatic melanoma. The overall objective of this study was to evaluate the therapeutic efficacy of an entirely novel approach in which excess Glu is removed from brain into blood as a result of blood Glu scavenging.

Materials and methods: mCherry RET melanoma cells were implanted intracranially in C57BL mice and treated with glutamate scavenger (BGS) vs. vehicle-control starting one hour after the implantation and for 7 consecutive days. CSF and blood Glu levels were measured at days 3 and 7 post implantation to confirm a continuous increase in Glu levels following the tumor progression, and to prove the scavenging activity of the treatment. The tumors' growth was examined 2- and 7-days post implantation by luciferase activity bioluminescence imaging. At day 7 mice were sacrificed and the tumors were analyzed for pro-apoptotic and DNA markers by immunohistochemistry.

Results: Our results demonstrate that in vehicle-control mice, Glu levels in the CSF have increased more than 5 folds at 7 days post cell implantation compared to the 3-fold in the BGS treated group. Moreover, BGS 7 days treatment has significantly increased expression of DNA suppressor marker 53BP1, active caspase-3 expression and has mediated CD8+ cells infiltration into the tumors. Importantly, BGS 7 days treatment has significantly decreased the tumor's growth in-vivo.

Conclusion: We have shown that the administration of blood Glu scavengers is highly effective in reducing the proliferation of RET melanoma cells in brain metastatic mice model. Our results suggest that BGS treatment is mediating DNA damage and apoptotic cell death in brain metastatic melanoma model. This is the first time that this approach is used in metastatic melanoma.

Targeted Prevention of Postpartum-Related Breast Cancer (PRBC)

Mark Sherman

Postpartum-related breast cancers (PRBCs), herein defined as breast cancers (BCs) diagnosed <5 years of childbirth, portend a poor prognosis¹⁻⁵. Although early age at first birth and multiparity lower risk of late onset BCs, childbirth itself transiently increases risks of estrogen receptor (ER)+ and ER- BCs for over two decades, with peak risks at 5 years postpartum⁶. In mouse models, post-partum involution (PPI), which restores the breast to a non-lactating state after weaning, is linked to activation of cyclooxygenase-2 (COX-2), immune suppression, and a "wound healing" microenvironment that drives BC progression, whereas non-steroidal anti-inflammatory agents (NSAIDs) inhibit PPI-related inflammation and PRBC development⁷. Among women, NSAID use is generally linked to lower BC risk overall⁸⁻¹⁴, and provides consistent protection among women with benign breast disease (BBD)^{15,16}. Because BBD lesions are often inflamed¹⁷ and increase BC risk¹⁸, NSAIDs may

offer a preventive benefit to BBD patients. Using NanoString Digital Spatial Profiling (DSP), we identified 8 markers in BBD biopsies of parous women that predicted BC risk <7 years, with an area under the curve (AUC) of 0.76 in Receiver Operator Characteristic Curve analysis (BAD, BCL-2, BCLXL, BIM, CD20, CD27, STING and TIM-3), largely independent of confounders. These BC risk markers overlap with those that distinguish breast tissues of parous from nulliparous women. Thus, we hypothesize that dysregulated PPI increases risk of BBD and PRBC. Further, we aim to demonstrate that anti-inflammatory therapy can reduce a PRBC immune score linked to BC risk, thereby providing the basis for proposing large scale prevention trials in BBD with anti-inflammatory agents. To test this hypothesis, we aim to define a PRBC immune signature to discriminate PRBC risk from PPI, and then test if NSAIDs can reduce PRBC signature scores in BBD biopsies performed <5 years of a birth. We address this hypothesis in three Aims listed below.

Specific Aim 1A: To define a PPI-specific immune signature score. We will discover RNA-based immune pathways and spatially resolved proteins that distinguish normal breast tissues of 70 nulliparous donors from those of 70 frequency age-matched parous donors (birth <5 years of donation) in the Komen Tissue Bank (KTB) using NanoString Immunooncology (IO) RNA and (DSP) protein assays. We will confirm <5 most discriminating markers / pathways in a similar independent sample set from 50 nulliparous and 50 parous donors and derive a composite PPI score. We will compare levels of arachidonic acid-derived eicosanoids (e.g., prostaglandins (PGs)), in 100 specimens from participants in the test set. Specific Aim 1B: To define epidemiological determinants of PPI immune scores and tissue eicosanoid levels. We will assess associations of BC risk factors with PPI scores (n=240) and with eicosanoid levels (n=100), adjusted for confounders, using multivariable regression. We propose that women with high score are potential candidates for chemoprevention with NSAIDs.

Specific Aim 2A: To test and refine a PRBC immune score. We will evaluate discrimination of a composite PRBC risk score in 75 BBD biopsies from parous patients <5 years of a birth who developed BC versus 75 age-matched parous BBD patients who did not, adjusted for BBD severity and follow-up time. The composite PRBC signature will be derived by quantitating 8 risk markers (above) in whole sections using Aperio algorithms. We will assess whether a dual stain for ER/Ki67 (double labeling suggests dysregulation) or γ -H2AX (DNA damage) improves prediction of the signature. Specific Aim 2B: To evaluate PRBC immune scores in BCs. We will compare the PRBC immune score in existing tissue microarrays (TMAs) of 707 BCs from women <40 years, overall, and by molecular subtype and parity in the Young Women's BC Study (YWBCS), in multivariate models.

Specific Aim 3: To evaluate the efficacy of aspirin in reducing immune responses linked to PRBC risk. We will enroll 100 women aged <45 years across Mayo Clinic sites and at Karmanos Cancer Institute (KCI) and University of North Carolina, Chapel Hill (UNC), as follows: 1) no prior BC; 2) no use of BC prevention agents or recent regular NSAID use; 3) scheduled for breast biopsy; 4) parous <5 years of last birth; and 5) mammogram does not show clear BC. Women with in-situ or invasive BC on final pathology will be replaced. We will obtain a questionnaire, blood, urine, and research tissue at the clinical biopsy, and ask participants to take aspirin 81mg QD for 6 weeks as provided. Post-treatment, patients will undergo surgery (if clinically indicated) or a contralateral research biopsy if surgery is not planned. We will evaluate intra-person changes in pre- versus post-treatment markers. Primary endpoint: change in PRBC immune signature score; secondary endpoints: change

in PPI signature score; percent epithelial cells positive for COX-2, ER/Ki67, γ H2AX (DNA damage) and p16 (senescence) in "normal" and in BBD lobules; changes in serum C-reactive protein, estrogens, insulin/IGFs, adipokines and changes in tissue and urine prostaglandins (PGs) and metabolites levels, particularly PGE2.

This innovative, high impact proposal will develop a mechanistically targeted, precision prevention strategy for PRBC, a lethal form of BC for which effective widely accepted approaches are currently lacking.

Immunohistochemical Labeling of Low-Density Lipoprotein Receptor and Scavenger Receptor Class B Type 1 Are Increased in Canine Lymphoma

Erica Behling-Kelly

Rapidly dividing cancer cells rely on a high uptake and or intracellular synthesis of lipids for essential metabolic and survival pathways. Two major lipoprotein receptors, the low-density lipoprotein receptor (LDL-R) and scavenger receptor class B, type 1 (SR-B1) are overexpressed in several solid cancer types in people. We performed a retrospective analysis of LDL-R and SR-B1 expression in canine lymphoma, the most common hematopoietic tumor in this species, using archived formalin-fixed tissue samples. Cases were immunophenotyped and classified according to World Health Organization (WHO) standards prior to immunostaining for the LDL-R and SR-B1 receptors. Staining intensity was compared between neoplastic and hyperplastic lymphoid tissue as were the relationships between histological score, tumor grade, and score and stage at presentation. Neoplastic lymphoid tissue expressed higher levels of both receptors compared to reactive lymph nodes. No relationship between LDL-R or SR-B1 staining score and tumor grade or phenotype was found. Serum cholesterol concentration was compared between dogs with high and low grade tumors, and correlations between cholesterol concentration and histological score, and between the score for the two receptors were determined. The high expression level of these lipoprotein receptors on most of the tumors could underlie the lack of relationship between score and tumor grade. Flow cytometric evaluation of lymph node aspirates revealed similar changes. A cytometric screening approach could therefore be used to select dogs for lipid encapsulated or lipoprotein receptor targeted therapeutic approaches in future studies.

Transient Receptor Potential Mucolipin-1 Channels in Glioblastoma: Role in Patient's Survival

Maria Beatrice Morelli

Transient receptor potential mucolipin 1 (TRPML1) channel belongs to a versatile ion channel family exhibiting complex regulatory patterns sensitive to several environmental factors.

Expressed on endosomal-lysosomal compartment this channel expression is frequently dysregulated in many types of cancer, the majority of whom is characterized by TRPML1 overexpression that confers a selective advantage to the cancer cells. However, my group presents the supporting evidence for the use of low TRPML1 expression as negative prognostic biomarker. Indeed, survival analysis on 66 glioblastoma patients showed a statistically significant increase in OS in tumors with high expression of TRPML1. Taken together, these data proposed TRPML1 as a new target for a different therapeutic approach in TRPML1-expressing GBM patients. Furthermore, we studied the effects of TRPML1

activation in vitro using T98 and U251 glioma cell lines, and also the biological advantage of TRPML1 loss for glioma cells.

In conclusion, the heterogeneous nature of glioblastoma, both within and across tumors, underscores the difficulty in developing efficacious treatments and provides a challenge both to understand the disease and to stratify patients for treatment. This novel biomarker will allow layering patients into prognostic groups, allowing personalized therapeutic choice depending on TRPML1 expression.

GD2 or HER2 targeting T cell Engaging Bispecific Antibodies to Treat Osteosarcoma

Jeong A Park, MD. PhD.

The cure rate for metastatic or relapsed osteosarcoma has not substantially improved over the past decades despite of multimodal treatment approaches, achieving long term survival in less than 30% of patients. Immunotherapy is an ideal alternative to cancer therapies by harnessing immune cells to fight against cancer cells. Although cytokines, immune checkpoint inhibitors (ICIs), and monoclonal antibodies targeting GD2 or HER2 were not successful in high-risk osteosarcoma, the efficacy of T cell engaging bispecific antibody (BsAb) remains largely unexplored. Anti-tumor activities of anti-GD2 BsAb or anti-HER2 BsAb were studied against a panel of osteosarcoma tumor cell lines in vitro and in vivo. T cells ex vivo armed with anti-GD2-BsAb (GD2-EATs) or anti-HER2-BsAb (HER2-EATs) were tested their efficacy using osteosarcoma cell line- (CDXs) or patient-derived xenografts (PDXs). To enhance the efficacy of EAT therapy and to overcome major hurdles for T cell immunotherapy against osteosarcoma, various combinatorial strategies were explored. First, to block PD-1/PD-L1 interactions between CD8(+) TILs and osteosarcoma tumor cells, anti-PD-1 (pembrolizumab) or anti-PD-L1 (atezolizumab) antibodies were combined with GD2- or HER2-EATs and tested their synergy against osteosarcoma. Second, to modulate immunosuppressive tumor microenvironment (TME) in osteosarcoma, monoclonal antibodies depleting myeloid-derived suppressor cells (MDSCs) or tumor-associated macrophages (TAMs) were combined with EAT therapy and tested their effect. Third, to overcome tumoral heterogeneity in osteosarcoma, multiple antigen targeting EAT (multi-EATs) strategies were explored and tested their efficacy and compared with single antigen targeting mono-EATs. This study supports further clinical investigations of GD2 and/or HER2 targeted T-BsAb therapy for osteosarcoma and various strategies to enhance anti-tumor efficacy of BsAb and T cell immunotherapy.

Plexin-A2 enables the proliferation and the development of tumors from glioblastoma derived cells

Shira Toledano

The semaphorin guidance factors receptor plexin-A2 transduces sema6A and sema6B signals and may mediate, along with plexin-A4, the anti-angiogenic effects of sema6A. When associated with neuropilins plexin-A2 also transduces the anti-angiogenic signals of sema3B. Here we show that inhibition of plexin-A2 expression in glioblastoma derived cells that express wild type p53 such as U87MG and A172 cells, or in primary human endothelial cells, strongly inhibits cell proliferation. Inhibition of plexin-A2 expression in U87MG cells also results in strong inhibition of their tumor forming ability. Knock-out of the plexin-A2 gene in U87MG cells using CRISPR/Cas9 inhibits cell proliferation which is rescued

following plexin-A2 re-expression, or expression of a truncated plexin-A2 lacking its extracellular domain. Inhibition of plexin-A2 expression results in cell cycle arrest at the G2/M stage, and is accompanied by changes in cytoskeletal organization, cell flattening, and enhanced expression of senescence associated β -galactosidase. It is also associated with reduced AKT phosphorylation and enhanced phosphorylation of p38MAPK. We find that the pro-proliferative effects of plexin-A2 are mediated by FARP2 and FYN because mutations in the FARP2 binding domain or in the FYN phosphorylation sites of the plexin-A2 intracellular domain inhibit the rescue of cell proliferation upon expression of the mutated intracellular domain in the knock-out cells. Our results suggest that plexin-A2 may represent a novel target for the development of anti-tumorigenic therapeutics.

Cell proliferation index estimation in lymph node melanoma biopsy images using deep learning networks

Prof. Mrinal Mandal, Salah Alheejawi, Richard Berendt, Naresh Jha, Santi P. Maity

Computer aided diagnosis techniques are increasingly used in pathological practices to reduce the burden on the pathologist from the manual diagnosing. Melanoma is a deadly type of skin cancer which typically begins on the skin and may spread to other parts of the body. Once melanoma is diagnosed by analyzing the skin epidermis/dermis layers, a lymph node biopsy is typically done to stage the melanoma. The cell proliferation index is widely used as an indicator for malignancy.

In this work, we present an automated technique to measure the cell Proliferation Index (PI) in the histopathological images. The PI calculation is performed for melanoma on the lymph nodes tissue images. The proposed technique consists of three steps. First, the melanoma regions are identified on a MART-1-stained lymph nodes tissue images and a region of interest (ROI) mask is generated. In the second step, the ROI mask is used to locate the tumor regions in the corresponding Ki-67-stained image. Finally, the nuclei in the Ki-67 ROI are then segmented and classified using a deep learning network and the PI value is calculated based on the number of the active and the passive nuclei. The deep learning network used in our work is a Convolutional Neural Network (CNN) with three parallel paths, which includes several convolutional, pooling and unpooling layers. Experimental results show that the proposed technique can robustly segment (with 94% accuracy) and classify the nuclei with a low computational complexity and the calculated PI values have less than 4% average error compared to the ground truth PI values. The fully automated technique is expected to be of great help in speeding up the overall diagnosis process.

L-plastin Knockdown Diminishes the Invasive Property of Prostate Cancer Cells in vitro via Inhibiting the Formation of Invadopodia

Meenakshi A. Chellaiah

Metastatic cancer cells use the actin-bundling process to constantly remodel the actin cytoskeleton for adhesion, migration, and invasion. L-plastin is an actin-bundling protein that belongs to the plastin family. L-plastin has been identified in several malignant tumors of the colon, prostate, and breast and contributes to cancer cell invasion in a phosphorylation-dependent manner. Our initial characterization in PC3 prostate cancer (PCa) cell line derived from bone metastases demonstrated L-plastin expression in PCa cells

but not in other PCa cell lines tested. Hence, this study aimed to identify L-plastin's role in the migration and invasion of PC3 cells. Immunostaining analysis demonstrated a punctate distribution of L-plastin and patchy actin staining in PC3 cells with a minimal colocalization between L-plastin and actin at the invadopodia. However, L-plastin overexpression in PC3 cells increased L-plastin's colocalization and actin at the invadopodia and during the invasion. In a wound-healing assay, these cells displayed a significant reduction in migration. L-plastin and invadopodia connections were confirmed using the L-plastin knockdown strategy in PC3 cells (PC3/Si). PC3/Si cells demonstrated an increased migration, which corresponded to punctate podosome-like structures. However, a decrease in the number of invadopodia contributed to a significant reduction in the invasion. Additionally, tumorsphere formation was significantly reduced in PC3/Si cells than in PC3 cells. In conclusion, our observations suggest that L-plastin regulates the formation of invadopodia required for prostate cancer invasion. Our results highlight that it could be a novel therapeutic target for androgen-independent metastatic prostate cancer.

Multiple Facets of the Androgen Receptor Signaling Leading to Prostate Cancer Progression

Simone Chevalier

Prostate cancer (PCa) is curable in most men but lethal if metastatic at diagnosis or upon recurrence on androgen deprivation after curative therapies. Current treatments for metastatic castration resistant disease (mCRPC) are mainly limited to androgen receptor inhibitors (ARIs) and taxanes, which both display limited efficacy. However, the androgen receptor (AR) is often overexpressed and transcriptionally active in advanced PCa, contributing to progression.

To better understand this paradox, we revisited AR expression through cell-by-cell quantification in PCa tissues of patients at different stages of disease. Results showed that progression is associated with decreasing proportions of AR-positive cancer cells and fibroblasts, with some AR-negative cancer cells expressing stemness or neuroendocrine markers and some AR-positive cells expressing ARV7 (a constitutively active AR variant). Combining these findings with the increasing expression of AR in the remaining AR-positive cells was predictive of progression-free survival.

Another mechanism of AR reactivation concerns its crosstalks with other pathways, such as the interleukin (IL)-6 pathway. We showed in PCa cell lines AR activation by the Fer kinase through phosphorylation of AR tyrosine(Y)-223 and STAT3 (signal transducer and activator of transcription) Y-705, allowing formation of nuclear complexes acting on the transcription of canonical pSTAT3 target genes. This crosstalk of Fer with AR and STAT3 in the nucleus of cancer cells also holds in prostate tissues, particularly in advanced disease.

This cellular and functional heterogeneity was further investigated by testing AR variants and genes pertaining to cell subtypes (luminal, stem, neuroendocrine) in the blood of mCRPC patients. No association was seen between gene expression and white blood cells, whereas some gene patterns were significantly associated with the choice of initial curative therapies and mCRPC therapies. Altogether, these findings highlight mechanisms through which AR can evade effects of androgens and ARIs in certain cancer cells. Moreover, they underscore the diversity of tumour cell subtypes, including AR-negative cells, which can explain the clinical heterogeneity of PCa. Tracing circulating cell-subtype genes in patients may be meaningful to stratify and follow disease evolution and predict response to

therapies. Such an approach may allow patient-tailored trials for personalized treatments impacting on this unpredictable lethal disease.

Activation of TRPV1 and TRPV2 channels in chronic myeloid leukemia.

Prof. Consuelo Amantini

Chronic myeloid leukemia is a myeloproliferative disorder characterized by accumulation of immature cells in bone marrow and peripheral blood. Although successful results were obtained with tyrosine kinase inhibitors, several patients show resistance. For this reason, the identification of new strategies and therapeutic biomarkers represents an attractive goal. The role of Transient Receptor Potential (TRP) ion channels as possible drug targets has been elucidated in different types of cancer. We firstly demonstrated that chronic myeloid leukemia cells express both TRPV1 and TRPV2 receptors. Then, by using FACS analysis, confocal microscopy, gene silencing and cell growth assay, we demonstrated that the activation of TRPV2 by cannabidiol inhibits cell proliferation, induces cell cycle arrest, promotes mitochondria dysfunction and mitophagy. These effects were associated with changes in the expression of OCT-4 and PU.1 markers regulated during cellular differentiation. Interestingly, a synergistic effect by combining CBD with the standard drug imatinib was found. In addition, we also investigated the effects induced by OLDA, a specific TRPV1 agonist and we showed that OLDA induces cell death by stimulating oxidative stress, ER stress, DNA damages and apoptosis. Therefore, the targeting of TRPV1 and 2 could be a promising strategy to enhance conventional therapy and improve the prognosis of CML patients.

Targeting Tumour Survival Pathways to Improve Treatment Response in Breast Cancer

Geoffrey J. Lindeman, James R. Whittle, Francois Vaillant, Elliot Surgenor, Antonia N. Policheni, Gökür Giner, Bianca D. Capaldo, Huei-Rong Chen, HeK. Liu, Johanna F. Dekkers, Norman Sachs, Hans Clevers, Andrew Fellowes, Thomas Green, Huiling Xu, Stephen B. Fox, Marco J. Herold, Gordon K. Smyth, Daniel H.D. Gray, Jane E. Visvader

Purpose: Although cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors significantly extend tumor response in patients with metastatic estrogen receptor-positive (ER β) breast cancer, relapse

is almost inevitable. This may, in part, reflect the failure of CDK4/6 inhibitors to induce apoptotic cell death. We therefore evaluated combination therapy with ABT-199 (venetoclax), a potent and selective BCL2 inhibitor.

Experimental Design: BCL2 family member expression was assessed following treatment with endocrine therapy and the CDK4/6 inhibitor palbociclib. Functional assays were used to

determine the impact of adding ABT-199 to fulvestrant and Palbociclib in ER β breast cancer cell lines, patient-derived organoid (PDO), and patient-derived xenograft (PDX) models. A syngeneic

ER β mouse mammary tumor model was used to study the effect of combination therapy on the immune system.

Results: Triple therapy was well tolerated and produced a superior and more durable tumor response compared with single or double therapy. This was associated with marked

apoptosis, including of senescent cells, indicative of senolysis. Unexpectedly, ABT-199 resulted in Rb dephosphorylation and reduced G1-S cyclins, most notably at high doses, thereby intensifying the fulvestrant/ palbociclib-induced cell-cycle arrest. Interestingly, a CRISPR/Cas9 screen suggested that ABT-199 could mitigate loss of Rb (and potentially other mechanisms of acquired resistance) to palbociclib. ABT-199 did not abrogate the favorable immunomodulatory effects of palbociclib in a syngeneic ER β mammary tumor model and extended tumor response when combined with anti-PD1 therapy.

Conclusions: This study illustrates the potential for targeting BCL2 in combination with CDK4/6 inhibitors and supports investigation of combination therapy in ER β breast cancer.

Kinome Plasticity in Response to Targeted Inhibitors

Michael Patrick East

My work focuses on the adaptive nature of the kinome at the transcriptional and protein levels. Until recently, we believed that kinases were stably and ubiquitously expressed similar to housekeeping genes and were regulated predominantly by post translational modification. However, kinases are among the most dynamically regulated classes of proteins and their expression is highly dynamic in response to cellular perturbation. This remodeling of the kinome in response to challenge has been shown to contribute directly to drug tolerance and resistance in preclinical models. My work examines the complexity and heterogeneity of kinome remodeling in response to different perturbations, in different cellular contexts, and within cell populations at single-cell resolution. I demonstrate this using cell culture models and window-of-opportunity trials in patients. I show that targeted inhibitors drive epigenetic remodeling and sweeping changes in the open chromatin state which is a primary mechanism of kinome plasticity and heterogeneity of response. I also show that kinome remodeling can be suppressed by treatment with combinations of targeted kinase inhibitors with epigenetic inhibitors resulting in synergistic growth inhibitory effects in triple negative breast cancer models. Because kinome remodeling presents such a clinically significant challenge for targeted therapies, I am also developing a targeted proteomics platform using parallel reaction monitoring and the Surequant software for absolute quantification of kinase abundance with very low sample requirements for use with tumor biopsies, fine needle aspirants, and patient derived organoids.

Using Computational Techniques for Melanoma Classification and Results

Sule Yildirim Yayilgan

In our research group, we are massively using computational techniques such as Artificial Intelligence and Machine Learning in healthcare particularly for skin lesion classification. One main area of research where we apply these techniques is melanoma classification. In this talk, I will particularly focus on computational techniques for pre-processing of images such as thin artifacts removal, conversion to gray from RGB, cropping, binary masks etc., feature extraction such as RSURF, Local binary patterns (LBP), color histograms etc. and deep network models. I will show our results for classification performance and point to future research directions in this field. The performance metrics used will also be defined.

Biography: Sule Yildirim Yayilgan is a professor from NTNU at the Department of Information Security and Communication Technology (IIK) since 2009. She received PhD degree Computer Science in (2002). She has worked more than 25 years in academia, and served as Head of the Department. Her main fields are artificial intelligence, machine

learning, digital crime, image processing, document classification and biometrics. She received funding from Horizon 2020, Eurostars, Erasmus+, the Research Council, and Ministry of Foreign Affairs, Norway. She has been supervising students at different academic levels and has been publishing more than 100 journal and conference papers.

Insights into Genetic Susceptibility to Melanoma by Gene Panel Testing: Potential Pathogenic Variants in ACD, ATM, BAP1, and POT1

Lorenza Pastorino

The contribution of recently established or candidate susceptibility genes to melanoma missing heritability has yet to be determined. Multigene panel testing could increase diagnostic yield and better define the role of candidate genes. Our preliminary paper characterized 273 CDKN2A/ARF and CDK4-negative probands through a custom-designed targeted gene panel that included CDKN2A/ARF, CDK4, and ACD BAP1, MITF, POT1, TERF2IP, ATM, and PALB2. We identified 16 (5.9%) pathogenic and likely pathogenic variants in established high/medium penetrance cutaneous melanoma susceptibility genes (BAP1, POT1, ACD, MITF, and TERF2IP), including two novel variants in BAP1 and 4 in POT1. Co-segregation, loss of heterozygosity (LOH)/protein expression analysis, and splicing characterization were performed to improve variant classification. We also found four deleterious and five likely deleterious variants in ATM (3.3%). Thus, including potentially deleterious variants in ATM increased the diagnostic yield to about 9%. Inclusion of rare variants of uncertain significance would increase the overall detection yield to 14%. At least 10% of melanoma missing heritability may be explained through panel testing in our population. To our knowledge, this is the highest frequency of putative ATM deleterious variants reported in melanoma families, suggesting a possible role in melanoma susceptibility, which needs further investigation.

Prostate Cancer: Novel Approaches to Diagnosis and Therapy

S.K. Tripathi, M. Kumari, B. Thapa, O. Dahlgren, C. Clark, E. Trabulsi, L. Gomella, M. Thakur

Introduction and Objectives: Despite the advances in understanding of its genomic and molecular basis, prostate cancer (PCa) continues to take one human life every 18 minutes. Digital rectal examination (DRE) and serum prostate specific antigen (PSA) measurements, trigger trans rectal ultrasound prostate biopsies, majority (>66%) of which find benign pathology but incur patient morbidity and healthcare costs. There remains, an unmet need for a simple and minimally invasive approach that shall diagnose PCa reliably and noninvasively. Amongst the theranostic agents, Lu-177-PSMA-617 (Pluvicto), has drawn considerable attention. Although effective, Pluvicto, can induce xerostomia, anemia, renal toxicity and fatigue. PSMA is expressed only on 80%-85% of PCa, compelling physicians to perform Ga-68-PSMA-11 scan to determine patient eligibility for Pluvicto treatment and to pretreat salivary glands and kidneys. Our goals were to develop a simple, noninvasive and reliable test to diagnose PCa and to evaluate a novel radiopharmaceutical to treat it.

Methods and results: Our approaches to diagnose and treat PCa stem from the high density genomic VPAC receptors expression in all PCa types, irrespective of their heterogeneity. We have developed a small molecule with high affinity (3.1×10^{-9} M) for VPAC. When conjugated with a near infrared fluorescence molecule, it (TP4303), serves a

diagnostic compound and when labeled with a β -emitting copper-67, it, (Cu-67-TP3805), depicts potential as a theranostic agent.

The diagnostic assay efficiently visualizes malignant PCa cells, shed in voided urine and collected on a glass slide. Ongoing evaluation performed on several hundred urine samples collected from clinically determined PCa and benign prostatic hyperplasia (BPH) patients and normal volunteers have shown >95% sensitivity.

The preclinical evaluation of Cu-67-TP3805, performed in athymic nude mice bearing human PCa depicted, as estimated independently, higher radiation dose per unit of Cu-67-TP3805 than that of Pluvicto. Furthermore, i) VPAC receptors are expressed on 100% of PCa type (as compared to 80-85% of PSMA), ii) unlike Pluvicto, Cu-67-TP3805 has no salivary gland uptake eliminating the risk for xerostomia and iii) has no urinary excretion minimizing the waste disposal issues imposed by Pluvicto..

Conclusions: Data promise that TP4303 can diagnose PCa effectively and Cu-67-TP3805 can treat it efficiently. Work is in progress,

Support: NIH, NCI 5R01CA249921 and the Philadelphia Prostate Cancer Research Program (BIOME).

Comparison of Combo Treatments of Curcumin, Vitamins and Steroids on Three Human Melanoma Cell Lines (BLM, 1205Lu, WM238)

Pandurangan Ramaraj

Previous in-vitro studies with progesterone (P), curcumin (cur), and vitamins gave the idea for a combination treatment of human melanoma cells. The aim was to study the combined effects of curcumin, vitamins (D3 and A), and steroids (P4 and RU-486) on human melanoma (BLM, 1205Lu, WM238) cell growth and IL-8 secretion in vitro. Human melanoma cells were incubated in a 96 well plate with a single (solo) compound or a double combo of the compounds or a triple combo of the compounds in various combinations. Supernatants were subjected to Elisarray and quantitation of the cytokine IL-8 secreted by the cells. Results from the three cell lines (BLM, 1205Lu and WM238) were compared. Solo or single compound treatment of Cur, P, RU, A and D3 resulted in 40 to 57% of BLM cell growth compared to its untreated control cell growth at 100%. Similarly, 1205Lu cell line treatments resulted in 37 to 59% growth compared to its untreated control cell growth at 100%. A double combo of compounds such as Cur+D3, Cur+P, treatments resulted in 19 to 42% of BLM cell growth and 17 to 37% of 1205Lu cell growth. Whereas WM238 cell line showed an 18 – 22% cell growth. A triple combo such as Cur+P+RU, treatments resulted in 21 to 30% of BLM cell growth and 19 to 30% of 1205Lu cell growth. Whereas WM238 cell line resulted in 19 to 20% cell growth. Elisarray of the supernatants pointed to the following two combo treatments A+RU, Cur+P+RU as having a basal secretion profile of various proinflammatory cytokines by the three cell lines with IL-8 as the only regulated cytokine. Hence, IL-8 in the supernatants of the two combo treatments was quantitated by Elisa. IL-8 secretion by the BLM cell line was 46.1 pg/ml and 31.08 pg/ml respectively in the supernatants of the two combos A+RU and Cur+P+RU. Whereas IL-8 secretion by the 1205Lu cell line was 17.5 and 8.0 pg/ml respectively and IL-8 secretion by the WM238 cell line was 0.515 and 0.926 pg/ml respectively.

Conclusion: Measurements based on cell growth, Elisarray and IL-8 quantitation indicated the two combos A+RU and Cur+P+RU fared well on the three melanoma cell lines,

suggesting a combination of compounds was more effective than the individual treatment of a compound.

Kinase Modulation of Androgen Receptor Signaling: Implications for Prostate Cancer

Neil Bradbury

Progression from early forms of prostate cancer to castration-resistant disease is associated with an increase in signal transduction activity. The majority of castration-resistance cancers persist in the expression of the androgen receptor (AR), as well as androgen-dependent genes. The AR is regulated not only by its associated steroid hormone, but also by manifold regulatory and signaling molecules, including several kinases. We undertook evaluation of the role of Lemur Tyrosine Kinase 2 (LMTK2) in modulating AR activity, as several Genome Wide Association Studies (GWAS) have shown a marked association of LMTK2 activity with the development of prostate cancer. We confirm that not only is LMTK2 mRNA reduced in prostate cancer tissue, but also LMTK2 protein levels are markedly diminished. Knockdown of LMTK2 protein in prostate cell lines greatly increased the transcription of androgen-responsive genes. In addition, LMTK2 knockdown led to an increase in prostate cancer stem cell populations in LNCaP cells, indicative of increased tumorigenicity. Using multiple approaches, we also demonstrate that LMTK2 interacts with the AR, thus putting LMTK2 as a component of a signaling complex modulating AR activity. Our finding that LMTK2 is a negative regulator of AR activity defines a novel cellular pathway for activation of AR-responsive genes in castrate resistant-prostate cancer. Moreover, pharmacologic manipulation of LMTK2 activity.

The Impact of The Immune Check Point Duration of use on Cost in Lung Cancer

Helmy M. Guirgis

Background: Monotherapy and combinations of Pembrolizumab (Pembro), Atezolizumab (Atezo) and Cemiplimab (Cemi), prolonged overall survival (OS) in advanced/metastatic non-small cell lung cancer (a/m NSCLC). Pembro later demonstrated 5-year OS. The duration of therapy of the immune check point inhibitors (ICI) has not been defined. One-year adjuvant Durvalumab (Durv) and Atezo significantly prolonged OS. Few cycles of neoadjuvant ICI resulted in positive outcomes. Costs are relatively expensive, multiplying with prolonged use. The estimated 2019 CAR-T cost was \$450,000. There is pressing an unmet need for innovative drug cost policies. We aimed 1- Explore the factors which impact ICI cost in various lung cancer stages 2- Navigate cost-saving pathways utilizing thresholds of \$450,000 for monotherapy and \$550,000 for combinations

Methods: Previous clinical studies results were quoted. Annual drug prices were calculated. **Results:** Estimated annual Pemetrexed (Peme) costs were \$113,793, generic chemicals < \$1,000, Bevacizumab (Bev) \$150,126 and Bio-similar Bev \$111,566. The mean 6 ICI was \$148,000. Pembro 2-year costs were \$334,652, 3- \$501,978 and 5- \$836,630. Atezo + Bev+ Peme combination had the highest 2-year \$722,977 costs. The lowest were demonstrated by Atezo + Peme of \$422,725, Pembro + Peme \$448,445 and Cemi + Peme \$425,385. Costs decreased by 25% using generics. Extending ICI use by 6-12 months increased combination costs by 25-50%. Adjuvant 1-year costs of Durv were \$148,013 and Atezo \$154,446. Using response rates, cost of neoadjuvant Nivolumab (Nivo) 2-4 cycles were \$25,000 - \$50,000.

Conclusion: Short duration of ICI use, neoadjuvant therapy and generics reduced costs. High costs of extended use of ICI mono and chemo-patent combinations support the application of utilization thresholds.

The Development of Novel Anti-Cancer Agents Targeting Glioblastoma

Kate F. Byrne, John C. Stephens, James F. Curtin, Gemma K. Kinsella

Glioblastoma (GBM) is the most common and aggressive malignant grade IV brain tumour. The current gold standard chemotherapeutic agent is Temozolomide (TMZ), which increases the patient median survival rate from 12 to 14.6 months whereby the percentage of patients alive after two years has risen from 10.4 % to 26.5 %. Notably, there has been no improvement in the 3–5-year survival rate in the last decade.

Recently, the anti-cancer properties of Metformin have been studied in combination with TMZ and/or irradiation induced a synergistic anti-tumoral response in glioma cell lines. An in-house compound with a similar mechanism of action to Metformin, exhibited activity in cancer-cell viability assays. Cell viability assays were carried out on a synthesised series of 14 substituted pyrazolo[1,5- α]pyrimidinones on a cancerous U-251MG cell line and a non-cancerous HEK293 cell line. Four hit compounds were determined whereby the lowest IC50 value obtained was 6.17 μ M. Computational techniques were utilised to rationally design and optimise these (and other) novel compounds with potential to pass the blood brain barrier.

Ongoing studies are exploring the potential mechanism of action for the hit compounds using an array of biological techniques such as 2D cell culture assays, flow cytometry, 3D cell culture and the development of a blood-brain-barrier model.

WGS of Basal Cell Carcinoma of Skin Reveals Distinct Mutational Landscape and the Role of HIPPO-YAP Pathway in Disease Progression

Sergey Nikolaev, Andrey A. Yurchenko, Fatemeh Rajabi, Oltin Pop, Konstantin Gunbin, Ismael

Basal Cell Carcinoma (BCC) is the commonest type of skin cancer which has not been yet studied by whole genome sequencing (WGS). We have assembled the largest to date BCC cohort representing major histological subtypes for genetic analysis by WGS (89), WES (310) and RNAseq (360).

Mutational profile in BCC is due to UV-light exposure, however it differs from melanoma by high fraction of COSMIC signature SBS7b mutations. We explained it by high contribution to mutagenesis in BCC of GC-rich early replicating regions, which in BCC are characterized by more condensed and difficult to repair chromatin. We report that loss of TP53 is the first event in BCC and precedes the loss of PTCH1. Moreover, we deduce from 17p copy neutral LOH regions that loss of TP53 results in a dramatic increase of mutation rates in BCC. In line with that BCC with TP53 mutations have 2.5-fold higher mutation burden than BCC with wt-TP53. We discovered novel BCC driver genes outside the Hh pathway. 65% of BCC harbor mutations in HIPPO-YAP and Contact Inhibition of Proliferation pathways: (FAT1(30%), NF2(9%), ARHGAP35(18%), CREBBP(21%), PTPN14(21%), LATS1(9%)). We validated the role of these genes in BCC cell line by siRNA screening followed by migration and proliferation assays. Promoter mutations of TERT were identified in 48% of BCC and

resulted in its overexpression. High-risk morpheiform BCCs were different from low-risk BCCs by activation of HIPPO-YAP pathway and fibrotic types of tumor microenvironment. BCC with intrinsic resistance to vismodegib demonstrated a hyperactivation of HIPPO-YAP pathway.

Modeling Stromal Effects in the Breast Tumor Microenvironment Using Microfluidic Models **Maria Virumbrales Munuz**

The tumor microenvironment (TME) is a complex niche in which the tumor develops. In breast cancer, the cellular and extracellular matrix (ECM) composition of the TME that harbors the tumor (i.e., stroma) highly influences cancer progression, leading to differential invasion, migration, and metastatic potential. Specific stromal components, such as fibroblasts and ECM proteins, have the potential to alter cancer cell migration. However, the lack of in vitro migration models that enable ECM customization limits our knowledge of how specific ECM components contribute to cancer progression. Here, a microfluidic model was used to study the effect of 3D heterogeneous ECMs (i.e., including fibroblasts and different ECM protein compositions) on the migration distance of a highly invasive human breast cancer cell line MDA-MB-231. To build our model, we used an established and highly biocompatible device that enables the patterning of two hydrogels of heterogeneous ECM compositions: one within a tubular 3D structure and another 3D ECM surrounding the tubular structure. Using this model, we can easily track cell migration and investigate cell-cell and cell-ECM crosstalk in specific environments and how ECM is able to modulate cell-cell crosstalk. Specifically, we show that in the presence of normal breast fibroblasts, a fibronectin-rich matrix induces more cancer cell migration. Analysis of the ECM via second harmonic generation imaging revealed that ECM remodeling depends on ECM and fibroblast compositions. Likewise, cancer-fibroblast crosstalk increased the secretion of metalloproteinases (MMPs) in co-cultures. Specific inhibition of MMPs was able to decrease the migration distance in all conditions except for the fibronectin-rich matrix in the co-culture with human mammary fibroblasts (HMFs). Our model can incorporate additional aspects of the in vivo invasion microenvironment, allowing the examination of cancer cell migration in a relevant context. All in all, our data showcases the capability of the model to pinpoint the contribution of different components of the TME.

RSK4: A New Therapeutic Target against Drug Resistance and Metastasis in Lung and Bladder Cancers

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Lung and bladder cancers are mostly incurable due to early development of drug resistance and metastatic dissemination. Hence, novel therapies that tackle these two processes are

urgently needed to improve clinical outcome. We have identified the kinase RSK4 as a promoter of drug resistance and metastasis in lung and bladder cancer cells and its silencing, either through RNA interference or CRISPR, sensitises to chemotherapy and hinders metastasis in vitro and in vivo. Conversely, overexpressing RSK4 promotes drug resistance and invasiveness. We identified the molecular mechanisms underlying these biological functions: regulation of drug resistance was through the control of the expression of antiapoptotic proteins (especially cIAP2) while the regulation of cell invasiveness was through the control of NFkB activity with p300 being a novel substrate for RSK4. Drug screening revealed several floxacins antibiotics as potent allosteric RSK4 activation inhibitors and trovafloxacin reproduces all effects of RSK4 silencing in vitro, in vivo in two separate mouse models and ex vivo in patients' tumour explants. Through X-ray structure determination, Markov transient and Deuterium exchange analyses, we identified the allosteric binding site for trovafloxacin on RSK4 and revealed how this compound blocks kinase activation. Finally, we show that patients undergoing chemotherapy and adhering to prophylactic levofloxacin, another floxacin targeting RSK4 activation, in the large placebo-controlled randomised phase 3 SIGNIFICANT Trial had significantly increased long-term overall survival times. We suggest that RSK4 inhibition may represent an effective therapeutic strategy for treating lung and bladder cancer.

Nanoemulsions as Delivery Systems for Poly-Chemotherapy Aiming at Melanoma Treatment

Luigi Battaglia

Advanced melanoma is characterized by poor outcome. Despite the number of treatments having been increased over the last decade, current pharmacological strategies are only partially effective. Therefore, the improvement of the current systemic therapy is worthy of investigation. Phospholipid stabilized injectable nanoemulsions have been used clinically as i.v. nutritional supplements for over 40 years. Their biocompatibility, and concomitant FDA approval, has led them to be a template for drug delivery. Amongst marketed formulations, nanoemulsions are used for repurposing of different compounds related to pain management, including anaesthetic, analgesic and anti-inflammatory agents. Based upon various mechanisms, they can be purposed also for anti-tumour drug delivery, aiming to melanoma treatment. Indeed, they can be loaded with combinations of drugs, with different physico-chemical properties and acting through various mechanisms, including kinase inhibitors, monoclonal antibodies and immunotherapies. Furthermore, they can be targeted by surface functionalization, either chemical or biological (cell ghosts wrapping). Encouraging preclinical results obtained on melanoma cell and animal models could drive towards clinical translation.

Cancer-Associated SF3B1 Mutations Confer a BRCA-Like Cellular Phenotype and Synthetic Lethality to PARP Inhibitors

Katrina M Lappin, Eliana M Barros, Satpal S Jhujh, Gareth W Irwin, Hayley McMillan, Fabio G Liberante, Cheryl Latimer, Melissa J La Bonte, Ken I Mills, D Paul Harkin, Grant S Stewart, Kieran I Savage

Mutations in SF3B1 have been identified across several cancer types. This key spliceosome component promotes the efficient mRNA splicing of thousands of genes including those with crucial roles in the cellular response to DNA damage. Here, we demonstrate that depletion of SF3B1 specifically compromises homologous recombination (HR) and is epistatic with loss of BRCA1. More importantly, the most prevalent cancer-associated mutation in SF3B1, K700E, also affects HR efficiency and as a consequence, increases the cellular sensitivity to ionizing radiation and a variety of chemotherapeutic agents, including PARP inhibitors. In addition, the SF3B1 K700E mutation induced unscheduled R-loop formation, replication fork stalling, increased fork degradation, and defective replication fork restart. Taken together, these data suggest that tumor-associated mutations in SF3B1 induce a BRCA-like cellular phenotype that confers synthetic lethality to DNA-damaging agents and PARP inhibitors, which can be exploited therapeutically.

Ant-Cancer Natural Health Products and Their Mechanism of Action and Interaction with Standard Chemotherapeutic Drugs: Possibility of Using Them as Supplement with Standard Treatment

Siyaram Pandey

Plant extracts and their active compounds have been used for medicinal purposes for centuries by various traditional medical practices including Ayurveda, traditional Chinese medicine. Interestingly, some of the most common anticancer drugs like taxol, vincristine are derived from plant extracts. Unfortunately, treatment of metastatic advanced cancers using adjuvant therapies (multiple compounds) leads only to a limited success, but severe side effects. We have previously demonstrated very potent anticancer activity of different plant extracts including dandelion root, lemongrass, long pepper and white tea extracts in different human cancer cells including lymphomas and leukemias. Since these extracts are safe and can be taken orally, the total extract (which is adjuvant of many compounds in itself) could be taken as supplements along with standard cancer treatments. One major hurdle is their potential interaction with standard chemotherapies and radiation therapy. Many oncologists strongly oppose taking any natural extracts as they think it could hamper the treatment of cancer patients. Therefore, it is critical to investigate drug-natural extracts interaction. Our hypothesis is that natural extracts would sensitize cancer cells to standard treatment as well as reduce toxicity related to these treatments for healthy tissue. We have demonstrated that Dandelion and Lemongrass extracts display positive interaction with different chemo regimens in colon and prostate cancer cell in vitro and in vivo. Furthermore, we have discovered that these extracts inhibit appearance of colon tumor in transgenic APC min mice indicating their preventative ability. Most of the results from our work on lymphoma and leukemia will be presented.

Defining Radiologic Complete Response Using A Correlation Of Presurgical Ultrasound And Mammographic Localization Findings With Pathological Complete Response Following Neoadjuvant Chemotherapy In Breast Cancer

Dorothy Makanjuola

Breast cancer affects a younger population in the Arabian Gulf and breast conservative treatment is highly preferred. Pathologic complete response to neoadjuvant chemotherapy particularly with HER2 positive and triple negative tumors promote breast conservation

management. von Minck witz, et.al. 2008 mentioned that “shrinking tumors need less surgery” while Kummeel, et.al. postulated that patients with pathologic complete response (pCR) would require only a reduced extent of surgery or potentially no surgery. The most important pre condition for prospective trials for the above hypothesis would be an exact diagnosis of pCR without surgery. This challenge therefore dictated the need to identify radiologic complete response (rCR). MRI which is more expensive and not widely available is said to be more accurate in identifying radiologic complete response. However, we noticed in our practice that ultrasound and mammography were able to identify rCR. Therefore, a retrospective study of 93 patients who had neoadjuvant chemotherapy for solitary lesions was undertaken. The views used were presurgical localization pictures. Three groups were involved. Firstly, those with ultrasound alone; secondly, with mammography alone, and thirdly, with combined mammography and ultrasound. The results revealed that the combined studies of mammography and ultrasound using the features of no mass with residual post biopsy clip overlying normal breast parenchyma (clip sign) in both mammography and ultrasound had a 93% concordance with pCR. A new BIRADS category e.g., 6nil, 6void is suggested to represent rCR for correlation with pCR and to signal vacuum biopsy or surgery. Several illustrations will be presented and limitation of the study will be discussed.

Highlights on the Racial, Demographic, Occupational, Tumor Characteristics and Burden of Metastasis of Metastatic Melanoma in Florida

Frederick Bebe

Recent decades have witnessed an increase in melanoma more than any other cancer in the US. Currently (2015-2019), the age-adjusted incidence rate (IR) and mortality rates are 22.3 and 2.7 per 100,000, respectively. Florida’s IR is the second highest in the nation and mortality rate has doubled since 1975. Although metastatic melanoma (MM) is less frequent among minorities, it has been increasing steadily over the years. This study describes the demographic, occupational, tumor characteristics and the burden of metastasis of patients diagnosed with metastatic melanoma in Florida between 1996 and 2010.

Materials and Methods: A dataset of 80,349 Non-Hispanic Whites (NHW), African Americans (AA) and Hispanics Whites (HW) stage III and IV metastatic melanoma patients at presentation was obtained from Florida Cancer Data System (FCDS). Demographic information, occupational status and measures related to age at diagnosis, primary site and laterality, histology, grade and staging are reported. Data were analyzed using SAS. Means \pm SD, frequencies, percentages and chi-square tests were employed at $P < 0.05$.

Results: Fifteen counties out of 67 accounted for 72% of all cases; 61% of the patients were married at time of diagnosis. Forty-eight percent reported having state-sponsored coverage, while 60% never smoked. Sixty-nine percent were diagnosed with tumors of the trunk, shoulder and hip; laterality was evenly-distributed between left 39% and right 37%. More AA and HW had tumors that were either moderately or poorly-differentiated.

Conclusions: This study confirms well-established race/ethnicity, gender and age disparities in metastatic melanoma diagnosis – majority white and male, and majority of the cases between ages 56 and 71. However, unlike previous studies, laterality was evenly-distributed and majority of AA and HW were diagnosed with moderately or poorly-differentiated tumors.

Keywords: Occupation, Demography, Tumor Characteristics, Metastatic melanoma, Ethnicity

Abnormalities in chemokine receptor recycling in chronic lymphocytic leukemia

Laura Patrussi

In addition to their modulation through de novo expression and degradation, surface levels of chemokine receptors are tuned by their ligand-dependent recycling to the plasma membrane, which ensures that engaged receptors become rapidly available for further rounds of signaling. Dysregulation of this process contributes to the pathogenesis of chronic lymphocytic leukemia (CLL) by enhancing surface expression of chemokine receptors, thereby favoring leukemic cell accumulation in the protective niche of lymphoid organs. Pharmacological drugs able to normalize the process of chemokine receptor recycling might represent a powerful therapeutic strategy for the treatment of CLL.

The Impact of a Bayesian Penalized-Likelihood Reconstruction Algorithm on Delayed-Time-Point Ga-68-PSMA PET for Improved Recurrent Prostate Cancer Detection

Tiago Vieira

The benefit of using Ga-68-PSMA PET for patients with biochemical recurrence after radical prostatectomy is high, and a delayed-time-point (DTP) acquisition protocol has proved to improve the capacity of Ga-68-PSMA PET to detect prostate cancer metastases. New hardware and reconstruction methods are challenging the resolution limits of PET imaging, and Bayesian penalized-likelihood reconstruction algorithms (BPLA) are paradigmatic of this ongoing revolution. BPLA allows an effective convergence, in contrast to Ordered Subset Expectation Maximization (OSEM), which must be stopped before contrast convergence to prevent excessive image noise. We present the Ga-68-PSMA PET images of a man with biochemical recurrence of prostate cancer (PSA = 0.51 ng/ml). A dual-time-point acquisition protocol (1 h and 2 h after radiopharmaceutical administration) was conducted in a Discovery IQ4R, and images were reconstructed using OSEM and BPLA. Early-time-point PET did not reveal foci of abnormally increased uptake, either using OSEM or BPLA. DTP images revealed a focus of increased uptake in a 3 mm right external iliac lymph node when using BPLA, not visible with OSEM. After robotic radiosurgery, PSA values decreased to undetectable, confirming the focus as a metastasis. Ga-68-PSMA PET is advantageous over other imaging techniques to detect prostate cancer recurrence, especially in patients with low PSA levels, but the reported detection rate of metastatic sites in patients with biochemical recurrence after radical prostatectomy in a PSA-range of 0.5-1.0 ng/ml does not surpass 73%. Applying a BPLA to a DTP protocol may further improve the detection rate of Ga-68-PSMA PET for recurrent prostate cancer.

STAT transcription factors in the pathogenesis and treatment of cancer

David A. Frank, MD, PhD, Christopher Brett Wolf Chair

The majority of treatments for patients with advanced cancer still relies on the use of non-specific, highly toxic cytotoxic drugs. The challenge going forward is to exploit our understanding of the molecular differences that distinguish a malignant cell from a normal cell, and to target these specifically. Fundamentally, the phenotype of a cancer cell is driven by the pattern of gene expression in that cell. Genes that control critical cellular functions,

such as proliferation, survival, pluripotency, and invasion, which are physiologically turned on and off in a tightly controlled manner, are expressed at inappropriate levels in a cancer cell. This mis-regulated gene expression is generally driven by the inappropriate activation of transcription factors.

One family of transcription factors that regulate these critical genes under physiological conditions are the STATs, or Signal Transducers and Activators of Transcription. These proteins are found inactive in the cytoplasm under basal conditions. When phosphorylated on a single tyrosine residue, STATs form activated dimers that translocate from the cytoplasm to the nucleus, bind to specific sequences in the regulatory region of target genes, and initiate transcription. Equally important, STATs are rapidly inactivated, allowing for the tight regulation of transcription of target genes. In a wide variety of human cancers, STAT family members, generally STAT3 and STAT5, are activated constitutively, and this directly drives cancer pathogenesis.

While continuous STAT activation is necessary for the survival of cancer cells, genetic and pharmacologic data from human and other systems has revealed that normal cells are very tolerant to the interruption of STAT signaling. This makes STATs very appealing targets for cancer therapy. A number of strategies have been utilized in recent years to target STATs, including molecules that directly bind to and inactivate or degrade these proteins, to approaches that leverage dependencies and indirect means to attenuate STAT-driven transcription. The finding that STAT inhibition may enhance immune-mediated killing of cancer cells makes these strategies even more appealing. As more of these approaches are tested in clinical trials, the likelihood that we will be able to exploit the inhibition of STATs and other oncogenic transcription factors becomes even greater.

Melatonin Antineoplastic Potential Against Glioblastoma

Gaia Favero, Enrico Moretti, Francesca Bonomini, Luigi Fabrizio Rodella, Rita Rezzani

Glioblastoma is the most aggressive and common primary brain tumor in adults and its treatment is extremely challenging and ineffective, so new therapeutic approaches are needed. Due to evidence demonstrating melatonin's (multitasking endogenous indoleamine) activity against several cancer hallmarks, there is growing interest in its use for preventing and treating cancer. We present the potential effects of melatonin, alone or in combination with anticancer drugs, against glioblastoma and melatonin targets and/or the intracellular pathways involved. Despite today there are too few clinical studies investigating the antineoplastic effects of melatonin against glioblastoma, melatonin is able to improve glioblastoma patients' quality of life and did not show significant adverse effects. Melatonin effects and mechanisms of action against glioblastoma require more research attention due to the unquestionably high potential of this multitasking indoleamine in clinical practice.

Magnetoplasmonic Au-Fe₃O₄ Nanoheterodimers for X-ray triggered cancer therapy

S. Klein, Erlangen/D

Radiation therapy is a non-invasive cancer treatment that uses an external ionizing radiation beam to destroy tumor tissue. Unfortunately, the X-rays damage both, the tumor and the surrounding healthy tissue. Therefore, the therapeutic efficacy of X-rays against the cancer cells should outweigh the physiological disadvantages for the healthy cells.

Radiosensitizers increase the susceptibility of tumors to the radiation-induced injury. High atomic number nanomaterials such as gold nanoparticles enhance the effectiveness of conventional radiation therapy due to their high X-ray absorption coefficient. In cells, the interactions of X-rays with drug-loaded superparamagnetic Fe₃O₄ nanoparticles causes the release of drugs into the cytosol. Simultaneously, the X-ray radiation activates the catalytic functionality of the Fe₃O₄ surfaces. Surface standing Fe²⁺ and Fe³⁺ ions effectively catalyze the Fenton and Haber-Weiss reaction. Due to alterations in the reactive oxygen detoxifying enzyme levels, cancer cells often have elevated H₂O₂ levels. H₂O₂ is converted to the highly toxic OH• radical, so that the Fe²⁺ driven Fenton reaction is favored. However, under ambient conditions surface Fe²⁺ ions gradually oxidize to Fe³⁺ ions. Fe₃O₄ nanoparticles epitaxially grown on gold nanoparticles yielding Au-Fe₃O₄ nanoheterodimers (NHDs) retain Fenton catalytic activity. In addition, X-rays release electrons from the gold component, leading to the synergistic formation of reactive oxygen species.

Since the as-synthesized NHDs are surface stabilized with oleic acid/oleylamine, ligand exchange is required for water solubility. The ligand exchange with nitrosyl tetrafluoroborate yields NO⁺-functionalized NHDs, which provide synergistic generation of reactive oxygen and nitrogen species under X-ray exposure [1]. To obtain NHDs with a radioprotective function in healthy cells, the NHDs are functionalized with the natural antioxidant and anti-cancer drug caffeic acid. Caffeic acid-functionalized NHDs are shown to act as radioprotectors in healthy breast epithelial cells, but as X-ray dose enhancers in breast cancer cells in (2D) monolayer cell cultures [2] as well as in (3D) multicellular spheroids [3-4]. Hence, the functionalization of Au-Fe₃O₄ NHDs with natural or synthetic anticancer drugs generates nano-therapeutics with a high X-ray dose enhancing potential and chemotherapeutic efficacy for bimodal cancer therapy.

Exercise as medicine across the lung cancer continuum

Vinicius Cavalheri

There is now substantial evidence that exercise training is safe, feasible and effective at improving several outcomes in people with lung cancer, especially in those with NSCLC. Therefore, exercise is now seen as medicine for people with lung cancer and has been playing an increasing role in lung cancer care. Exercise is beneficial across the lung cancer disease and treatment pathway, including in patients with early-stage disease before and after surgery, and in patients with advanced disease. In this talk, A/Prof Cavalheri will describe the impact of lung cancer and lung cancer treatment on patient health outcomes and will summarise the aims, safety, feasibility and effects of exercise training in the context of both early stage and advanced stage lung cancer.

Case Series of Non-Ampullary Duodenal Adenomas

Amitabh Yadav

Duodenal adenomas are benign tumours of the duodenum which carry a malignant potential. They present either sporadically or with familial syndromes. Majority of the cases are treated endoscopically but in select cases, surgical resection is a better alternative to endotherapy. Endotherapy is associated with higher chances of local recurrence and require frequent check endoscopies in the follow up period, while surgery offers a one-time treatment option. Identification and a local duodenal resection sparing ampulla becomes difficult in large lesions of the 2nd part of duodenum. Passage of a catheter from the cystic duct, through common bile duct to the duodenum aids in identification of the ampullary area and is helpful in performing a local/wedge resection of the duodenum containing adenoma without injuring ampullary orifice.

The Challenge of Rehabilitating Young Adults with Cancer**Mary-Ann Dalzell, MSc, Pht.**

Greater numbers of young adults with cancer (Age 18-45) are being diagnosed with aggressive cancers and undergo aggressive treatment in an effort to preserve and extend life. The functional impact of combined surgical, radiological and systemic treatment interventions frequently have long term consequences on the quality of survivorship. Within the context of a specialized clinic for AYA's at the Segal Cancer Center physiotherapists and exercise specialists from the Rehabilitation and Exercise Oncology Program (REOP) clinically profiled the functional status of a variety of patients undergoing treatment for breast, gastrointestinal, CNS, and hematological cancers. Rehabilitation interventions prescribed and compliance with exercise prescription were recorded. In addition, a long term randomized control trial focused on the impact of exercise interventions on the time course of recovery including pain relief, range of motion, and return to work for young adults with breast cancer was conducted. This presentation will focus on the results of these studies, the unique functional problems associated with young adult cancers, psychosocial challenges of rehabilitating patients in this age demographic, and types of rehabilitation interventions recommended.

Patient-derived cancer models and pharmaco-proteogenomics toward novel therapy**Yuki Yoshimatsu, Yutaka Sugihara, Keigo Amari, Rei Noguchi, Tadashi Kondo**

Patient-derived cancer model is a pivotal tool to promote cancer research, and a significant number of cancer models have been developed and deposited in public biobanks in the past several decades. However, considering the complexity of disease, further development of models is required for various cancer types. Rare cancers are typical examples for such cancer types. Because of the rarity of disease, the rare cancer models are generally hard to obtain, and the development of novel therapies is badly hindered by a paucity of adequate cancer models. The common cancers have multiple subgroups when they are divided according to the genetic backgrounds which cause the unique clinical features, and the models for such subtypes are also difficult to obtain from public biobanks. To address this issue, we establish patient-derived cell lines using surgically resected tumors, and apply them for the pharmaco-proteogenomics study. In proteogenomics, the genome and proteome data are obtained from identical samples, and integrated by bioinformatics

methods. We developed unique software by which a virtual sample specific proteome database is generated for mass spectrometric protein identification. We screened the anti-proliferative effects of oncology drugs in the panel of patient-derived cell lines, and the results were interpreted with those of proteogenomics data. We obtained unique results, which may reflect the clinical observations; the presence of mutations in targetable genes did not link to the anti-proliferative effects of corresponding molecular targeted drugs. Moreover, we identified oncology drugs whose clinical use was approved in the different malignancies, suggesting the expanded indication of those drugs. In conclusion, the integration of genotype and phenotype of malignancies towards novel therapy will be achieved by the paharmaco-proteogenomics using patient-derived cancer models. The technical issues such as the difficulty of model establishment and the discrepancy between the in vitro models and the real clinical tumors will be the issues to be addressed in further studies.

Unique morphologic and genetic characteristics of myeloid neoplasms with chromothripsis.

Madina Sukhanova

Chromothripsis is a unique single catastrophic event of fragmentation of one or several chromosomes followed by re-ligation of chromosomal fragments resulting in a number of copy number alterations (CNAs). Chromothripsis has been reported in a wide range of cancers and gained a reputation of a high-risk prognostic marker. However, the clinicopathologic features associated with chromothripsis in myeloid neoplasms (MNs) are not well described. We performed SNP-array analysis (Affymetrix®) on series of MNs and selected cases with chromothripsis [11 AML and 2 MDS cases] for further evaluation. Review of the clinicopathologic features of our AML study cases revealed that chromothripsis is exclusively seen in AML-MRC. We compared the clinicopathologic features of AML-MRC cases with chromothripsis vs selected group of 16 AML-MRC cases without chromothripsis. Chromothripsis-positive cases had more severe clinical outcome compared to cohorts without chromothripsis. All chromothripsis-positive cases display prominent multilineage dysplasia. Blasts are characterized by abundant cytoplasm with cytoplasmic blebbing, vacuolization and occasional cytoplasmic granules. Two MDS cases with chromothripsis revealed blasts morphology similar to chromothripsis-positive AML-MRC cases. Cases with chromothripsis showed higher karyotypic complexity with frequent marker, derivative and ring chromosomes and an apparently non-random common complex signature of CNAs with gains significantly enriched on chromosomes 8, 11q, and 22 and focal deletions at chromosomes 3p, 15, 16, 17, and 18 in addition to recurrent losses at 5q and 7q and mutations in the TP53 gene. The observed unique genetic signature in chromothripsis may prompt additional genetic studies to identify genes and pathways responsible for treatment resistance and severe outcome in patients.

Specific Compositions of Cannabis sativa Compounds Have Cytotoxic Activity and Inhibit Motility and Colony Formation of Human Glioblastoma Cells In Vitro

Hinanit Koltai

Cannabis sativa is widely used for medical treatments. C. sativa is widely used to alleviate numerous symptoms associated with medical conditions and recently, a large number of studies demonstrated that phytocannabinoids have anti-cancer activity in vitro and in vivo.

Yet, cannabis produces hundreds of different compounds, and the optimal combinations of molecules with best activity for the treatment of medical conditions are unknown. Glioblastoma multiforme (GBM) is highly invasive and lethal subtype of glioma brain tumors. Individual phytocannabinoids have been shown to trigger GBM cell death. We identified fractions from a high Δ^9 -tetrahydrocannabinol (THC) cannabis strain that substantially reduced human GBM cell viability and their ability to migrate. The fractions also reduced the ability of GBM cells to form neuro-spheres in 2D and 3D models. These neuro-spheres are associated with the resistance of GBM to chemotherapy. Hence, these results suggest that the cannabis treatment may also have potential for reducing the development of GBM resistance to current therapies. Yet, clinical trials are needed in order to determine the effectiveness of the fractions and combinations of cannabis compounds against GBM.

Effectivity of long antigen exposition dendritic cell therapy (LANEX-DC®) in the treatment of gastrointestinal cancers

Prof. Dr. Frank Gansauge

Introduction

Besides breast cancer, prostate and lung cancer malignancies of the gastrointestinal tract are the most common cancers worldwide with lethality rates ranging between 30% (colon cancer) to over 90% (pancreatic cancer). Dendritic cell therapy has been evaluated in many types of cancer showing promising result in the palliative situation. In here we present our data of dendritic cell therapy in gastrointestinal cancer patients in the palliative situation and for the first time also for the adjuvant situation.

Patients and methods

Dendritic cells (LANEX-DC®) were produced as described recently. The group of pallatively treated patients comprised all patients treated at the surgical unit of GPS-center, Neu-Ulm Germany between 2001 – 2021. All patients receiving dendritic cell therapy also underwent the S3-guideline-conform therapies as radio- or chemotherapy. The adjuvantly treated patients comprised all patients treated between 2001-2016 to keep the 5-year observation time. Following groups were treated: Pancreatic cancer palliative treatment (PCP): 198 patients, pancreatic cancer adjuvant treatment (PCA): 31 patients, colorectal cancer palliative treatment (CRP): 51 patients, rectal cancer adjuvant treatment (RCA): 72 patients and colon cancer adjuvant treatment (CRA): 73 patients.

Results

In all dendritic cell treatments no serious side effects were observed and dendritic cell therapy was very well tolerated. In the palliative groups mean survival according to Kaplan.Meier-analysis was in pancreatic cancer (PCP) 11,6 months and in colorectal cancer (CRP) 31,3 months. In the adjuvantly treated pancreatic cancer patients (PCA) the mean survival was 31,5 months. The relapse rates (5-years) in the adjuvantly treated colon cancer patients were 12,3% and in the rectal cancer group 15,3%.

Conclusion

Our data of a single institution analysis suggest that the additional treatment with dendritic cells (LANEX-DC®) could be highly beneficial in the multimodal treatment of gastrointestinal malignancies.

Comparing the molecular profiles of prostate cancers between men with African and European ancestry

Joshua D Campbell

African American (AFR) men have the highest mortality rate from prostate cancer (PCa) compared with men of other racial/ancestral groups. Differences in the spectrum of somatic genome alterations in tumors between AFR men and other populations have not been well-characterized due to a lack of inclusion of significant numbers in genomic studies. To identify genomic alterations associated with race, we compared the frequencies of somatic alterations in PCa obtained from four publicly available datasets comprising 250 AFR and 611 European American (EUR) men and a targeted sequencing dataset from a commercial platform of 436 AFR and 3018 EUR men. Mutations in ZFH3 as well as focal deletions in ETV3 were more frequent in tumors from AFR men. MYC amplifications were more frequent in tumors from AFR men with metastatic PCa, whereas deletions in PTEN and rearrangements in TMRSS2-ERG were less frequent in tumors from AFR men. Genomic features that could impact clinical decision making were not significantly different between the two groups including tumor mutation burden, MSI status, and genomic alterations in select DNA repair genes, CDK12, and in AR. Although we identified some novel differences in AFR men compared with other populations, the frequencies of genomic alterations in current therapeutic targets for PCa were similar between AFR and EUR men, suggesting that existing precision medicine approaches could be equally beneficial if applied equitably.

Outreach to Primary Care Patients in Lung Cancer Screening: A Randomized Controlled Trial

Ronald Myers

Current guidelines recommend annual lung cancer screening (LCS), but rates are low. The current study evaluated strategies to increase LCS.

This study was a randomized controlled trial designed to evaluate the effects of patient outreach and shared decision making (SDM) about LCS among patients in four primary care practices. Patients aged 50-80 years of age at high risk for lung cancer were randomized to Outreach Contact plus Decision Counseling (OC-DC, n = 314), Outreach Contact alone (OC, n = 314), or usual care (UC, n = 1,748).

LCS was significantly higher in the OC/OC-DC group versus UC controls (5.5% vs. 1.8%; hazard ratio, HR = 3.28; 95% confidence interval, CI: 1.98 to 5.41; p = 0.001). LCS was higher in the OC-DC group than in the OC group, although not significantly so (7% vs. 4%, respectively; HR = 1.75; 95% CI: 0.86 to 3.55; p = 0.123). LCS referral/scheduling was also significantly higher in the OC/OC-DC group compared to controls (11% v. 5%; odds ratio, OR = 2.02; p = 0.001). We observed a similar trend for appointment-keeping, but the effect was not statistically significant (86% v. 76%; OR = 1.93; p = 0.351).

Outreach contacts significantly increased LCS among primary care patients. Research is needed to assess the additional value of SDM on screening uptake.

The Etiology, Epidemiology, Prevention of Liver Cancer

Xuehong Zhang

In this talk, Dr. Zhang will introduce research findings on liver cancer. In the United States, liver cancer had one of the most rapidly increasing incidence rates among both men and women, coupled with a median survival of less than one year. Hence, identification of modifiable risk factors to prevent the development of liver cancer is one of the key priorities to reduce liver cancer morbidity and mortality. The etiology of liver cancer remains poorly understood in the US, where chronic hepatitis infections are relatively low. One of Dr. Zhang's research goals is to identify new modifiable risk factors for liver cancer to inform primary prevention strategies. In this talk, Dr. Zhang will share some research findings on diet, lifestyle, bacterial infection and liver cancer. These findings have the potential to inform disease etiology, and strategies for liver cancer prevention.

Mortality Due to Melanoma in Mexico Increases

Diego Armando Hernández-Domínguez, Fernando Aldaco-Sarvide, Guadalupe Cervantes-Sánchez, Aura Argentina Erazo-Valle-Solís, Perla Pérez-Pérez, Laura Torrecillas-Torres, Patricia Cortés Esteban, Alejandro Juárez-Ramiro, Guadalupe Díaz Alvarado

Malignant melanoma is the most aggressive form of skin cancer. its incidence and mortality vary widely throughout the world. GLOBOCAN 2020 data published by the International Agency for Research on Cancer report 324,635 new cases and 57,043 deaths in that year worldwide. Australia and New Zealand have the highest incidence rate 35.8×10^5 and mortality 2.7×10^5 , the lowest rate corresponds to South-Central Asia with an incidence of 0.33×10^5 and mortality 0.19×10^5 . In Mexico we do not have updated information on mortality due to this neoplasm that allows us to evaluate our actions as health professionals and/or analyze and improve the functioning of our health system.

Objective: To present the evolution of melanoma mortality in Mexico during the last 19 years (1998-2016).

Material and methods: The official death certificates for melanoma were analyzed from the database of the National Institute of Statistics and Geography and the population estimates and projections of the National Population Council.

Results: The overall mortality rate due to melanoma in Mexico has increased by 78%. Last data available for 2016 show a national average rate of $0.57/10^5$ (men: $0.65/10^5$; women: $0.49/10^5$); the State with the highest rate is Mexico City ($1.04/10^5$) and the State with the lowest rate is Coahuila ($0.17/10^5$); the age group most affected is that of 60 years or more, with a rate of $3.69/10^5$, the mortality rate for the group of 30 to 59 years is 0.48%, which is below the national average, while the group of 0 to 29 years is the least affected, with $0.03/10^5$.

Conclusion: Mortality due to melanoma in Mexico has increased in the last 19 years regardless of the sex and age, which forces us to implement and restructure actions in our health system to reduce mortality, otherwise and in addition to the population epidemiological transition it will be an important health problem, both welfare and economic.

GPR183 mediates the capacity of the novel CD47-CD19 bispecific antibody TG-1801 to heighten ublituximab-umbralisib (U2) anti-lymphoma activity

Gael Roué, PhD

Targeted therapies have considerably improved the survival rate of B-cell non-Hodgkin lymphoma (B-NHL) patients in the last decade; however, most subtypes remain incurable. TG-1801, a bispecific antibody that targets CD47 selectively on CD19+ B-cells, is under clinical evaluation in relapsed/refractory B-NHL patients either as a single-agent or in combination with ublituximab, a CD20 antibody, which is also being combined with the PI3K δ /CK1e inhibitor, umbralisib (“U2”-regimen). We recently demonstrated that TG-1801 potentiated ublituximab-mediated antibody-dependent cell death (ADCC) and antibody-dependent cell phagocytosis (ADCP), leading to an additive anti-tumour effect of the TG-1801/U2 combination in B-NHL co-cultures. Accordingly, in a B-NHL xenotransplant model, the triplet achieved a 93% tumour growth inhibition, with 40% of the animals remaining tumour-free 35 days after the last dosing. Transcriptomic analysis further uncovered the upregulation of the G protein-coupled receptor, GPR183, as a crucial event associated with TG-1801/U2 synergism, while pharmacological blockade or genetic depletion of this factor impaired ADCP initiation, as well as cytoskeleton remodelling and cell migration, in B-NHL cultures exposed to the drug combination. Thus, our results set the preclinical rationale and support a combination strategy of TG-1801 with PI3K δ - and CD20-targeting agents in patients with B-NHL.

The Will Rogers phenomenon in the staging of breast cancer – does it matter?**Cheng-Har Yip**

The Will Rogers phenomenon is obtained when moving an element from one set to another set raises the average values of both sets, and is based on a following quote attributed to comedian Will Rogers “When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states”. Alvan Feinstein first used the term Will Rogers phenomenon to describe the effect of the “stage migration” he observed in patients with lung cancer, where the stage specific survival appears to have improved in a 1997 cohort compared to an earlier cohort, but this change was due to migration of cases from a less advanced stage in the older cohort to a more advanced stage in the 1977 cohort, due to newer diagnostic techniques used in the 1997 staging. This phenomenon has been described as one of the most important biases limiting the use of historical cohorts when comparing survival or treatment. Staging of cancers is important to select appropriate treatment and to estimate prognosis. The AJCC system was developed by the American Joint Commission on Cancer for describing the extent of disease Introduction in cancer patients based on the TNM scoring system (tumour size, lymph nodes and metastases). Amendments are made to the staging system to reflect recent clinical evidence or widespread clinical consensus. The most extensive and significant revisions that have ever been made in the breast cancer staging system occurred when the 5th Edition (AJCC5) was updated to the 6th Edition (AJCC6) in January 2003. The principal changes were related to the size, number, location and method of detection of regional metastases to the lymph nodes. The 6th Edition (AJCC6) was updated to 7th Edition (AJCC 7) in Jan 2010, with minor changes. However the 7th Edition was then amended to the 8th Edition, which was a prognostic staging system, utilising estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and this led to major stage migration, with a change in the stage specific survival. Stage shift leads to an erroneous impression

that women are presenting with later or earlier stages and stage-specific survival is improving. Hence standardizing cancer staging is important when reporting stage and survival in different time periods

A case of systemic mastocytosis mimicking POEMS syndrome

Xiaofeng Shi

Rationale: POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome is a rare and complicated disease related to multiple organs and systems. Here, we report a case of systemic mastocytosis (SM) that was misdiagnosed as a POEMS syndrome.

Patient concerns: A 42-year-old man presented with skin changes, diarrhea, and limb numbness. **Diagnoses:** Positron emission tomography/computed tomography revealed extravascular volume overload, organomegaly, lymphadenopathy, and bone lesions with mixed lesions of osteosclerosis and osteolysis. Therefore, POEMS syndrome was suspected. Further histopathological and immunohistochemical examination of the bone marrow, lymph nodes, and gastric mucosa suggested a diagnosis of mastocytosis. The c-Kit D816V mutation confirmed the diagnosis of SM.

Interventions: The patient received the treatment of pegylated interferon-alpha weekly and glucocorticoid daily.

Outcomes: The symptoms relieved significantly.

Lessons: There are many similar features between POEMS syndrome and SM, probably leading to misdiagnosis. This study analyzed the different points between them which can provide help for differentiation.

Development of ¹³¹I-ixolaris as a theranostic agent: metastatic melanoma preclinical studies

Sergio Augusto Lopes de Souza

Ixolaris is a tick salivary protein that binds to Factor Xa or Factor X as a scaffold for inhibition of the Tissue Factor (TF)/Factor VIIa (FVIIa). TF is not normally expressed in cells that are in direct contact with blood. However, TF is abnormally expressed under several pathological conditions, including inflammation, infectious diseases, and cancer. It is known for decades that TF is a risk factor for metastasis, and in mouse models, TF drives metastasis in a coagulation-dependent manner. For these reasons, TF has recently been described as a potential target that can be exploited to image aggressive tumors. Ixolaris has been successfully used to treat some pre-clinical cancer models. It also has been shown its' radiolabeling for diagnostic and therapeutic purposes. The aim of this article is to show that Ixolaris could be an interesting tool to diagnose cancer and also treat it in a near future. Some key findings presented here are that TF has recently been described as a potential target that can be exploited to image aggressive tumors, once it is often associated with migration, invasion, proliferation, metastasis, the inhibition of apoptosis, and the production of several pro-aggressive factors.

Is There a Correlation Between the Presence of Neoplastic Cells in the Inflammatory Infiltrate and Poor Prognosis for Patients with Cutaneous Melanoma In Situ?

Luciana Pantaleão

Background: In recent years, diagnosis of cutaneous melanoma in situ (MIS), considered of excellent prognosis, have been increasingly frequent. However, some authors have reported rare cases of MIS presenting recurrence, metastasis and death. Many clinical and histological variables have been suggested, however, to date, no study has defined the causes of this unexpected behavior.

Methods: Retrospective study of lesions initially diagnosed as MIS. Immunohistochemistry with Melan-A and HMB-45 was performed, to look for melanocytes in the dermis and to measure its depth. These data were correlated with disease-free survival time (DFS).

Results: We identified 445 MIS in 368 patients with a mean age of 54 years old. The number of diagnosed cases has increased over the years. Brisk inflammatory infiltrate was found in 115 cases, nonbrisk in 181 and 149 cases showed no inflammatory infiltrate. We performed immunohistochemical study with Melan-A and HMB45 antibodies with satisfactory samples obtained in 421 cases and found neoplastic cells in the dermis in 53 cases. Breslow thickness of these 53 cases was from 0.09 mm to 0.88 mm (mean 0.39 mm). Nine cases had bad outcome, six with relapse and three with regional metastasis. All nine cases had inflammatory infiltrate, two with brisk type and seven with nonbrisk infiltrate. Among those, two had neoplastic cells in the dermis after immunohistochemical analysis and in one case, the sample was not satisfactory. The Mann-Whitney test indicates no statistically significant difference ($p > 0.05$) between DFS for cases with and without neoplastic cells in the dermis, evaluated by immunohistochemistry. The variables that showed statistically significant correlation with poor outcome were: age, site (head and neck and lower limbs) and presence of inflammatory infiltrate (regardless of type).

Conclusions: MIS develop recurrence or metastasis in about 2.02% of cases, usually in patients 12.7 years older than the group with good outcome. The presence of inflammatory infiltrate, shows a statistically significant correlation with the presence of neoplastic cells in the dermis, identified only by immunohistochemical study, and also with the poor outcome of patients initially diagnosed with MIS. The presence of melanocytic cells in the dermis, hidden by the inflammatory infiltrate and identified only with the immunohistochemical technique does not affect DFS, in a statistically significant way. Further studies are needed.

Planetary relations of melanoma diagnoses and their origin.

Konstantin Zioutas, professor (emer.)

Melanoma diagnoses show striking periodicities, which coincide with fixed orbital periods of solar system bodies. The orbital period of Mercury (88 days) was the first to observe. An independent analysis of the same dataset from USA confirmed this finding while recovering the same periodicity also in major cancer types, pointing at a ubiquitous cancer oscillatory behaviour. Interestingly, this melanoma component is not related to solar activity. Surprisingly, the analysis of another dataset from Australia shows that (daily) diagnosed melanoma cases (~12%) are even exo-solar in origin. As with a number of physics observables from Sun's and Earth's atmosphere, which are unexpected within known physics, planetary lensing of streaming particles from the dark sector (aka "dark matter") fits in as the only viable explanation. Because the alternative remote gravitational planetary effects are extremely feeble to cause any noticeable impact.

Further reading: <https://arxiv.org/abs/1812.10332> ; <https://arxiv.org/abs/1809.02555> ; <http://dx.doi.org/10.1142/S1793048020500083> ; <https://arxiv.org/abs/2108.11647>

Tumor cell-organized fibronectin maintenance of a dormant breast cancer population

Shelly R. Peyton

Malignant cells can disseminate and undergo long periods of dormancy before eventual metastatic outgrowth. The extracellular matrix (ECM) component of the tumor microenvironment is known to play a role in invasion at the primary site, but its role in mediating entrance into dormancy and the transition to outgrowth is contested. Although entrance and exit from dormancy are dynamic processes, *in vivo* preclinical models of dormancy are discontinuous. To address this critical need, we created a tunable biomaterial model of the tissue microenvironment, which can induce dormancy, survival, and reactivation in a continuous manner. We created a biomaterial platform to parse the role of the cancer cell- and stromal cell- assembled ECMs in regulating both dormancy and outgrowth in controlled microenvironments. From a large screen of many breast cancer cells against designer ECM matrices, we found that collagen I was required for entrance into a dormant-like phenotype during serum deprivation, while long-term survival required the creation of a rich, organized insoluble fibronectin matrix generated via cell tension through ROCK. Survival appears to critically depend on fibronectin adhesion via $\alpha_5\beta_1$ integrin and ERK activation. The fibronectin matrix can be created by the latent cancer cells themselves, or by local stromal cells (fibroblasts and mesenchymal stem cells) recruited via TGF β . Most striking for potential therapeutic intervention, cancer cell outgrowth after long-term dormant culture requires MMP-2-mediated fibronectin disassembly. This approach provides a new method to study dormant cell reactivation, as well as several potential targets to inhibit the metastatic outgrowth of cancer cells at distant sites.

Improving surgical outcomes for specialty site melanomas: A paradigm for change in medicine**Christopher Miller**

Specialty site melanomas on the head and neck, hands and feet, and genitalia have a 10% risk for positive margins or local recurrence after conventional excision. Mohs micrographic surgery with frozen section melanocytic immunostains (MMS-I) detects and removes subclinical melanoma with comprehensive microscopic margin assessment prior to reconstruction, leading to improved local cure rates. Despite resistance, use of MMS-I for melanoma has proliferated in the United States over the last two decades, and consensus guidelines now include indications for MMS-I for melanoma. This lecture reviews how melanoma surgery is evolving to improve patient outcomes, and it tells a story of surgical innovation relevant to anyone interested in changing how we practice medicine.

Quantification of Bevacizumab Activity Following Treatment of Patients with Glioblastoma**Michael G. Tovey, Christophe Lallemand, Rosa Ferrando-Miguel, Michael Auer, Sarah Iglseeder, Theresa Czech, Anouk Gaber-Wagener, Franziska Di Pauli, Florian Deisenhamer**

The anti-vascular endothelial growth factor-A (VEGFA) monoclonal antibody bevacizumab (Avastin[®]) is used extensively to treat recurrent disease in patients with glioblastoma who have failed first line therapy. Although, bevacizumab treatment results in a high initial response rate the effect is transient and most patient's tumors eventually progress. The mechanisms of bevacizumab treatment failure are poorly understood and an accurate assessment of the treatment response in individual patients is key to a better understanding of the most effective means of optimizing bevacizumab treatment. Highly sensitive reporter-gene assays have been developed that allow both circulating and membrane-

bound VEGF activity to be quantified rapidly and specifically as well as the neutralizing activity of bevacizumab and the ability of bevacizumab to activate antibody dependent cellular cytotoxicity (ADCC). The use of these assays has shown that in longitudinal samples from patients that respond to bevacizumab therapy from a small cohort of patients with glioblastoma, that there is a reasonably good correlation between bevacizumab drug levels determined by ELISA and bevacizumab activity, determined using either the VEGF-responsive reporter gene or ADCC assays. Drug levels were consistently higher than bevacizumab activity determined using the reporter gene assay in serial samples from secondary non-responders and ADCC activity was markedly lower in all samples from these patients suggesting that bevacizumab activity may be partially neutralized by anti-drug neutralizing antibodies. (NAb). These results suggest that ADCC activity may be correlated with the ability of some patients to respond to treatment with bevacizumab while the use of the VEGF-responsive reporter-gene assay may allow the appearance of anti-bevacizumab NAb to be used as a surrogate maker of treatment failure prior to the clinical signs of disease progression.

The Road Not Taken in Cancer: Host-Driven Oncology

Sookyung Lee

Cancer has made many advances in diagnosis and treatment in the last century, but it is still one of the leading causes of death and remains a conundrum for humankind.

I define the nature of cancer with three essential properties: clonal evolution, metastasis, and drug resistance. Cancer shows intertumor and intratumor heterogeneity by the continuous clonal evolution, free movement inside an individual through invasion and metastasis, and uncontrollable resistance acquired from previously experienced drugs. Cancer can be cured by overcoming these fundamental properties of cancer.

The nature of cancer can be fully understood by recognizing changes in the tumor and the host, based on the stream of time and the expansion of space within the human body. Thus, it is necessary to treat cancer from a host-centered viewpoint.

Cancer research has been zooming in on tissues, genes, and even a single cancer cell. However, cancer does not exist as a single cell in the human body but as a mass of multiple tumor cells. It does not exist in isolation but interacts with surrounding tissues and various organs in the body. The tumor grows and proliferates interacting with various life phenomena in the human body. Therefore, studies with fixed subjects in a controlled experimental environment have limitations in identifying the reality of cancer in the human body. For instance, antiangiogenic agents based on the angiogenesis mechanism rather increase tumor invasion and metastasis as a hypoxic tumor response. Targeted therapeutics prolonged progression-free survival but showed limitations in overall survival.

I propose a host-centered top-down approach to cancer with a macro perspective. The methodology of research and treatment of cancer with a host-centered perspective is not easy and is even vague. However, it will be necessary to go on the road not taken because humanity has yet defeated cancer. If we bring the existing tumor-centered bottom-up research together with the host-centered top-down research, we will find the key solution to cancer.

“Under construction”: Hospital based support for Return To Work in Cancer patients in Belgium:

Huget Désiron; To Simons; Kirsten Van Kelst; Theo Brunois; Thomas Otte; Stéphane Camut; Elke Van Hoof; Dominique Van de Velde; jeroen Mebis; Annemie Spooren; Lode Godderis

Background

Increasing scientific evidence emphasises the importance of early administrated support in cancer-survivors when aiming on return to work. Implementation of these insights into daily practice in oncological hospital units gains interest but remains challenging.

Objective

In this project, we investigate how research-efforts can be connected to care-practice, and how these efforts can lead to the development and integration of a RTW-guideline for hospital based care for cancer patients.

Methodology:

Of first, an intervention mapping protocol was used to develop an evidence based RTW intervention (2016). Secondly, a mimic RCT was set up to roll out this intervention in 2 Belgian hospitals, aiming to evaluate feasibility of the intervention (including a process evaluation) (2018).

Thirdly, results of the mimic RCT were used to initiate qualitative research to collect “practice based evidence” from Belgian oncology-healthcare professionals (using interviews and focusgroup-discussions) (2020).

Next, analysis of the previous input will found a “RTW-manual” to guide the daily efforts of onco-healthcare providers when integrating RTW-support in onco healthcare. A follow-up study will investigate effectivity and usability of that “RTW-manual”, aiming to contribute to the final goal of this research trajectory: an evidence- and practice-based RTW guideline. In the presentation, results of each study shall be discussed.

Conclusions

Implementing scientific evidence into daily care practice is far from evident, yet trials and case-based efforts by healthcare professionals provide very useful insights in how such implementation can be realised. More intense collaboration between intern and extern stakeholders would be beneficial for success in RTW in cancer patients. Coordination of such collaboration by a specialised (hospital based) casemanager would facilitate a tailored RTW-process and thereby support a nation-wide approach that could improve RTW for cancer patients.

Development of 3D cancer cell culture models for anti-tumor drug testing

Bojana Obradovic, Jasmina Stojkowska, Jelena Petrovic, Ivana Banicevic, Milena Milivojevic, Milena Stevanovic, Radmila Jankovic, Miodrag Dragoj, Milica Pesic

A need for reliable, long-term 3 dimensional (3D) cell culture systems has been recognized for a considerable length of time due to many weaknesses of traditional 2 dimensional (2D) cell culture systems that fail to correctly imitate the tumor environment, often leading to unsuccessful and contradictory results of drug testing. Tumor engineering as one of the approaches addressing this problem, is based on the use of biomaterials as artificial extracellular matrices (ECMs) and biomimetic bioreactors providing biochemical and physical signals to the cells, thus mimicking physiological conditions in tumors. In the

present study we have developed biomimetic systems based on the use of a perfusion bioreactor and two types of cell carriers. Ca-alginate hydrogel in the form of microfibers (< 1 mm in diameter) imitating soft tumor ECM was selected as a suitable carrier for rat glioma C6, human U87 glioblastoma and human NCI-H460 lung cancer cell lines. On the other hand, macroporous composites based on Ca-alginate hydrogel and particulate mineral phase (β -tricalcium phosphate and hydroxyapatite) imitating the bone tissue ECM were developed for immobilization and culture of murine K7M2-wt osteosarcoma cells. Both carrier types with immobilized cells were cultured in perfusion bioreactors ("3D Perfuse", Innovation Center of the Faculty of Technology and Metallurgy, Belgrade, Serbia) under continuous medium flow providing efficient mass transfer and suitable shear rates characteristic for bone tissue. The flowrates were optimized for each culture system yielding the superficial medium velocities in the range 20 – 100 $\mu\text{m/s}$, which provided higher cell viability and proliferation as compared to control static cultures. In addition, in selected culture systems (*i.e.* human U87 glioblastoma, human NCI-H460 lung cancer cell lines and murine K7M2-wt osteosarcoma cells) application of anti-tumor drugs such as temozolomide, cisplatin and doxorubicin was shown to increase drug resistance-related gene expression in 3D cultures as compared to control 2D cultures. Thus, here we demonstrate that the use of biomaterials and biomimetic bioreactors shows high potentials for establishment of physiologically relevant 3D cancer cell culture systems capturing some of the key features of the *in vivo* tumor microenvironment relevant for anti-tumor drug testing.

OPHTHALMOLOGY

Phase I Trial of Anti-Vascular Endothelial Growth Factor/Anti-angiopoietin 2 Bispecific Antibody RG7716 for Neovascular Age-Related Macular Degeneration

Katrijn Bogman

Faricimab is a novel bispecific antibody that simultaneously binds vascular endothelial growth factor (VEGF) and another key angiogenic factor, angiopoietin 2. The phase I study of intravitreal faricimab was conducted to evaluate single-dose and multiple-dose safety in patients with neovascular age-related macular degeneration.

Single intravitreal doses of 0.5 mg, 1.5 mg, 3 mg, and 6 mg faricimab were administered in stepwise dose-escalation groups, each with 3 patients. In the multiple-dose phase, 6 patients were enrolled and received 3 treatments each of 3 mg and 6 mg faricimab

There were no dose-limiting toxicities in either the single-dose or multiple-dose group. Treatment-emergent ocular adverse events were mild. In the combined single-dose groups and in the 6-mg multiple-dose group, BCVA increased from baseline to 28 days after the last dose administration by a median of 7 letters (range, 0-18 letters) and 7.5 letters (range, 3-18 letters), respectively. The corresponding median reduction from baseline in CST were 42 μm (range, -101 to 10 μm) and -117 μm (range, -252 to -7 μm), respectively. After multiple 3-mg faricimab doses, no changes were observed in either BCVA (median, -0.5 letters; range, -9 to 8 letters) or CST (median, -9 μm ; range, -188 to -1 μm).

The Phase I study has shown that faricimab was well tolerated and exhibited an overall favorable safety profile, with evidence of improvements in BCVA and anatomic parameters. The data supported further evaluation in phase II and III trials. In January 2022, the U.S. Food and Drug Administration (FDA) has approved faricimab for the treatment of neovascular age-related macular degeneration and diabetic macular edema.

**Pharmacological modulation; stress response; Nrf2; retinal diseases - ARE they effective?
Activation of Nrf2-mediated protective pathways and its relevance for stress response in
retinal pigment epithelial cells**

Marialaura Amadio

The retinal pigment epithelium (RPE) maintains the good health of photoreceptors and the whole retina through many essential functions. RPE alterations contribute to visual impairment/loss in various progressive and irreversible ocular pathologies, including age-related macular degeneration (AMD). RPE is physiologically exposed to high levels of oxidative stress during its lifespan and preserves own homeostasis by efficient antioxidant and detoxifying systems. The pathway of Nrf2 (nuclear factor E2-related factor 2) is an essential primary system used by RPE to neutralize oxidative stress, maintain cellular homeostasis, and promote survival. Nrf2 transcription factor boosts detoxifying and antioxidant genes following either oxidative stimulation or exposure to pharmacological Nrf2 activators. Nrf2-signalling has been found to play a direct role also in anti-inflammatory response, maintenance of proteostasis, mitochondria and metabolism. Literature evidence suggests that, in aged and especially in AMD RPE, there is an imbalance between the increased pro-oxidant stress and impaired endogenous detoxifying systems, finally reverberating on RPE functions and survival – and, consequently, on the retina itself.

This in vitro study investigated the effects of some AMD-related noxae on Nrf2-pathway in a human RPE cell line (ARPE-19), by evaluating Nrf2 activation and changes in the expression of selected downstream Nrf2-target genes coding important factors for RPE homeostasis. To confirm the relevance of Nrf2 as an endogenous protective factor, both wild-type and Nrf2-silenced cells were used.

Literature reported that Nrf2-pathway activation is protective against oxidative stress; with the aim to find new pharmacologically active compounds potentially useful for AMD, some nature-inspired hybrids (NIHs) were tested as Nrf2 activators for their capability to promote RPE protection against different noxae. Pharmacological activity of NIHs was investigated in ARPE-19 cells. In particular, NIHs were tested for Nrf2 activation (gene expression, nuclear translocation, up-regulation of Nrf2-target genes), cell tolerability, ROS-scavenging, anti-inflammatory, and cytoprotective effects from noxae.

This study confirmed that Nrf2-pathway activation is a physiological, essential protective response of RPE to various stress, and that an Nrf2 deficit predisposes these cells to a higher vulnerability to AMD-related detrimental factors. The beneficial effects exerted by NIHs confirm that Nrf2-pathway is a valuable pharmacological target in RPE and contexts characterized by high oxidative stress, and its activation represents an efficient defensive strategy to prevent stress-induced damages.

Thymosin Beta-4: A Novel Adjunct Treatment for Bacterial Keratitis

Gabriel Sosne, Elizabeth Berger, Yuxin Wang, Abdul Shukkur Ebrahim

Microbial keratitis is a rapidly progressing, visually debilitating infection of the cornea that can lead to corneal scarring, endophthalmitis, and perforation. Corneal opacification or scarring, a complication of keratitis, is among the leading causes of legal blindness worldwide, second to cataracts. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the two bacteria most commonly associated with this type of infection. Risk factors include patients who are immunocompromised, those who have undergone refractive corneal surgery, and those with prior penetrating keratoplasty, as well as extended wear contact

lens users. Current treatment of microbial keratitis primarily addresses the pathogen using antibiotics. Bacterial clearance is of utmost importance yet does not guarantee good visual outcome. Clinicians are often left to rely upon the eye's innate ability to heal itself, as there are limited options beyond antibiotics and corticosteroids for treating patients with corneal infection. Beyond antibiotics, agents in use, such as lubricating ointments, artificial tears, and anti-inflammatory drops, do not fully accommodate clinical needs and have many potential harmful complications. To this end, treatments are needed that both regulate the inflammatory response and promote corneal wound healing to resolve visual disturbances and improve quality of life. Thymosin beta 4 (T β 4) is a small, naturally occurring 43-amino-acid protein that promotes wound healing and reduces corneal inflammation and is currently in Phase 3 human clinical trials for dry eye disease. Our previous work has shown that topical T β 4 as an adjunct to ciprofloxacin treatment reduces inflammatory mediators and inflammatory cell infiltrates (neutrophils/PMN and macrophages/M Φ) while enhancing bacterial killing and wound healing pathway activation in an experimental model of *P. aeruginosa*-induced keratitis. Adjunctive T β 4 treatment holds novel therapeutic potential to regulate and, optimally, resolve disease pathogenesis in the cornea and perhaps other infectious and immune-based inflammatory disease. We plan to establish the importance of T β 4 as a therapeutic agent in conjunction with antibiotics with high impact for immediate clinical development.

Sarcoid Uveitis and Systemic Manifestations

Priya Darshni Samalia

Sarcoidosis is a multisystem inflammatory condition characterised by non-caseating granulomas and is a leading cause of inflammatory eye disease. The disease has a bimodal age distribution, at age 20-30 years and 50-60 years. Many organ systems may be affected by sarcoidosis, most frequently the lymphatic system, lungs, skin and eyes.

Ocular involvement occurs in up to 80% of individuals and ocular manifestations can be the presenting feature prior to an underlying systemic diagnosis. Sarcoidosis can affect all parts of the eye. The most common ocular manifestations are uveitis, dry eye and conjunctival nodules. Ocular involvement is the presenting feature in approximately 20-30% of subjects, prior to a systemic diagnosis.

Uveitis is a common and important vision-threatening manifestation, occurring in 30-70% of individuals with sarcoidosis. Although sarcoidosis has been shown to be more likely in men, females seem more prone to uveitis. Sarcoid uveitis is usually bilateral and tends to follow a chronic course. Uveitis develops early in sarcoidosis, usually developing before or within a year of systemic diagnosis. Chorioretinal lesions have been shown to be a marker of microcirculatory damage in sarcoidosis. Subjects with choroidal involvement are at increased risk of cardiac involvement.

Ophthalmologist should ensure that all subjects with ocular sarcoid have a systemic assessment, particularly for pulmonary and cardiac involvement.

Angle Surgery in Children

Allen Beck

A comprehensive review of angle surgery techniques for childhood glaucoma with a focus on primary congenital glaucoma. Circumferential angle surgery approaches will be emphasized by focusing on recent publications on this topic. Technological advances to facilitate circumferential surgery will be discussed with an emphasis on improved glaucoma control and visual outcomes.

OSTEOARTHRITIS**Pre-clinical models aimed at assessing the role of muscles in knee joint osteoarthritis****Walter Herzog**

Recent advances in technology have increased our understanding of the mechanisms causing osteoarthritis onset and progression, shifting from a paradigm based on a “wear and tear”, to mechanisms involving biomechanical, metabolic, and inflammatory components. When reviewing the risk factors associated with knee joint osteoarthritis, one might conclude that muscle function is a common denominator uniting them. Besides producing force, joint loading and movement, muscles are primary organs for the regulation of body metabolism, and they are thought to perform a central role in preventing joint damage resulting from systemic factors. In my presentation, I will discuss the potential role of muscles in three pre-clinical models of knee joint osteoarthritis: i) post-traumatic osteoarthritis, ii) muscle weakness/imbalance-induced osteoarthritis, and iii) obesity/metabolic disease-associated osteoarthritis. Results obtained from these pre-clinical models provide evidence that muscle weakness and imbalance is a risk factor for the onset and progression of knee osteoarthritis. Similarly, diet induced obesity and associated metabolic disease can cause muscle atrophy, fat infiltration, fibrosis, and local inflammation in the quadriceps muscles that precedes knee joint degeneration. This metabolic knee joint osteoarthritis can be prevented using an oligofructose-based fibre diet supplementation, and/or aerobic exercise. To date, the mechanistic interplay between muscle and joint health in post-traumatic, muscle weakness and obesity models of knee joint osteoarthritis remains elusive but the strong associations between muscle and joint degeneration suggests an intricate relationship that may contain crucial information for rehabilitation programs for people at risk of knee joint osteoarthritis.

Cardiovascular Risk in Osteoarthritis: Meta-Analysis and Patients Management**Sylvain Mathieu**

Introduction: Higher cardiovascular risk found in rheumatoid arthritis or psoriatic arthritis is largely due to systemic inflammation. In osteoarthritis (OA), occurrence of systemic inflammation has already been sometimes reported, but the possible association between OA and increased cardiovascular risk remains unclear. In this meta-analysis, we aimed to assess the incidences of myocardial infarction (MI) and stroke, and the cardiovascular risk factors in OA patients.

Methods: We searched PubMed, EMBase, and the Cochrane Library to find references of interest up to June 2018. MI and stroke incidence were calculated using meta-proportion analysis. Differences in cardiovascular risk factors between OA patients and controls were expressed as standardized mean differences using the inverse of variance method.

Results: The reviewed studies reported 227 MIs in 3550 OA patients (incidence, 7.5%; 95% CI:3.0–13.8%) and 616 MIs among 12,444 control subjects (incidence, 6.0%; 95% CI:2.8–10.3%). Meta-analysis of the three longitudinal studies revealed a significantly increased MI risk among OA patients (RR = 1.22; 95% CI: 1.02–1.45). We also found a significantly increased stroke risk in OA patients (RR = 1.43; 95% CI: 1.38–1.48). Concerning cardiovascular risk factors, OA patients exhibited a pro-atherogenic lipid and glycemic profile including high levels of fasting glucose, total cholesterol, and LDL cholesterol and a high body mass index. Concerning atherosclerosis markers, OA patients exhibited a higher risk of metabolic syndrome, and increased pulse wave velocity.

Discussion: Our meta-analysis results revealed higher cardiovascular risk in OA patients. More recent articles confirmed this association between osteoarthritis and cardiovascular risk. The reasons for this higher risk seems multiple. First, OA patients have a pro-atherogenic lipid profile with high levels of total and LDL cholesterol. Second, OA patients had metabolic syndrome with high levels of fasting glucose and overweight. Third, NSAID treatments, often prescribed in OA patients to decrease pain intensity, are known to increase cardiovascular risk in case of long use, especially in older patients.

Conclusion: To decrease this higher cardiovascular risk in OA patients, exercise should be encouraged to loose weight and increase HDL cholesterol. A lipid profile assessment should be prescribed every year to search dyslipidemia and to advise mediterranean dietary or use statins in case of higher total or LDL cholesterol. Smoking should be avoided or decreased and other cardiovascular risk such as hypertension should be treated. Finally, NSAIDs treatment should be used with caution, as short a time as possible and with the lowest efficient dose.

Predicting Knee Replacement in Participants Eligible for Disease-Modifying Osteoarthritis Drug Treatment with Structural Endpoints

C K Kwoh, H Guehring, A Aydemir, M J Hannon, F Eckstein, M C Hochberg

Objective: Evaluate associations between 2-year change in radiographic or quantitative magnetic resonance imaging (qMRI) structural measures, and knee replacement (KR), within a subsequent 7-year follow-up period.

Method: Participants from the Osteoarthritis Initiative were selected based on potential eligibility criteria for a disease-modifying osteoarthritis (OA) drug trial: Kellgren-Lawrence grade 2 or 3; medial minimum joint space width (mJSW) ≥ 2.5 mm; knee pain at worst 4-9 in the past 30 days on an 11-point scale, or 0-3 if medication was taken for joint pain; and availability of structural measures over 2 years. Mean 2-year change in structural measures was estimated and compared with two-sample independent t-tests for KR and no KR. Area under the receiver operating characteristic curve (AUC) was estimated using 2-year change in structural measures for prediction of future KR outcomes.

Results: Among 627 participants, 107 knees underwent KR during a median follow-up of 6.7 years after the 2-year imaging period. Knees that received KR during follow-up had a greater mean loss of cartilage thickness in the total femorotibial joint and medial femorotibial compartment on qMRI, as well as decline in medial fixed joint space width on radiographs, compared with knees that did not receive KR. These imaging measures had similar, although modest discrimination for future KR (AUC 0.62, 0.60, and 0.61, respectively).

Conclusions: 2-year changes in qMRI femorotibial cartilage thickness and radiographic JSW measures had similar ability to discriminate future KR in participants with knee OA, suggesting that these measures are comparable biomarkers/surrogate endpoints of structural progression.

The degradation prediction of structural Mg-based implant for orthopaedic applications

Luen Chow Chan

Magnesium (Mg) alloys with a porous structure have been found to serve as highpotential orthopaedic biomaterials due to its super lightweight, closer elastic moduli to that of natural bones, which would minimize stress shielding and implant loosening. Therefore, a novel design of Mg implant having a coral-like open-cell porous interior and an outer solid casing was achieved. Different porosities of porous interiors, combined with different wall thicknesses of outer casing, were designed. By implementing a modified continuum damage mechanics (CDM)-based biodegradation model into finite element (FE) simulations, the mechanical properties and degradation rates of the implant were predicted. A suitable porous implant structure was then determined and fabricated with comprehensively considering the tissue regeneration and implantation strength. An in-vivo rabbit model was employed to evaluate the degradation behaviours of the implant at different time points. In addition, the CDM-based model was applied for the degradation prediction of the solid-type Mg implant, microstructural configurations of Mg-Zn-Mn (ZM) alloys that depicted from SEM were employed as the geometrical FE models, in which the Mg matrix, grain boundary and second phase were included. Predicted results revealed that the grain boundary had poor corrosion resistance while the second phase facilitated delaying corrosion expansion. Furthermore, in-vitro tests were carried out and consistent results were obtained, i.e., the grain refinement made the entire corrosion process more uniform and severe corrosion in local areas was avoided, and the intergranular second phase was beneficial to delay the corrosion process. This study suggested that designing implant structures from a biomimetic structure perspective is an effective way to meet the strength requirements and meanwhile benefit the ingrowth of bone tissue and expedite the healing process. Moreover, the application of FE simulation, rather than experimental testing, is believed to be an efficient method for the degradation evaluation of Mg-based implants.

Role of Pro-Inflammatory Cytokines in Knee Osteoarthritis and Related Current Treatment Modalities

Erdem Aktas

Osteoarthritis is still the most common joint disease and debilitating condition especially in the elderly population. Although it is known to be a degenerative disease, current research has pointed out an enflamatory pathway in its etiology and progression. Apart from the cartilage, subchondral bone, synovial tissue, macrophages, chondrocytes, fibroblasts and proinflammatory cytokines such as; TNF-a, IL-1b, IFN- gama, matriksmetalloproteinase 1-3-9-13 play an important role in knee osteoarthritis pathogenesis. Current research focus directly on the impact of these molecules on knee functions and new trend is to develop treatment modalities to block the degrading effect of these pro-inflammatory cytokines during the early phase of the disease.

Cartilage Biomechanics: A Key Factor for Osteoarthritis Regenerative Medicine**Daniel Martínez**

Osteoarthritis (OA) is a joint disorder that is highly extended in the global population. Several pieces of research and therapeutic strategies have been probed on OA but without satisfactory long-term results in joint replacement. Recent evidence shows how cartilage biomechanics plays a crucial role in tissue development. We will discuss how physics alters cartilage and its extracellular matrix (ECM); and its role in OA development. The ECM of the articular cartilage (AC) is widely involved in cartilage turnover processes being crucial in regeneration and joint diseases. We also expose the importance of physicochemical pathways following the external forces in AC. Moreover, new techniques probed in cartilage tissue engineering for biomechanical stimulation are reviewed. The final objective of these novel approaches is to create a cellular implant that maintains all the biochemical and biomechanical properties of the original tissue for long-term replacements in patients with OA.

The most pressing need in cartilage tissue engineering (CTE) is the creation of a biomaterial capable of tailoring the complex extracellular matrix of the tissue. Despite the standardized use of polycaprolactone (PCL) for osteochondral scaffolds, the pronounced stiffness mismatch between the PCL scaffold and the tissue it replaces remarks the biomechanical incompatibility as the main limitation. To overcome it, the present work was focused on the design and analysis of several geometries and pore sizes and how they affect cell adhesion and proliferation of infrapatellar fat pad derived mesenchymal stem cells (IPFP-MSCs) loaded in biofabricated 3D thermoplastic scaffolds. A novel biomaterial for CTE, the 1,4-butanediol thermoplastic polyurethane (b-TPUe) together with PCL were studied to compare their mechanical properties.

Since b-TPUe is a biomaterial with mechanical properties like cartilage, but it does not provide the desired environment for cell adhesion, then, scaffolds were functionalized with two methods, one based on collagen type I and the other in 1-pyrene butyric acid (PBA) as principal components. Alamar Blue and confocal assays displayed that PBA functionalized scaffolds support higher cell adhesion and proliferation for the first 21 days. Further, both functionalized methods induced ECM synthesis, and the presence of chondrogenic markers (Sox9, Col2a, and Acan). These results indicate that the two methods of functionalization in the highly hydrophobic b-TPUe enhanced the cell-biomaterial interactions and the improvement in the chondro-inductive properties, which has a great potential for application in cartilage tissue engineering.

The evaluation of results of periprosthetic fracture treatment in patients with hip osteoarthritis caused by residual dysplasia of the hip joint with dislocation of type III and IV according to the Crowe's classification.

Andrzej Sionek, Adam Czwojdzinski, Jarosław Czubak

Introduction/objectives: One of the accepted methods of operative treatment of young adults with osteoarthritis (OA) coming as the sequelae of developmental dysplasia of the hip with dislocation (DDH) is total hip arthroplasty (THA). Femoral canal of patients with DDH is narrow and periprosthetic fractures (PF) are frequent in this group.

Aims: The aim of this study was to determine the frequency of periprosthetic fractures occurring and to assess the results of treatment of this complication.

Methods: In years 2009-2015 we operated 91 hip joints of 81 patients with OA as a sequelae of DDH with dislocation of type III and IV according to Crowe's classification. Mean age was 32 years old (ranging from 15 to 64). Mean limb length discrepancy was 3,5 cm (1,5-6 cm). For the purpose of the study two groups of patients operated from posterolateral approach were established. Group "A" consisted of 10 hips of 10 patients treated with the use of Accolade stems. Group "B" consisted of 81 hips of 71 patients, treated using Wagner's stems. In group "A" the follow-up period lasted from 3 to 7 years, and in group "B" from 1 to 7 years. Frequency of periprosthetic fractures was noted. The results were assessed clinically according to HHS as well as radiologically. PF was observed in 4 out of 10 hips from group "A" and in 6 from 81 hips from group "B". The difference was statistically significant (student t-test, $p < 0,001$). In group „A“ all six PF occurred intraoperatively during implantation of the final stem and were of type B1 from Vancouver classification.

In group „B“ PF occurred in 2 patients during implantation of trial implant and in 3 subjects during implantation of final stem.

One PF was noted postoperatively in 68 – year old obese female with BMI over 35 and occurred during verticalization in the sixth day after operation. All patients with PF were treated using metal cables or cerclage. In none of the patients from both groups fracture of acetabulum was observed.

Results: Decreased incidence of periprosthetic fractures in patients with OA as a sequelae of DDH was noted in all patients treated using cone stems. In clinical and radiological assessment improvement was obtained in all patients. In clinical assessment carried 3 months after the surgical treatment, improvement in HHS classification was obtained in all examined patients. Mean number of points before treatment was 30 (ranging from 2 to 40) and increased after operative treatment to 70 points (60 - 80). The biggest improvement was noted in the scale of pain complaints, increase in range of motion and decrease in limb length discrepancy, mean 0.5 cm (0 - 1.5 cm). In 72 patients the painful conditions resolved. Neurological complications occurred in 9 patients. Transient paraesthesia was observed in 6 patients, transient paresis of the sciatic nerve and paraesthesia in 2 patients. Sciatic nerve palsy was noted in 1 patient with preoperative limb shortening by 5 cm. In the examined groups no acetabular fracture, delayed healing, infections, nor dislocation of the endoprosthesis occurred.

Discussion: Only few studies present the incidence and results of PF treatment in patients with OA caused by residual DDH with high dislocated hip. Perka et al published unsatisfactory results of DDH treatment with the use of small sized trapezoidal stems and femur shortening osteotomy. In 7 from 17 patients of Crowe's group IV periprosthetic fracture occurred.

Schub et al presented good results of DDH arthrosis treatment with the use of Wagner cone stems in 69 patients. The authors observed PF in 2 patients (3%). They did not quote however, how many of the operated hips were classified to groups III and IV according to Crowe.

Conclusions: Patients with OA as a sequelae of DDH with hip-joint dislocation of type III and IV according to Crowe's classification should be treated using cone stems.

Keywords: Periprosthetic Fracture, Residual Hip Dysplasia With Dislocation, Total Hip Replacement, Wagner Cone Stem.

Parkinson's disease and symptomatic osteoarthritis are independent risk factors of falls in elderly

Anneli Teder-Braschinsky

Objectives: Deteriorating functionality and loss of mobility, resulting from Parkinson's disease, may be exacerbated by osteoarthritis, which is the most common form of joint disease and causes pain and functional impairment. We assessed the association between symptomatic hip or knee osteoarthritis, falls and ability to walk among patients with Parkinson's disease compared to a control group.

Methods: 136 patients with Parkinson's disease from Tartu and Põlva districts of Southern Estonia and 142 controls were enrolled in retrospective case-control study (average age 75 years old). Information on falls and related fractures during the previous year was collected.

Results: Patients with Parkinson's disease were at increased risk of falling compared to the control group and higher risk of getting fractures. Symptomatic knee or hip osteoarthritis was a significant independent predictor of falls in both groups: patients with Parkinson's disease and controls. Risk factors for falls were also female gender and the inability to walk 500m.

Conclusions: Symptomatic hip and knee osteoarthritis increase the incidence of falls and related fractures among elderly populations with and without Parkinson's disease. The inability to walk 500m could be used as a simple predictive factor for the increased likelihood of falls among elderly populations.

Key-words: Parkinson's disease, risk factors, falls, osteoarthritis, elderly.

Predicting knee replacement in participants eligible for disease-modifying osteoarthritis drug treatment with structural endpoints

C. Kent Kwoh

Objective: Evaluate associations between 2-year change in radiographic or quantitative magnetic resonance imaging (qMRI) structural measures, and knee replacement (KR), within a subsequent 7-year follow-up period.

Method: Participants from the Osteoarthritis Initiative were selected based on potential eligibility criteria for a disease-modifying osteoarthritis (OA) drug trial: Kellgren-Lawrence grade 2 or 3; medial minimum joint space width (mJSW) ≥ 2.5 mm; knee pain at worst 4-9 in the past 30 days on an 11-point scale, or 0-3 if medication was taken for joint pain; and availability of structural measures over 2 years. Mean 2-year change in structural measures was estimated and compared with two-sample independent t-tests for KR and no KR. Area under the receiver operating characteristic curve (AUC) was estimated using 2-year change in structural measures for prediction of future KR outcomes.

Results: Among 627 participants, 107 knees underwent KR during a median follow-up of 6.7 years after the 2-year imaging period. Knees that received KR during follow-up had a greater mean loss of cartilage thickness in the total femorotibial joint and medial femorotibial compartment on qMRI, as well as decline in medial fixed joint space width on radiographs, compared with knees that did not receive KR. These imaging measures had similar, although modest discrimination for future KR (AUC 0.62, 0.60, and 0.61, respectively).

Conclusions: 2-year changes in qMRI femorotibial cartilage thickness and radiographic JSW measures had similar ability to discriminate future KR in participants with knee OA, suggesting that these measures are comparable biomarkers/surrogate endpoints of structural progression.

Candidates for Intra-Articular Administration Therapeutics and Therapies of Osteoarthritis

Masato Sato

Osteoarthritis (OA) is a disease mainly characterized by cartilage degeneration, pathological changes in entire joint, such as joint capsule thickening, osteophyte formation, subchondral sclerosis, and synovitis. A prolonged low-grade inflammation is thought to play a pivotal role in OA initiation and progression. Activation of innate immunity by the decomposition products of the joint matrix generated by trauma or mechanical overload causes synovitis. Synovitis induces production of proinflammatory mediators from synovial cells, immune cells, chondrocytes, or cells in subchondral bone. Risk factors for OA, such as aging, injury history, obesity, and some genetic backgrounds are thought to trigger or prolong inflammation. Since knee OA is not a life-threatening disease, minimally invasive treatment at an outpatient level is preferred; intra-articular (IA) injections of corticosteroids and Hyaluronan are commonly employed for knee OA. Since OA progresses over a long period of time, early intervention is important so that symptoms can be controlled throughout life. The development of a disease-modifying osteoarthritis drug (DMOAD) that can be administered by IA injection, which is attracting attention as a point-of-care therapeutic, is desired. However, no DMOADs have been developed. Novel treatment options are being developed with the expectation of controlling inflammation and promoting cartilage regeneration in OA. Options include recombinant protein, gene therapy, platelet-rich plasma, and cell therapy. I will present the current status and challenges that the new biologics bring to treating OA, especially protein therapeutics, gene therapy, and nucleic-acid therapeutics.

Osteoarthritis-Like Changes in Bardet–Biedl Syndrome Mutant Ciliopathy Mice (Bbs1^{M390R/M390R}): Evidence for a Role of Primary Cilia in Cartilage Homeostasis and Regulation of Inflammation

David Kooyman

Osteoarthritis (OA) is linked to inflammation and co-morbidities associated with chronic inflammation. Emerging as a central figure in the chondrocyte stress response are primary cilia, which direct a wide range of cellular processes including modulation of inflammation as well as mechanical force. Primary cilia lengthen in response to IL-1 β (Wann, 2012), and in areas of the articular surface where erosion is occurring (McGlashan, 2008). Primary cilia have emerged as a target for treating OA since they are associated with some of the important physiological stressors confronting chondrocytes associated with cartilage degeneration. We have shown that defects associated with primary cilia cause OA-like changes in Bardet-Biedl Syndrome mice. We examined the role of dysfunctional primary cilia in OA in mice through the regulation of the previously identified degradative and pro-inflammatory molecular pathways common to OA. We observed an increase in the presence of pro-inflammatory markers as well as cartilage destructive proteases. We also observed morphological differences in cartilage thickness in Bbs1^{M390R/M390R} mice compared to wild type. We have further observed that primary cilia regulate Ca⁺⁺ channels in response

to mechanical stimulation. Primary cilia appear to be involved in the upregulation of biomarkers, including pro-inflammatory markers common to OA.

OSTEOSARCOMA OXIDATIVE STRESS

Effect of Hyperbaric oxygen therapy on oxidative stress and mitochondrial biogenesis

Schottlender N., Maya Gal, Ashery U.

Dementia is a major cause of disability and dependency among older population. Alzheimer's disease (AD) is the leading cause of dementia in late adult life. AD's pathophysiological markers include hyperphosphorylated TAU, accumulation of amyloid- β and elevated oxidative stress markers. Though, many pharmacological treatments are available for AD patients, none inhibit cognitive decline. Hyperbaric oxygen therapy (HBOT) has been shown to alleviate cognitive decline symptoms in AD case studies. Oxygen plays a critical role as a substrate for metabolism and as a signaling molecule regulating cellular activities, but under certain conditions, it is converted to a highly reactive molecule, known as reactive oxygen species (ROS), ready to oxidize other molecules in the cell and cause damage. As HBOT increases the solubility of oxygen in the blood and tissues, it can cause an increase in the levels of ROS. Therefore, it is important to understand what the effects of HBOT on oxidative stress are. Accordingly, we utilized HBOT on a mouse model of AD (5xFAD) to better understand the effects on oxidative stress and antioxidant scavenger enzymes. Our experimental protocol consists of 20 HBO sessions of 1h treatment at 2 Atmosphere absolute over a period of a 1 month that are given for both WT and 5xFAD mice. Following the treatment, we assess oxidative stress, antioxidant enzymes and mitochondrial activity. We found that HBOT treated mice showed a significant elevation in antioxidant (SOD and Catalase) activity in the cortex and we are currently examining other factors. This result supports the hypothesis that HBOT is accompanied by an increase of alleviating mechanisms and increases antioxidant enzymatic activity. Thus, in addition to the mitigating effects of HBOT on AD pathophysiology, it might also be beneficial in reducing the levels of oxidative stress.

Clinical strategy for managing oxidative stress in premature infants, taking into account the sex of the newborn

Jean-Claude Lavoie, Ph.D.

Oxidative stress is present in preterm newborns born <30 weeks of gestation. This stress is an important trigger of several pathological complications related to prematurity, including bronchopulmonary dysplasia (BPD) which affects \approx 50% of these infants. Supplemental oxygen and parenteral nutrition, inherently contaminated with peroxides, received by these neonates due to immaturity are associated with higher oxidative stress and the development of BPD. The gender of infants is another factor influencing the incidence of BPD, which is higher in baby boys. The association between pathological complications of prematurity and markers of oxidative stress has been widely studied in this population. From studies that have assessed the impact of sex, we learn that among the markers of oxidative stress measured in the extracellular compartments, only the plasma level of isoprostane differs according to sex, higher in males. From intracellular compartments, markers of oxidative stress such as carbonyl, peroxides and nitrotyrosine are higher in

placenta of males while components of glutathione (antioxidant) metabolism measured in erythrocytes, leucocytes and placenta, favor girls. Thus, a higher incidence of BPD is observed in newborn males, who have lower levels of glutathione as measured in leucocytes isolated from pulmonary aspirations. Animal studies show that addition of glutathione in parenteral nutrition prevents pulmonary oxidative stress and alveolar loss (a main feature of BPD). Therefore, it has been proposed to supplement parenteral nutrition with glutathione to prevent the development of BPD. Such a phase I clinical trial is planned. Knowing that the sex difference in glutathione metabolism has been demonstrated in intracellular compartments and not in plasma, it will be important to take into account that the same dose of glutathione could lead to a similar correction of glutathione level in plasma (extracellular compartment) while the clinical outcome could differ depending on the sex of the preterm infant.

PEDIATRICS

Necrotizing Enterocolitis: Lessons to be learnt by disease similarity between neonates and adult/Geriatric Population

Renu Sharma

Necrotizing enterocolitis (NEC) primarily affects premature infants. It is less common in term and late preterm infants. Compared with NEC in term and late preterm infants in whom hypoxia-ischemia is a common precursor, recent advances in our understanding of NEC at the molecular level suggest that an inflammatory response to microbes contribute significantly to the pathogenesis of NEC in very premature infants. The aberrant inflammatory response to the abnormal intestinal micro-ecology distorted by exposure to an array of antibiotics has been shown to play inciting role. In addition to the permeable and fragile mucosal barrier, immaturity of intestinal absorptive and secretory functions propagate milk stasis and facilitate microbial translocation into submucosa and circulation. Dysmotility contributes to distended bowel loops, ischemia of anti-mesenteric border, and impairment of luminal integrity. Human milk facilitates gut motility, and if it is maternal milk, it further adds to the favorable intestinal micro ecology because of immune factors in maternal milk

Adult NEC has been described among immune compromised adults e.g., organ transplant recipients on immune suppressive medications, and those who are on aggressive systemic chemotherapy. It has also been linked with *Clostridium perfringens* type C enterotoxin among population of Papua New Guinea and pacific region. Although there are few factors common between premature infants and immune compromised adults, the unique aspect of neonatal NEC is the immaturity of secretory and absorptive intestinal functions. In this respect, one has to address neonatal NEC not as a unique disease but as the unique response of a premature host to the unfavorable intestinal microbiome and pathogens. Adults expel pathogens and respond to substances harmful to intestinal mucosa presenting as gastroenteritis (vomiting, diarrhea, bloody stool, colitis); in contrast, premature infants with NEC in whom secretory response (e.g., watery diarrhea) is blunted, this response manifests as bloody mucoid stool, increased gastric residuals, ileus, abdominal distention pneumatosis, and hypoxic ischemic necrosis of gastrointestinal tract in the form of NEC.

Compared to adult NEC, preventing strategies against neonatal NEC should be focused on measures aimed at promoting maturity of GI functions, maternal milk feedings, immunomodulation, and modifying microbiome.

Conclusion: Despite similarities between Adult and Neonatal NEC, preventive measures in addressing immaturity of GI and immune functions may play pivotal role in preventing and managing NEC.

The Evolution of Precision Medicine in Paediatric Hepatology

Alastair Baker

The US National Research Council's Toward Precision Medicine adopted the definition of precision medicine from the President's Council of Advisors on Science and Technology in 2008 as: "The tailoring of medical treatment to the individual characteristics of each patient", in order "to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment." (1.) The power of precision medicine lies in its ability to guide health care decisions toward the most effective treatment for a given patient. This model of health care delivery relies heavily on data, analytics, and information. Meanwhile in the UK in 2015 the future of the NHS was strategised as personalised medicine service with genomics at its core, according to a new strategy adopted by NHS England. Tests are collected locally and processed nationally by the NHS Genomic Medicine Servicethrough a network of seven Genomic Laboratory Hubs (GLHs).

Historically, paediatric liver diseases were identified descriptively, based on clinical features. For example, jaundice and pale stools in infants has long been recognised to be associated with a fatal prognosis. In the 19thcentury this syndrome became recognised to be associated with a fatal prognosis if caused by congenital biliary destruction, which given the diagnostic title 'Biliary Atresia'. However, this diagnosis was by no means exclusive to these features, nor were these features specific to biliary atresia, which itself is probably more than one condition.

No treatment for the Biliary Atresia was found until the Kasai operation was described by Morio Kasai in 1951. Thereafter, gradually, other clinical conditions were also identified that are associated with neonatal cholestatic jaundice with different treatments and prognoses to Biliary Atresia. The practice of paediatric hepatology developed based on the premise of subdividing similar clinical phenomena into syndromic, biochemical, radiological, infectious, histological and latterly genetic subgroups with different possibilities for specific treatments. The fact that the presenting syndromes tended to be so similar meant that investigations were undertaken by protocol, divided into phases because of the volume of blood required and the cost with rarer conditions and more expensive tests tending to be prioritised later. Liver biopsy was a key guide to aetiology and prognosis as well as a confirmation of clinical results of other tests, but remains associated with risk of morbidity and mortality.

The introduction of genetic tests for cholestatic disorders, ciliopathies, hepatic inborn errors of metabolism and many other relevant conditions have led to a review of the phased processes of investigation of several of the syndromes presenting to paediatric

hepatologists. At our centre a historic 4 phase pathway started with screening for commoner conditions, for example in neonatal cholestasis biochemical based tests such as Alpha-1-antitrypsin phenotype was followed by liver biopsy in the second phase, rarer conditions suggested by the biopsy in the third phase and exclusion or confirmation of specific genetic conditions in the fourth phase. Currently we have progressed so that genetic tests in panels are included as the second phase, although sometimes included in the first phase. Liver biopsy is only undertaken when it will confirm or refute need for surgical intervention as in possible Biliary Atresia. Third phase tests are performed if genetic tests are negative, which may include Whole Exome Sequencing or Whole Genome sequencing or tests for assessment of the phenotype of an established genetic diagnosis. Delay due to genetic test turnover times requires counselling of parents.

Genetic tests have allowed the rapid evolution of the diagnostic taxonomy of various of the paediatric hepatological syndromes, including for example the 'Benign Recurrent Cholestasis - Progressive Familial Intrahepatic Cholestasis spectrum', where sub diagnoses with different prognoses for progressive liver disease and risk of hepatocellular carcinoma have been recognised. Inborn errors of bile acid synthesis can also be diagnosed much more accurately than by bile acid FAB-MS. Mitochondrial disorders and Perforin defects can also be diagnosed with much more confidence allowing treatments to take account of their prognosis.

Rapid development of genetic testing has transformed most of paediatric Hepatology. The transformation is not yet complete for the following reasons: The timescale for receiving results the UK is often less than ideal at 10-12 weeks, being particularly important in acute liver failure; a diagnosis is not always obtained even in cases with a high level of suspicion of a genetic diagnosis; and the centralisation of genetic testing for a UK National Service may mean that small specialities such as paediatric Hepatology may have difficulty in competing to develop new genotype-phenotype correlations and so recognising new conditions among existing patients and syndromes.

Differences in Anthropometric and Ultrasonographic Parameters between Adolescent Girls with Regular and Irregular Menstrual Cycles: A Case-Study Of 835 Cases

Ubavka Radivojevic

Adequate pubertal development of genital organs is important for attainment of reproductive function in girls. We explored the relation between age, time since menarche, anthropometric parameters and the volume and size of uterus and ovaries in a population of 835 postmenarcheal girls. Patients were grouped in two distinct groups. First group consisted of 428 patients with irregular menstrual cycles and the second group comprised of 407 patients with regular cycles. Results of our study showed that girls with regular and irregular cycles differed in height, weight, body mass index, percentage of body fat and ovarian volumes. The size of the ovaries decreases in group of girls with regular cycles ($r = 0.14$; $p < 0.005$), while it increases in girls with irregular cycles ($r = 0.15$; $p < 0.001$). Uterine volume in all patient increases gradually with increasing age reaching consistent values at 16 years ($r = 0.5$; $p < 0.001$). Age at menarche with age, time since menarche, height, weight, body mass index and percentage body fat correlated with uterine volume. Ovarian

volume correlated with weight, BMI and percentage of fat. Ovarian/uterine ratio inversely correlated with age, time since menarche, height and weight in all examined patients.

In conclusion, results of our study indicate that the uterus continues to grow in postmenarchal years, with increasing height and weight of girls, regardless of the regularity of cycles. Postmenarcheal girls with irregular cycles are found to have heavier figures and larger ovaries.

Intralymphatic Immunotherapy, the Future of Allergy Treatment

Amber Patterson, MD

Allergen immunotherapy has been a well-established treatment for allergies for over a century. Historically, allergen immunotherapy has been administered subcutaneously (SCIT) or sublingually (SLIT). Both methods require considerable levels of dedication to complete a full 3–5-year treatment course, many times resulting in non-adherence and early discontinued treatment.

Researchers discovered a new way to administer allergen that is significantly more efficient and can be completed with only 3 injections over 8 weeks. Dr. Patterson will explore the science and common sense behind intralymphatic immunotherapy, the future of allergy treatment.

Simulation to Improve Pediatric Patient Outcomes: University and Hospital Collaborative

Kimberly P. Stephens

A collaborative venture between a local university in southwestern Pennsylvania and a rural community hospital enhanced learning and improved pediatric patient outcomes. The partnership led to the development and implementation of an evidence-based pediatric peripheral intravenous (PIV) insertion program. Using simulation technology and debriefing techniques at the pediatric PIV insertion program, pediatric PIV insertion skills of the medical–surgical nursing staff improved, as evidenced by fewer pediatric PIV insertion attempts.

A 10-Year History of Using Of 5-Hydroxytryptophan for Severe Insomnia in A 15-Year-Old With Autism, Seizures, And Sleep Apnea; Cause For Concern?

Melody Hawkins

The body produces 5-Hydroxytryptophan (5-HTP) from the essential amino acid L-tryptophan (LT). 5-HTP is also produced commercially and sold as an over-the-counter food supplement. 5-HTP is extracted from the seeds of the African plant, Griffonia simplicifolia. Typically, 5-HTP is the rate limiting step of conversion of LT to serotonin. Serotonin levels regulate sleep, mood, appetite, temperature, pain, and aggressive or sexual behaviors. 5-HTP is found in many commercial combination products and also used alone for sleep onset, depression, anxiety, and to decrease appetite.

A 15-year-old male with autism, absence seizures well controlled on Lamotrigine, food and environmental allergies presents to sleep clinic for concerns of loud snoring for several

years. His mother reports a lifelong history of severe insomnia and short sleep duration as an infant. Since the age of 5 years she has been treating his insomnia with 5-HTP; the nightly dose is 200mg at 20:30 with no side effects observed. He has a stable sleep schedule but does not awake refreshed after 9 hours of sleep per night. He has nasal congestion with mouth breathing and sleeps with his neck hyperextended. His BMI is 18.9 kg/m² with normal vital signs. Physical exam was significant for a low-lying palate with normal oropharynx and 2+ tonsils. A sleep study revealed moderate obstructive sleep apnea (OSA) with mild carbon dioxide retention.

Serotonin cannot cross the blood brain barrier and must be made in the central nervous system. Therapeutic use of 5-HTP increases serotonin levels in the brain due to easily crossing the blood brain barrier. Serotonin is a key neurotransmitter in regulating sleep-wake cycles and is converted into melatonin in the presence of darkness. Typical doses of 5-HTP for insomnia are 50-200mg given in the evening. 5-HTP has been shown to increase REM sleep which can cause vivid dreams or nightmares and potentially worsen REM related sleep apnea. There is a risk of serotonin syndrome when used with selective serotonin reuptake inhibitor antidepressants or monoamine oxidase inhibitors. There is also a risk of weight loss due to an appetite depressant effect.

Our patient was treated for his moderate OSA with nasal steroids, Montelukast, and referred to ENT for surgical evaluation of airway obstruction. The mother was counselled to be aware of the risks of 5-HTP including medication interactions, changes in sleep architecture, and appetite reduction. Providers must be aware of mechanism of action, potential medication interactions, and typical dosages of commonly used supplements in order to have an educated discussion with families who turn to over the counter medications to treat sleep problems.

Nutritional Supplements use by the adolescents - Friend or Foe?

Christina Tsitsimpikou, MSc, PhD, ERT

Nutritional supplements (NS) are complexes of nutrients with variant activity that may infer reversal to nutrient depletion. They tend to be popular amongst social categories associated with the healthy life style, such as the elite and amateur athletes, military people and the general population, especially adolescents. Although the use of nutritional supplements by adult athletes has been extensively studied, information on supplements consumption by adolescent athletes is still limited. From a thorough literature review on nutritional supplements, cases of adulteration or unintentional contamination of commercial products with abusing substances (doping substances, narcotics etc.) or toxic compounds (heavy metals, plant toxics) have shed light to an emerging public health issue, while drug interactions particularly of herbal supplements and cases of hepatic toxicity thereof (troixis necrosis) require immediate action from the regulators. From the safety/ quality point of view, nutritional supplements lack of harmonisation and sovereign laws/ institutional controls on the market and their commercialization world-wide.

Migrations in Latin American countries. A look from Pediatrics.

Rodrigo Vasquez De Kartzow

It is estimated that 281 million people in the world live in a country other than the one where they were born, equivalent to almost 4% of the world's population, 12% of whom are boys and girls under 18 years of age. In recent decades, the migratory phenomenon has become stronger in Latin American countries. Traditionally, migration was to northern countries, mainly to the United States, but a new migratory flow has emerged to southern countries of the continent, mainly to Chile. It is estimated that 1 in 5 migrants in Latin America is a child or adolescent under 18 years of age. People are considered to have a higher degree of vulnerability and this is even higher in the pediatric population. We will review the main characteristics of the migrant child population, their myths and realities.

Prenatal Exposure to Perfluoroalkyl Substances and Immune Dysfunction in children**Granum B.**

The immune system of the fetus and neonate develops extensively, and a normal maturation of the immune system is dependent upon specific processes that occur at different time points and in different body compartments. This makes the early-life immune system a moving toxicological target for interaction with environmental chemicals.

Perfluoroalkyl substances (PFASs) is a class of synthetic compounds that have widespread use in consumer and industrial applications, and they are ubiquitously found in nature, wildlife and humans. Diet is the major source of PFAS exposure for most humans, but other routes such as dust ingestion and indoor air inhalation may also contribute substantially.

There are studies providing evidence for immunosuppressive effects of prenatal exposure to PFASs seen as an increased risk of common infectious diseases and decreased antibody responses to childhood vaccines. With regard to effects of PFASs on health outcomes such as asthma and allergic diseases, contradictory results have been reported. When it comes to the mechanisms responsible for the observed immunotoxic effect of PFASs, there are some support for modulation of gene regulation via peroxisome proliferator-activated receptors (PPARs), nuclear factor κ B (NF- κ B) and/or regulation of apoptosis. The mechanisms are still not well understood and more studies are needed.

In 2020, the European Food Safety Authority (EFSA) published a risk assessment on four PFASs (sum of PFOA, PFNA, PFHxS, PFOS) where effects on the immune system were considered the most critical effect. They established a tolerable weekly intake (TWI) of 4.4 ng/kg body weight per week. Based on information on PFAS exposure, EFSA concluded that parts of the European population exceed this TWI, which is of concern.

A Randomized Controlled Trial of Allergen Trigger Reduction Strategies to Improve Pediatric Asthma Outcomes**Felicia Rabito**

Background: Asthma is a serious, complex, and highly prevalent childhood disorder. In the U.S., pronounced disparities exist with the highest disease burden borne by low-income, minority children living in urban environments. Disparities are due, in large part, to greater exposure to asthma triggering allergens in the home. Guidelines based care recommends interventions targeting all allergens to which children are sensitized. However, it is unclear

whether this is the most effective allergen reduction strategy. Numerous studies of inner-city cohorts have found that exposure to cockroaches may be driving disparities in asthma outcomes in inner city residents. The impact of reducing cockroaches on clinical outcomes is not known.

Methods: One hundred and two children ages 5-17 years with moderate to severe asthma were enrolled in a 12-month randomized controlled trial testing the use of insecticidal bait on cockroach counts and asthma morbidity. Homes were visited six times and asthma outcomes were assessed every 2 months.

For binary outcomes a logistic regression model was applied. For continuous outcomes, a semi-parametric model was applied.

Results: After adjustment, intervention homes had significantly fewer cockroaches than control homes (mean change in cockroaches trapped 13.14, 95% CI: 6.88, 19.39, $p < 0.01$). Children in control homes had more asthma symptoms and unscheduled healthcare utilization in the previous 2 weeks (1.82, 95% CI: 0.14, 3.50, $p = 0.03$; 1.17, 95% CI: 0.11, 2.24, $p = 0.03$, respectively) and a higher proportion of children with FEV1 < 80% predicted (OR 5.74, 95% CI: 1.60, 20.57, $p = 0.01$) compared to children living in homes receiving the cockroach abatement intervention.

Conclusions: Clinical guidelines recommend a multi-component approach to allergen trigger reduction in the home. We found that the strategic placement of insecticidal bait which is inexpensive, has low toxicity, and is widely available, resulted in sustained cockroach elimination over 12 months and was associated with improved asthma outcomes. This single intervention may be an alternative to multifaceted interventions currently recommended to improve asthma morbidity in households with cockroach exposure.

Acquired Pathologies of the Child's Skeleton

Mathilde Payen

Our purpose is to deal with the main outlines of the diagnosis, classification and therapeutic principles of acquired orthopaedic pathologies encountered in the daily practice of general medicine. Therefore, we exclude all congenital or malformative pathologies (Developmental dislocation of the hip unsuited to birth, foot's congenital deformities). On the other hand, we have opted to talk about congenital or malformative pathologies, whose diagnosis can be made secondarily during growth within the framework of the etiological assessment of a known acquired anomaly (scoliosis, leg length discrepancies, etc.). The classification of these pathologies is based on the circumstances and signs revealing these pathologies. We therefore deal successively with the diagnosis of limping and gait disorders in children, frontal and rotational deformities of the lower limbs, knee pain diagnosis, growth apophysis, acquired deformities of the foot, osteoarticular infections, spinal and pectus deformities, and finally, a point on the upper limb deformities. Each revealing sign will be defined, deepened and applied according to the age of the child when the pathology is discovered. The purpose of this work is to provide the main diagnostic guidelines for the pathologies of the child's skeleton during the general clinic.

Keywords: Perthe's disease, Slipped upper femoral epiphysis (SUFE), Flat foot, Cavus foot, Osteomyelitis, Septic arthritis, Osteochondritis dissecans, Kyphosis, Scoliosis, Pectus carinatum, Pectus excavatum.

A Pilot Study to Monitor the Effect of An Amino Acid Diet on Symptom Management in Children with Spinal Muscular Atrophy Type 1: SMAAD Study

Graeme O'Connor, Agnieszka Szmurlo, Lisa Edel, Sarah Raquq, Melissa Bowerman, Isobel Hardy, Mary Fewtrell, Giovanni Baranello

Background: An increasing number of families are incorporating the amino acid diet into their child's feeding regimens. Characteristics of the diet include high carbohydrates, low fats, probiotics, vitamin D, co-enzyme Q10 and oral hydration solutions. Anecdotally, families have reported improvements in airway secretions, drooling, respiratory infections, constipation, and gastroesophageal reflux.

However, due to insufficient evidenced based research clinicians are unable to prescribe or endorse. Furthermore, the diet has been linked with hypertriglyceridemia and non-alcoholic fatty liver disease.

Working with families we devised an adapted version of the traditional diet and named it SMA amino acid diet (SMAAD). Our aim was to assess the tolerability and safety of SMAAD compared to a standard whole protein enteral formula.

Results: Fourteen children were recruited, mean age was 4.1 years (1.2 SD), of which 64% were female. At recruitment, all 14 children required cough assist at least twice a day with 13 of 14 (93%) on biphasic positive airway pressure. All children were receiving Nusinersen, an approved gene-based therapy for SMA.

The most common gastrointestinal complaint prior to switching to SMAAD was constipation, reported in 12 of 14 (85%), of which 10 of the 12 (83%) children required medication to help bowels open daily. Reflux was reported in 5/14 (35%) children.

Within one week of switching to SMAAD families reported a significant improvement in constipation symptoms. All the 12 families who originally reported constipation symptoms saw an improvement with 10 out 12 (83%) stopping or reducing medication for constipation. Improvements in reflux was seen in 4 of 5 (80%) children, and a reduction in oral secretion was reported in 6/14 (43%).

Appropriate weight gain was observed while children were following SMAAD for the eight-week trial (baseline weight z-score: -0.7 kg [0.9 SD] vs -0.5 kg [0.7 SD], $p=.03$).

Due to improved symptoms within one week of starting SMAAD, only two families chose to add additional carbohydrate and 12 families refused to revert to original feed formula after the eight-week trial. The two families who did revert to their previous formula reported resumption of constipation within one week and requested to restart SMAAD. An Amendment category C: 295489 21SH01-2 17 Jan 2022 reference 143229 was submitted to report change in original protocol.

Conclusion: Advances in SMA Type 1 therapy poses new challenges, particularly in relation to the management of gastrointestinal symptoms, which can be exacerbated by intestinal dysbiosis from the routine admission of prophylactic antibiotics and a decrease in effective peristalsis. Children with SMA Type 1 who are displaying gastrointestinal symptoms such as constipation and reflux may benefit from an amino acid formula that is fortified with probiotics, prebiotic and contains medium chain triglycerides. Our pilot study reports a reduction or cessation in constipation medication within two weeks of commencing SMAAD. A larger validation study is warranted to substantiate our preliminary findings.

Acknowledgement: We would like to thank the families who have lived in experience of SMA and contributed to the virtual meetings to help with the design of this study especially

in relation to adapting the SMA AAD. Additionally, we would like to thank Nutricia for supplying the amino acid formula.

Voices from Parents with children with Autism Spectrum Disorder - Can Provider's improve the experience of families?

Deborah Lynn Kasman MD, MA

One in 44 eight-year-old children in the US are now diagnosed with Autism Spectrum Disorder (ASD). It is known that parents, and other caregivers of autists suffer more anxiety, depression, divorce and lower scores in physical, emotional, social and financial well-being. Yet, it is still uncommon to treat children with ASD from a family perspective or approach.

This talk presented by a physician, bioethicist as well as a mother of child with ASD, will give the opportunity for attendees to hear the voices of parents through narrative, poetry and art. By gathering literature studies and narratives from many parents, the speaker will share a model of a predictable trajectory of emotions and needs that parents and caregivers experience in loving their child and barriers they may experience when accessing healthcare.

Providers can improve parental experiences and provide support that enhances the well-being of not only the child with ASD, but other family members as well, by switching one's lens of treating the child with ASD to a family -systems approach of treating children with ASD. The talk will conclude with brief review of the limited work being done in this field, while encouraging a proactive approach to include and support parents and caregivers of ASD kids.

The Longview on Near-sightedness: A overview of modern myopia management

Jill Rotruck

Myopia, or near-sightedness, is developing and worsening at a striking rate around the globe. This session provides an overview of the scope of the problem, ocular pathology associated with myopia, risk factors for myopia development, and modern strategies for minimizing myopic progression.

Quality Analysis of Publicly Available Videos for Pediatric Strabismus Surgery

Martha Howard

Objective: The purpose of this study was to analyze the quality and accuracy of YouTube videos on surgical management of pediatric strabismus.

Methods: YouTube.com (San Bruno, CA) was searched for the period July 1, 2008, to July 1, 2018. Videos with >100 views and an average of at least 1 view per day were selected for inclusion to approximate videos representative of actual access patterns.

Two independent observers who were both resident ophthalmology physicians who completed their core pediatric ophthalmology rotation and were masked to each other's results graded each video using a customized CRAAP criteria rubric (current, relevant, accurate, authority, purpose), as shown in Table 1.

An attending pediatric ophthalmology specialist graded a 20% sample of the videos.

Results: Of the 49 videos analyzed, 14 (29%) were primarily educational videos, 11 (22%) were primarily advertisements, and 24 (48%) were testimonials

Conclusions: This analysis of pediatric strabismus surgery videos found that many videos lack useful information, and some provide disinformation that may be harmful to pediatric eye care.

Implementing a Child Mental Health Intervention in Child Welfare Services: Stakeholder Perspectives on Feasibility and Acceptability

Geetha Gopalan, LCSW, PhD; Kerry-Ann Lee, MSW, PhD; Caterina Pisciotta, MSW

Despite high rates of behavioral difficulties (e.g., oppositional, aggressive, disruptive behavior) among children involved in child welfare (CW) services in the United States, mental health service utilization, particularly among those youth who remain at home with their families, remains poor. Limited availability of qualified providers is a frequent barrier. Given that child behavioral difficulties are significant risk factors for future maltreatment, innovative ways to increase access to and utilization of effective evidence-based interventions (EBIs) for such families are needed. One potential solution involves utilizing task-shifting strategies and implementation science theoretical frameworks to implement mental health EBIs in CW settings. This pilot study integrated quantitative and qualitative data using a triangulation design with a convergence model to examine the feasibility and acceptability of implementing a modified version of a multiple family group behavioral parent training intervention (The 4Rs and 2Ss for Strengthening Families Program [4Rs and 2Ss]) in CW placement prevention services. This study elicited perspectives of participating caregivers (n = 12) and CW staff (n = 12; i.e., 6 caseworkers, 4 supervisors, and 2 administrators). Quantitative surveys were administered to caregivers and CW staff followed by semi-structured interviews to examine the factors impacting the feasibility and acceptability of implementing the modified 4Rs and 2Ss program. Results indicated that quantitative benchmarks for high feasibility and acceptability were met in all assessed areas (e.g., family recruitment, caseworker fidelity ratings, caregiver reports on program satisfaction, CW staff feasibility, appropriateness, and acceptability ratings) except for family attendance, which was markedly lower than desired. Factors facilitating feasibility and acceptability included agency culture and research support, intervention training and ease-of-use, perceived benefits to existing CW practice, logistical supports (e.g., food, transportation, childcare, etc.) promoting attendance, family members' satisfaction, friendly environment, and perceived helpfulness of material. Factors hindering feasibility and acceptability included conflicts between research-based eligibility criteria and existing client population demographics, research-related processes resulting in delays, CW staff role conflicts, added workload burden, complex family issues, and power differentials inherent to CW services which complicated families' voluntary participation. Findings may inform other cross-system implementation efforts for similar EBI's.

Intervention versus Observation in Mild Idiopathic Scoliosis in Skeletally Immature Patients

Shu-yan Ng

Observation is the treatment of choice for idiopathic scoliosis with Cobb angles between 15-20o in growing children. This passive approach does not address the anxiety of the patient and the stress of the parents. In this paper, we attempt to identify skeletally

immature patients with mild scoliosis curvatures that are more at risk of progression and propose possible intervention for this group of subjects.

The literature was searched in Pubmed, and additional references are searched manually in the literature.

Many studies have shown that low serum 25[OH]D level, bone mineral density (BMD), and body mass index (BMI) are related to the curve severity or progression of the curve.

We suggest that skeletally immature patients (< Risser 2) with mild curves, be divided into two groups, viz. Group O (observation) with a lower risk of progression, and Group I (intervention), with a higher risk of curvature progression. We propose early intervention for the latter group.

It is suggested that pre-menarcheal, skeletally immature patients with mild idiopathic scoliosis, and low vitamin D, BMD, and BMI should be treated. Also, asymmetric foot biomechanics should be addressed, although nutrition and foot orthoses are regarded to have no role in the management of idiopathic scoliosis. The outcome of early intervention may be utterly different from late treatment when the curvature becomes more structural, and the patient more skeletally mature.

Early Language Learning Profiles of Young Children with Autism: Hyperlexia and Its Subtypes

ChuSui Lin

This study utilized a standardized and comprehensive computer-aided language assessment tool to identify the early learning characteristics (e.g., hyperlexia) of young children with autism. The tool consisted of six subtests: decoding, homographs, auditory vocabulary comprehension, visual vocabulary comprehension, auditory sentence comprehension, and visual sentence comprehension. Thirty-five children with ASD between the ages of 4 and 6 from Tao-Yuan County in Taiwan participated in the study. Fifteen children with ASD whose decoding performance was 1 standard deviation above the norm of age-matched typically developing children were identified as hyperlexic and selected for further analysis. Five potential hyperlexic subtypes of language learning profiles emerged from this group of children with ASD. This study revealed the heterogeneous nature of language learning characteristics of young children with autism. Such findings have important implications for preschool teachers and other early interventionists who seek to develop specific strategies that capitalize on the learning strengths of young children with ASD

Rocky Mountain Spotted Fever in Children

Charles R. Woods

This session will provide an overview of clinical presentations of Rocky Mountain Spotted Fever (RMSF), will review the current epidemiology of spotted fever rickettsioses globally, and discuss diagnostic testing, differential diagnosis and treatment options. RMSF usually begins as a nondescript febrile illness. Spots occur later. Many cases can be self-limited but septic shock and/or cerebral edema can develop and may lead to death when RMSF goes unrecognized beyond a few days. Serology and histopathology remain mainstays of diagnostic confirmation. Doxycycline is the treatment of choice at all ages. A new area of endemicity has emerged in the southwestern US and Mexico.

University-sponsored Pediatric Emergency Preparedness and Response Exercises

Elizabeth N. Austin

Emergency preparedness exercises help to prepare communities for the collaboration required for successful navigation of disasters. Such exercises also provide an avenue to introduce university and other students to the concepts of disaster and the need to prepare for mass casualty events. Towson University's College of Health Professions sponsored seven mass casualty exercises over a span of eight years. The exercises included students from multiple disciplines in the University, local fire and emergency medical service responders, local hospitals, military units, senior centers. In addition, two local schools participated with eighth graders and students who were deaf. Multiple agencies gained valuable training in the full-scale exercises. Emergency preparedness exercises are complex events that require significant planning, attention to detail, debriefing, funds, and attention to security details that include the ability to respond to actual emergencies that may occur within the exercise.

Acute In Vivo Evaluation of the Pittsburgh Pediatric Ambulatory Lung

Katelin Omecinski

Respiratory disease remains a pervasive medical condition amongst the pediatric health population. Mechanical ventilation and extracorporeal membrane oxygenation (ECMO) are used to bridge patients to transplant or recovery when conventional therapy fails. Patients undergoing these treatments may be sedated for extended periods of time, resulting in deconditioning of the patient's musculature. Patients who remain awake on ECMO, however, can participate in physical therapy and combat muscle wasting. Typical ECMO circuits are complex and present a major consumer of hospital resources for these patients undergoing rehabilitation and ambulation. Our research group has pursued the integration of mechanical circulatory and respiratory assistance into a compact platform device, the ModELAS, to address this clinical need. This aim of this review is to summarize published work on the pediatric application of the ModELAS. A breadth of topics will be reviewed, including the design requirements, device evolution, in-vitro results, and in-vivo results of the device.

Relevance of available caregiver resources to maintain the homeostasis of the oral cavity and the respiratory organs

Winifred J. Booker, DDS, ABPD, FAAPD 1 CEO & Director of Development, Brushtime Enterprises and The Children's Oral Health Institute

Introduction: The provisions for routine oral care and sustenance for people with certain health conditions often requires adaptation of the skills and the availability of prerequisite resources that caregivers and health professionals use every day are provided by the oral-medical-dental care device known as Mouth Almighty™. This system of routine oral hygiene maintenance deployed promptly after the delivery of a meal or medication offers an extraordinary resource for many caregivers to effectively utilize. The (a) diagnosis, (b) the oral manifestations of the condition, disease, or illness, (c) the medical and dental billing codes, (d) the Standard of Care Prevention Guidelines and (e) the fourteen uses, (1-14), thoroughly demonstrate the potential for the impact on human health and relevance of the

Mouth Almighty device to dental, medical, and oral health care industries. Evidence-based, prevention management of oral and dental conditions that can compromise the oral mucosa, lips, teeth, throat, esophagus, lungs, the ability to swallow, speech production, and food consumption can significantly improve the quality of life. The number of people, children, and adults world-wide that are afflicted by many of these conditions clearly demonstrates the commercial viability of Mouth Almighty. The 2019 National Teaching Institute & Critical Care Nurses Exposition provided the forum for The Children's Oral Health Institute to collect survey data from 402 critical care unit (CCU) nurses from 44 states, Washington, DC, Puerto Rico and Canada to glean their confidence on how effectively they are able to manage patient oral health. The data collected offers insight into the management of patient oral-medical-dental health care during the hospital stay. The concentrated goals for the purpose of this abstract are to consider two findings. First, to demonstrate the significance and appeal for the interprofessional collaboration between medicine and dentistry. Second, to transfer data knowledge into action by exploring resource enhanced oral care for the differently-abled, infirmed and hospitalized patient populations. The introduction of enhanced oral-medical-dental health care measures could help to influence improve function and help to maintain the hemostasis of the oral cavity and the respiratory organs, and avert deterioration.

Methods: 402 critical care unit nurses completed two separate surveys over two-days. These surveys were each made up of twenty-one questions. The patient load CCU nurse routinely care for during a work shift were taken into account. The responses to prescribed routine oral care management of the mouth were considered, including (1) brushing the teeth, (2) cleaning the soft tissue, (3) cleansing and exercising the tongue, and (4) moistening and exercising the lips of all CCU patients.

Results: Analysis of the management of oral conditions that could compromise the oral and potentially the respiratory organs are provided in this outcome data. Existing product inefficiencies (use of toothettes), and frustration regarding the number of times during a shift that nourishment followed by oral care is prescribed were the two most common points critical care nurses communicated as challenges. When these impediments emerge, nurses communicated not feeling fully poised to execute oral care tasks especially for the critically ill and for the neediest of patients. This includes the fact that 87% CCU nurses provided care for as many as 5 patients at a time during a single shift. 7% of these nurses provided care for 6 to 10 patients during a single shift, and 5% provided care for 10 or more patients. 75% of critical care unit (CCU) nurses report providing care for ventilated patients during a work shift.

While, 97% of nurses agree that oral health care is a part of their routine maintenance and management of patients, 80% report having interest in better oral health maintenance and management training. According to one nursing fundamentals course, Basic Principles of Mouth Care,^{i ii} nurses and physicians receive this instruction. 88% report interest in the inclusion of the dental hospitalist as part of the CCU team.

Conclusions: The provisions for routine oral care and sustenance for people with certain health conditions does require adaptation of the skills that caregivers and health professionals must use every day. Oral microbiome is crucial to health as it can cause both oral and systemic diseases. It rests within biofilms throughout the oral cavity and forms an ecosystem that maintains health in a state of equilibriumⁱⁱⁱ. Therefore, it is principally important to elevate the relevance of available caregiver resources to help maintain the

homeostasis of the oral cavity and the respiratory organs. The health care industry must be endeared to fully appreciate the survival aspect of the health care equation that unified oral-medical-dental care maintenance unquestionably affords patients throughout periods of hospitalization and infirmity, or simply throughout the existence of dependent individuals.

These surveys describe the need and offers promise for progressive options that may help to advance the acceptance of unique oral care delivery systems especially for patients at risk of compromised oral health that could lead to compromised respiratory health. The findings support the value placed on the importance of creativity and innovation to help reduce systemic deterioration and pneumonias secondary to poor oral health.

Finally, the dedicated composition of the operational components offered by the oral-medical-dental health care device known as Mouth Almighty are exclusively designed to improve function, avert deterioration, and maintain functioning. The efficacious utilities provide by this comprehensive unit has the ability to safely afford caregivers, including nurses, physicians, dentists, and other health professionals accelerated support for all those entrusted to any form of assisted living circumstances, from hospital care to home care. The inclusion of this innovation in the preventive health care resource product pipeline, supports the service, training and devotion of caregivers to help achieve wellness and enhance the human condition.

Pulmonary edema post-adenotonsillectomy in children

Elaf Ahmed

Post-adenotonsillectomy pulmonary edema (pATPE) is a life-threatening condition that necessitates immediate clinical intervention. The early diagnosis and detection of the signs of this condition is vital to its treatment and patient outcome. We did review article to present epidemiological data on the prevalence of pATPE, and address the mechanisms of development, types, etiology, pathophysiology, and management of pATPE. In order to minimize postoperative intensive care unit admission rates of pATPE, utilization of preoperative clinical assessment, operative/postoperative monitoring tools, and procedural precautions are discussed.

Simulation for Newborn Resuscitation in Community Emergency Departments

Christie Bruno

Background:

Prior to and since the start of the coronavirus pandemic of 2020, many changes have occurred to the structure of various hospitals and hospital systems with removal and re-allocation of staff and resources. Some of these changes include the closing of labor and delivery services along with the removal of neonatal providers whose primary role is to perform newborn resuscitations. The 2020 March of Dimes Maternity Desert Care report demonstrates that in 2017 nearly 500,000 infants were born in the United States in areas where their mothers had limited or no access to maternity care. Neonatal care providers are limited in these areas as well. This has led to the need for Emergency Department(ED) providers, without specific training in newborn resuscitation, to be the leads for neonatal resuscitations should a mother present and deliver at these hospitals. Recent studies

demonstrate that newborns born outside of tertiary care centers and without optimal resources including neonatal resuscitation teams had increased neonatal mortality rates or mortality rates prior to hospital discharge highlighting the need for education and systems assessment in community hospitals.

Research Question:

Can serial simulation exercises with equipment and performance assessments improve provider confidence and performance in newborn resuscitations in the community emergency department?

Methodology:

We implemented neonatal simulations and debriefings at three community ED's specific to the management and care of newborns requiring resuscitation post-delivery. Our objectives included an assessment of ED readiness to care for newborns with a focus on personnel training, equipment, and resources through detailed equipment and procedural readiness checklists to measure compliance with evidence based practice. With these assessments, we plan describe the quality of care delivered to preterm infants in community ED's. The goal of this education and research plan is to improve the survival and short and long term outcomes of newborn infants resuscitated by ED providers by enhancing ED readiness for neonatal resuscitations and then repeating assessments to explore if our interventions(simulations with debriefings and procedural and equipment assessments) improve neonatal resuscitation performance in repeated simulations and clinical care

Results:

Our preliminary work in performing and studying the implementation of neonatal resuscitation simulations with procedural and clinical checklists/assessments in community ED's demonstrates increased provider confidence and competence in performing neonatal resuscitations including knowledge of the management of newborn infants post-delivery. The majority of participants(n=28) reported that they could appropriately evaluate a newborn, perform initial resuscitation steps with adherence to neonatal resuscitation guidelines as well as plan and explain care to families after the simulations/debriefings. These results were true amongst a variety of providers that included attending physicians, residents, advanced practice providers, nurses, technicians, and emergency medicine services providers.

Discussion/Conclusions:

Optimal resuscitation of newborns through early establishment of adequate ventilation and adherence to neonatal resuscitation guidelines has been demonstrated to improve outcomes in newborn infants. This is the continued goal of our research in the community ED setting through the improvement in quality of care delivered to neonates through a longitudinal collaborative simulation intervention.

Phenotypes of a family with XLH with a novel PHEX mutation

Yasuhisa Ohata

X-linked hypophosphatemic rickets (XLH) is an inheritable type of rickets caused by inactivating variants in the phosphate regulating endopeptidase homolog X-linked (PHEX) gene, which results in the overproduction of fibroblast growth factor 23 (FGF23). The mechanism by which PHEX impairment leads to FGF23 overproduction is unknown.

Because little is known regarding the genotype–phenotype correlation in Japanese XLH, we summarized the available clinical and genetic data and analyzed the genotype–phenotype relationships using 3-dimensional (3D) structure modeling to clarify the XLH pathophysiology.

We retrospectively reviewed the clinical features and performed genetic analysis of 39 Japanese patients with XLH from 28 unrelated pedigrees carrying any known or novel PHEX variant. A total of 10 male and 29 female patients were included. When we analyzed only the probands, familial histories were positive in 11 cases, and 17 cases were apparently sporadic. The median age of the patients was 25 months, ranging from 6 months to 720 months at the time of assessment. The SDS of height prior to treatment was low (-2.17 ± 0.99). We tested the biochemical parameters before any treatment, which revealed high levels of i-FGF23 (82.9 ± 26.3 pg/mL), whereas Pi levels and tubular maximum phosphate reabsorption per glomerular filtration rate (T_{mp}/GFR) were below the lower limit of the normal range in all age subgroups. In pediatric patients < 10 years of age, alkaline phosphatase levels were higher than the normal range for the age subgroup. Although calcium levels were within the normal range, the level of intact parathyroid hormone was slightly elevated.

Genetic analysis revealed 23 PHEX variants, including eight novel variants. No gene dosage effect or genotype–phenotype correlation was observed when truncating and non-truncating variants were compared. However, the conservation of the zinc-binding site and cavity in PHEX had an impact on the elevation of i-FGF23 levels.

Via genotype–phenotype relationship analysis using 3D modeling, we showed that the zinc-binding site and cavity in PHEX can play a critical role in its function. These findings provide new genetic clues for investigating the function of PHEX and the pathogenesis of XLH.

Association between bullying and suicide ideation and attempts among adolescents—moderation of risk and protective factors

Anat Brunstein Klomek

There is a well-known association between bullying and suicide risk among adolescents, but the moderating factors are still unclear. The current study examined the various risk and protective factors moderating the associations between three types of bullying victimization (physical, verbal, and relational bullying) with suicide ideation/attempts.

The study included 11,110 students (mean age = 14.9) recruited from 168 schools in 10 European Union countries involved in the Saving and Empowering Young Lives in Europe study. A self-report questionnaire was used to measure victimization types, depression, anxiety, parental and peer support, and suicide ideation and attempts.

Results indicated that verbal victimization was associated with suicide ideation among adolescents with depression who perceived low parental support. Similarly, low peer support increased the associations between verbal victimization and suicide ideation. Verbal victimization was associated with suicide attempts among adolescents with anxiety who perceived low parental support.

These findings support the need to take into account the type of bullying, symptomatology, and availability of interpersonal support while examining the association between bullying and suicide risk among adolescents.

Reading and coherent motion perception in school age children

Evita Kassaliete

Reading skills develops with age. The development can be influenced by anatomical, neurological and physiological factors as well as external factors such as the phonological complexity of individual languages, socio-economic and personal contribution, etc. According to Fletcher's classification, 10-15% of children have problems with information processing speed and automatic orthographic recognition of words, so cold the Magnocellular deficiency hypothesis - based on both anatomically smaller magno cells and their slower visual information transfer. It was found, when coherent sensitivity is reduced, reading difficulty is also observed at the appropriate age. The centers of motion and reading analysis are located in different areas of the cerebral cortex, that show a significant interaction between the two mechanisms in the dorsal stream. There are many studies confirming that dyslexic patients and in patients with reading difficulties, autism, schizophrenia and Williams syndrome the psychophysical threshold of coherent motion perception is reduced.

The aim of this study was to determine credible coherent motion perception thresholds for children in typical stages of development at varying reading skill levels. This study included 2,027 children-participants (aged 7 to 18 years). The experiment stimulus consisted of 100 moving black dots, displayed for 0.25 seconds on a 12° white rectangular background at a distance of 50 cm. Both signal and noise dots traveled at identical velocities of 2, 5, or 8 deg/s.

The children's motion detection thresholds decreased with age for all dot velocities. The participants' motion perception thresholds were significantly higher at 8 deg/s ($p < 0.0001$), with a mean value of $51.3\% \pm 0.7$, while the mean values for 2 and 5 deg/s, respectively, were $31.7\% \pm 0.6$ and $33.7\% \pm 0.6$. The only significant difference in motion perception between strong and weak readers occurred at a velocity of 2 deg/s ($p = 0.045$). The cognitive features of the children's reading language do not affect coherent motion perception; it develops slowly and steadily. 16% of school-aged children who have been categorized as slow readers exhibit high motion perception thresholds. For weak readers, the perception of coherent motion at a slow speed is different from strong readers due to vulnerability of the dorsal perceptual pathway in the developmental process.

Bullying Victimization and Suicide Ideation and Behavior Among Adolescents in Europe: A 10-Country Study

Anat Brunstein Klomek

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support increased the associations between verbal victimization and suicide ideation. Verbal victimization was associated with suicide attempts among adolescents with anxiety who perceived low parental support.

These findings support the need to take into account the type of bullying, symptomatology, and availability of interpersonal support while examining the association between bullying and suicide risk among adolescents.

Prenatal meditation and infant behaviour

Dr Ka-Po CHAN

Meditation is important in facilitating health. Pregnancy health has been shown to have significant consequences for infant behaviors. In view of limited studies on meditation and infant temperament, my study in 2007-2009 was aimed to explore the effects of prenatal meditation on these aspects. The conceptual framework was based on the postulation of positive relationships between prenatal meditation and infant health. A randomized control quantitative study was carried out at Obstetric Unit, Queen Elizabeth Hospital in Hong Kong during 2007 to 2009. 64 pregnant Chinese women were recruited for intervention and 59 were for control. Outcome measures were cord blood cortisol, infant salivary cortisol, and Carey Infant Temperament Questionnaire. Cord blood cortisol level of babies was higher in the intervention group ($p < 0.01$) indicates positive health status of the newborns verifies that prenatal meditation can influence fetal health. Carey Infant Temperament Questionnaire showed that the infants of intervention group have better temperament ($p < 0.05$) at fifth month reflects the importance of prenatal meditation in relation to child health. Present study concludes the positive effects of prenatal meditation on infant behaviors and recommends that pregnancy care providers should provide prenatal meditation to pregnant women.

Treatment of Insomnia Across Childhood

Melisa Moore

Insomnia disorder is both widespread and persistent across the span of childhood. It impacts myriad aspects of children's functioning including risk for psychopathology, somatic complaints, and behavioral and academic problems. Components of cognitive behavioral therapy for insomnia (CBT-I) adapted for children, are efficacious for symptoms such as bedtime problems and night wakings. CBT-I can be effectively delivered to children in a variety of modes with a range of comorbidities. Secondary outcomes may also be improved.

Health-related quality-of-life and radiological outcome in adolescent idiopathic scoliosis, patients 25 years after treatment

Ane Simony, MD, PhD

Introduction: Since 1962 to the mid-eighties the Harrington Rod instrumentation was the Golden standard for surgical treatment of Adolescent Idiopathic Scoliosis (AIS). The Boston braces were introduced in the 1970's and are still used as a conservative treatment, for curves less than 40°. Although treatment for AIS is prophylactic and aimed at preventing curve progression, very few studies report long-term outcomes of treatment. The purpose

of this study was to evaluate the long-term health related outcome and radiological changes of the spine, in a cohort of AIS patients, treated 25 years ago.

Method: 219 consecutive patients treated with Boston brace (Brace) or posterior spinal fusion (PSF) using Harrington- DDT instrumentation between 1983 and 1990 at Rigshospitalet Copenhagen, were invited to participate in a long-term evaluation study. A validated Danish version of the Scoliosis Research Society 22R (SRS22R) and Short Form-36 (SF36v1) were administered to the patients two weeks before the clinical and radiological examination. 36-inch standing radiographs were obtained after patient consent. Cobb angles were compared with pretreatment and immediate post treatment radiographs. Any evidence of adjacent-level disease or local kyphosis was also observed. Medical conditions, previous cancer and Spine surgery performed after termination of scoliosis treatment was also recorded.

Results: 159 (72,6 %) patients participated in the clinical follow up and questionnaires, 11 patients participated only in the questionnaires, 8 emigrated, 4 were excluded due to progressive neurological disease and 2 were deceased. The total follow up was 170 patients (83 %), and the average follow up was 24.5 years (22–30 years). There was a statistically significant curve progression of 2.9° in the PSF group. There was a greater degree of curve progression in the braced group (5.5°), but this was not statistically significant.

SRS22R domain scores were within the range described as normal for the general population with no statistical difference between the groups except in the Satisfaction domain, where the PSF group had better scores than the braced group. The SF36 PCS and MCS scores in both AIS cohorts were similar to the scores for the general population.

Conclusion: In this cohort with an average follow-up of 24.5 years, with 78% available for follow-up. The braced and surgically treated patients had a very small degree of curve progression, with a small incidence of distal segment degeneration and reoperation. HRQOL as measured by the SRS22R and SF-36, of adult AIS patients treated with Boston brace or PSF during adolescence were similar to the general population. No clinical progression of the deformity has been detected during the 25-year follow up period. The PSF group had a small but statistically significant higher score in the Satisfaction domain compared to the braced group.

Trial registration: S-20110025 Regional Committees on Health Research Ethics for Southern Denmark.

Level of evidence: III.

PHARMACOLOGY

Influence of Pharmaceutical Company Engagement Activities on the Decision to Prescribe: A Pilot Survey of UK Rare Disease Medicine Prescribers

Ravi Jandhyala

Introduction. Traditionally, the pharmaceutical industry has used “promotional personal engagement” activities, which involve interactions between sales forces and prescribers, in order to generate ‘sales’ – or prescriptions – of their new medicinal product(s). There appears to be now a favouring of “non-personal engagement” (external information sources or activities existing outside the direct control of the company) and “non-promotional personal engagement” activities (focussed around creating a peer-to-peer relationships between prescribers and pharmaceutical physicians).

Objectives. The purpose of this study is to examine the influence of non-personal engagement and non-promotional personal engagement activities on prescribing habits of British healthcare professionals, using the traditional promotional personal engagement activities as a comparator.

Methods. A questionnaire was distributed to 122 prescribers (physicians, nurses and pharmacists) working with two selected products for pulmonary arterial hypertension. The participants were asked to rate the influence that listed activities had on their decision to prescribe each of the two products using a scale of 0-10, where 0 = 'no influence' and 10 = 'most important influence'; 34/122 (27.9%) responded to the survey.

Results. Of the 122-targeted healthcare professionals who received the questionnaire, 34 (27.9%) responded within the 2-week time limit. (24 physicians, 5 Nurse Prescribers and 5 Pharmacists). The findings of the survey have a confidence level of 90% and margin of error of 12% given that 34 out of 122 people responded.

All proposed activities were scored by the respondents as having some influence on their prescribing. Personal engagement activities are effective for influencing prescribing, but non-promotional personal engagement activities may be more influential than promotional personal engagement activities. Furthermore, non-personal engagement activities may be more effective in influencing prescriptions of a product than either non-promotional or promotional personal engagement activities.

Conclusions. All personal engagement activities affect HCP prescribing behaviours; however, they appear to be more influential when performed on a non-promotional basis by representatives of the company's medical department.

Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning **Juan Sanchez-Ramos**

Drugs that modulate serotonin (5-HT) synaptic concentrations impact neurogenesis and hippocampal (HPC)-dependent learning. The primary objective is to determine the extent to which psilocybin (PSOP) modulates neurogenesis and thereby affects acquisition and extinction of HPC-dependent trace fear conditioning. PSOP, the 5-HT_{2A} agonist 25I-NBMeO and the 5-HT_{2A/C} antagonist ketanserin were administered via an acute intraperitoneal injection to mice. Trace fear conditioning was measured as the amount of time spent immobile in the presence of the conditioned stimulus (CS, auditory tone), trace (silent interval) and post-trace interval over 10 trials. Extinction was determined by the number of trials required to resume mobility during CS, trace and post-trace when the shock was not delivered. Neurogenesis was determined by unbi-ased counts of cells in the dentate gyrus of the HPC birth-dated with BrdU co-expressing a neuronal marker. Mice treated with a range of doses of PSOP acquired a robust conditioned fear response. Mice injected with low doses of PSOP extinguished cued fear conditioning significantly more rapidly than high-dose PSOP or saline-treated mice. Injection of PSOP, 25I-NBMeO or ketanserin resulted in significant dose-dependent decreases in number of newborn neurons in hippocampus. At the low doses of PSOP that enhanced extinction, neurogenesis was not decreased, but rather tended toward an increase. Extinction of "fear conditioning" may be mediated by actions of the drugs at sites other than hippocampus such as the amygdala, which is known to mediate the perception of fear. Another caveat is that PSOP is not purely selective for 5-HT_{2A} receptors. PSOP facilitates extinction of the classically conditioned fear

response, and this, and similar agents, should be explored as potential treatments for post-traumatic stress disorder and related conditions.

Engineering cell-derived vehicle for cancer immunotherapy

Wang Chao

Immunotherapy utilizes the patient's own immune system to fight against disease. For example, cancer immunotherapy has been proved successful to treat cancer, remarkably improving the therapy efficacy in clinic. However, some limitations still need to be addressed, such as low response rate and immune-related adverse events (irAEs) caused by off-targeting. Therefore, new target strategy should be developed for improve the immunotherapy. In recent years, a variety of novel biomaterials and strategies have been reported to targeted deliver therapeutics for immunotherapy. Among them, cell and cell-based nanoparticles, such as red blood cells, platelets, cell-derived nanovehicle and exosomes, as a kind of important bio-nanomaterial that has been extensively studied for drug delivery. In this talk I will present our recent strategies based on cell-derived systems for immunotherapy delivery for treatment of cancer and inflammation.

Healthy Living Pharmacy - its role in medicines optimisation and safety, prevention and protection within an integrated health system

Michael Holden

Healthy Living Pharmacy was established as an innovative model in England in 2009 in response to a UK government White Paper (Pharmacy in England: building on strengths - delivering the future). It was subsequently developed through a national pathfinder programme and is has been embedded in the English Community Pharmacy Contractual Framework since 2020.

The aim is to utilise the accessibility of community pharmacists and their teams to deliver a wider range of quality health interventions to improve health awareness and health outcomes, and reduce health inequalities. This requires improved leadership, improved healthy lifestyles knowledge and healthy conversation skills, and necessitated a pharmacy to meet a range of specific workforce, premises and community engagement criteria.

The real gain is when this model is fully integrated within a local health system to optimise patient health outcomes and medicines safety. This means ensuring that the holistic needs of a patient are fully met including adherence to their prescribed treatment and reducing health risks through informed healthier lifestyle choices.

To some, an integrated approach comes naturally as it is based on a foundation of good professional relationships. For others it can be challenging based on no or poor historical relationships and perceived financial and professional domain threats. Developing a mutual understanding, aligning purpose, improving population health literacy, and putting the health of the population at the centre with the right levers, mindset and culture shift should remove these obstacles.

Clinical Pharmacology and Safety of Trifarotene, a First-in-Class RAR gamma-selective Topical Retinoid

Nathalie Wagner

Trifarotene is a new drug with retinoic acid receptor activity and selectivity for retinoic acid receptor-gamma. Trifarotene 50 µg/g cream is approved for the treatment of acne vulgaris

on the face and/or trunk in adult and adolescent patients. The clinical pharmacology program aimed at assessing the clinical pharmacology and safety of trifarotene.

Systemic exposure to topically applied trifarotene up to 100 µg/g was investigated through 4 clinical studies: 2 studies were maximal usage pharmacokinetic trials (MUSt) conducted in subjects with moderate to severe acne vulgaris. The 2 other studies were conducted in healthy volunteers: 1 clinical drug-drug interaction (DDI) study and 1 thorough QTC study to assess the potential for cardiac repolarization delays. Considering the pharmacologic class of trifarotene (retinoids) and the class-associated potential teratogenicity, and because trifarotene is intended to be used by women of childbearing potential, a DDI study was conducted to assess the potential trifarotene effects on contraceptive steroids. Safety assessments included adverse event reporting and assessment of erythema, scaling, dryness, and stinging/burning using a scale from 0 = none to 4 = severe, as well as the evaluation of the systemic safety of trifarotene through routine laboratory testing.

Systemic absorption of trifarotene 50 µg/g cream was generally unquantifiable in adults and adolescent patients with acne vulgaris, including patients with severe acne. Daily use of trifarotene was not associated with cardiovascular effects and did not reduce the systemic exposure to oral contraceptives such as levonorgestrel or ethinyl estradiol. Safety analyses did not show local or systemic safety concerns with trifarotene up 100 µg/g, a dose twice as high as the marketed dose.

The present pharmacology studies confirmed that trifarotene 50 µg/g cream is well tolerated and safe, even when applied under maximized conditions in adults and adolescent patients with acne vulgaris.

The Influence of Intervening on the Pharmaceutical Consultation Targeting Outpatients with Advanced Non-small Cell Lung Cancer Receiving Erlotinib Treatment

Seira Toyosat

Erlotinib is used to treat advanced non-small-cell lung cancer (NSCLC), the common serious adverse events are skin disorders. The dose intensity of erlotinib should be maintained as much as possible by an appropriate control of adverse events in order to maintain its efficacy. Therefore, the management of these adverse events related to skin disorders would enable a continuous erlotinib treatment without interruption and dose reduction. This study assessed the effect of pharmaceutical consultation in outpatients who received erlotinib. Participants included patients with NSCLC who received erlotinib therapy for more than 6 months between December 2007 and March 2019. The participants were divided into two groups: the intervention group that included patients who received pharmaceutical consultation targeting outpatients by a pharmacist and the nonintervention group that included patients who did not. We retrospectively investigated patient characteristics, treatment regimens, and treatment efficacy. We included a total of 33 patients (18 and 15 patients in the nonintervention and intervention groups, respectively) in this study. The intervention group had a significantly higher median relative dose intensity (RDI) of erlotinib than the nonintervention group ($p=0.0437$). In addition, the pharmaceutical consultation targeting outpatients was identified as a factor contributing to the maintenance of $RDI \geq 90\%$ ($p=0.0269$). The present study indicated that there was improvement in RDI with pharmaceutical consultation targeting outpatients with advanced NSCLC.

Genetically Modified Silk Fibroin Nanoparticles in Oral Nanotherapeutics for Colon Diseases

Dingpei Long

The incidence of colon diseases, mainly including inflammatory bowel diseases and colon cancer, is rapidly rising. Oral nanotherapeutic has been considered as a promising strategy in the treatment of colonic diseases. Silk fibroin (SF), a natural protein extracted from the cocoons of the silkworm (*Bombyx mori*), has been used in silk-based medical devices for sutures and as a support structure during reconstructive surgery. SF-based nanoparticles (SF-NPs) exhibit intrinsic anti-inflammatory activity, wound-healing capacity, high drug encapsulation efficiency, and the ability to undergo lysosomal environment-responsive drug release. Exogenous fusion proteins/polypeptides with different functions introduced by genetic modification will participate in the self-assembly of SF in the silk glands of transgenic silkworms, thus endowing transgenic SF and genetically modified SF-NPs (GMSF-NPs) with new characteristics (e.g., high-level cell-targeting and cell-entry efficiency) while retaining the original excellent properties of SF, and effectively promoting the application of GMSF-NPs in the field of nanomedical drug delivery for colon diseases. So far, there have been no reports of nano-drug delivery materials based on GMSF-NPs for the treatment of colon diseases. Here, our research group took the lead in using GMSF-NPs as drug-delivery systems (DDSs) to carry out the study of oral nanotherapeutic of colon tumors. Firstly, we developed a novel green fluorescent protein (GFP)-based GMSF-NPs with drug tracer and long-term sustained-release characteristics in vitro cultured intestinal cells and orally administered colitis associated cancer (CAC) mice. Compared with natural SF-NPs, the modified GFP-based GMSF-NPs can more efficiently encapsulate doxorubicin (DOX) and prolong the sustained release time of DOX in vitro cultured intestinal cells and mouse intestines. Therefore, a single dose of DOX-loaded GMSF-NPs can suppress cancer cells for a long time, and achieve the same therapeutic effect as repeated use of non-carrier drugs. In addition, we have also developed a major ampullate spidroin I (MaSpl)-based GMSF-NPs that can promote controlled drug release and improve endocytosis. The chemotherapeutic drug camptothecin (CPT)-loaded GMSF-NPs achieved much stronger in vitro and in vivo anti-colon cancer capacities than CPT-loaded natural SF-NPs based on colon epithelial cancer cell lines and an orthotopic colon cancer mouse model.

Transethosomes a Novel Transdermal Drug Delivery System for Antifungal Drugs

Barik S. Mohammed

The skin, particularly the stratum corneum considered a barrier to the entry of drugs, Antifungal drugs, are widely used for the treatment of fungal infections and they are given either systemically or topically. Antifungal drugs are not fully effective due to many factors like poor skin penetration, inability to reach target sites, short residence time, systemic side effects, and low bioavailability due to hepatic metabolism which in turn require high or frequent dosing and decrease the compliance of the patients, Hence approaches have recently been focused on a novel transdermal drug delivery of antifungal drugs, One such approach are vesicular nanocarrier delivery systems these systems can produce sustained release of the drug, which minimizes the side effects, The frequency of dosing and increase patient compliance. Transethosomes as a novel vesicular carrier system introduced to minimize these drawbacks of antifungal drugs. Transethosomes increase the stability and

solubility of antifungal drugs and hence increasing their efficacy in eliminating the infection. The drug is given as a semisolid dosage form lead to increase patient compliance.

Keywords: Transethosomes, Antifungal, Transdermal, Drug Delivery, Vesicular Delivery

Advancing Drug Discovery via Artificial Intelligence

Shiyu wang, Horst Vogel, Shuguang Yuan

Modern drug discovery is a long and tedious process which costs at least 12 years and 2 billion USD in average. G protein coupled receptors (GPCRs) are the most important drug target for modern drug discovery. About 40% of the marketed drugs are targeting at GPCRs. Resolving or predicting the structures of GPCRs play more and more important roles in the area of GPCR drug discovery. How to speed up this expensive process in an accurate way has become one of the most essential topics in pharmaceutical industry. With the progresses in both artificial intelligence and computational biology, advancing modern drug discovery via computational pharmacy plays more and more important roles. In this talk, Dr. Yuan will talk about ultra-efficient computational drug discovery which includes new drug target identification, computational high throughput screening, homology modelling, large scale drug-like compounds, lead optimization, binding energy calculation, ADMET predication, toxicity prediction and others. In addition, Dr. Yuan will also talk about his successfully story on how to advance "first-in-class" drug molecules into clinical trials as well as how his team performed perfectly in the global GPCR-DOCK contest.

Gut Organoid as a New Platform to Study Alginate and Chitosan Mediated PLGA Nanoparticles for Drug Delivery

Nathan Peroutka-Bigus, Adam Mullis, Kruttika Phadke, Balaji Narasimhan, Bryan H Bellaire

The bacterium *Burkholderia pseudomallei* is the cause of the disease melioidosis and is classified as a Tier 1 Select agent due to its potential for use as a biowarfare weapon. It's feasibility for use as a biowarfare agent is due in part to its inherent antibiotic resistance, high mortality and morbidity, ability to form persistent infections, and infectious via aerosol route. Owing to its antibiotic resistance, mortality is as high as 40% with conventional antimicrobial therapy. Polyanhydride nanoparticles can improve the effectiveness of encapsulated drugs by facilitating navigation of biological barriers. We designed and synthesized amphiphilic nanoparticles encapsulating antibiotics recommended for treating melioidosis and compared their *in vitro* antimicrobial activity to standard, soluble delivered drugs against *B. pseudomallei* utilizing the viability reagent resazurin and CFU enumeration. Encapsulation of meropenem into nanoparticles resulted in a 5-fold reduction in antibiotic concentration needed to reduce the viability of the bacteria by 50% (IC₅₀), along with an increase in bactericidal activity. In separate experiments, encapsulation of ceftazidime resulted in a 2-fold reduction in IC₅₀ value. Results demonstrate that individual encapsulation of meropenem and ceftazidime into polyanhydride nanoparticles improves *in vitro* antimicrobial activity compared to soluble delivery of drugs. With these improvements over conventionally delivered antibiotics we expect that the use of these nanoparticles could lead to improved patient outcomes in the case of melioidosis and could prove invaluable to public health

Pharmacogenetics in Diffuse Large B-cell Lymphoma Patients Treated with R-CHOP

Stefania Nobili, Gabriele Perrone, Enrico Mini

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma representing approximately one third of all non-Hodgkin lymphomas. Unfortunately, about 40% of patients do not benefit of the first-line immune-chemotherapeutic treatment that is represented by the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone plus the anti-CD20 rituximab (R-CHOP regimen). R-CHOP is administered as up-front therapy to almost all the new diagnosed patients. independently from the stage of disease and other prognostic factors. Other pharmacological treatments are in fact administered to selected patients who cannot receive R-CHOP. Currently, biomarkers predictive of response to R-CHOP has not been identified and validated. Thus, the prognosis of DLBCL is predicted by the International Prognostic Index and by molecular classifiers based on the cell of origin. Germline polymorphisms of genes involved in the mechanism of action of drugs included in R-CHOP have been suggested to play a role in the efficacy and/or in the toxicity of this drug regimen. Thus, further prospective clinical studies should be implemented to validate pharmacogenetic biomarkers able to predict the R-CHOP outcome in DLBCL patients. The status of the art on pharmacogenetic biomarkers predictive of DLBCL response to R-CHOP will be presented (e.g. polymorphisms related to genes involved in the transport, metabolism, detoxification of drugs included in R-CHOP). Data from a GWAS prospective pharmacogenetic study we performed in DLBCL patients treated with R-CHOP will also be shown.

The Superfecta of Healthy Aging**Joseph M Keenan**

You who are familiar with horse racing know that a Superfecta bet is the most profitable/rewarding bet you can make on a single race and involves choosing the top 4 horses and their order of finish. My Superfecta of healthy aging is a combination of four supplemental agents that can improve the health of any adult but have multiple benefits unique to improving the health of older persons and can help them do their best in the Human Race. These agents are 1) Nicotinic Acid-Intermediate release; 2) Dihydroberberine SR; 3) Dihydroquercetin SR; and 4) Mixed Tocotrienols. I would like to give my research and clinical experience as well as the research of others to detail the benefits, and how to best manage dosing and monitoring of each agent to optimize benefits and prevent side effects and toxicity. A longer and more detailed abstract is available if desired.

Are Polycarboxybetaines Stealth Polymers?**Takeshi Mori**

Zwitterionic polycarboxybetaines (PCBs) have gained attention as alternative stealth polymers whose liposomal formulation and protein conjugates were reported not to elicit anti-polymer antibodies. Here, we re-examined the blood retention and antigenicity of liposomes modified with PCB. We successfully reproduced long blood half-life of PCB-modified liposomes that was somewhat superior to PEGylated liposome. However, PCB-liposome elicited specific IgM. We observed dose-dependent production of specific IgM to PCB-liposome, i.e., high doses of PCB-liposomes reduced the production of specific IgM, termed immunological tolerance. These results indicate that the importance of investigating the effect of dose to clarify the existence of antigenicity of stealth polymers.

Pharmacological Strategies in The Management of Delusional Disorders: Challenges and New Opportunities

Alexandre González-Rodríguez

Delusional disorder (DD) is an underresearched disorder that has been considered difficult-to-treat and characterized by poor insight and poor clinical outcomes. The vast majority of studies indicate that patients suffering from DD show poor adherence and poor response to psychotropic medications. The strategy showing the highest level of evidence is cognitive-behavioral therapy which has been tested in randomized controlled trial designs. Although antipsychotics are the first line treatment, the use of antidepressants has been suggested in the last decades, in patients with comorbid depression, and in patients with somatic types.

Despite this common pessimistic point of view, other authors emphasized that poor outcomes are not well-documented and evidence for it is low, suggesting that future studies should be focus on other clinical outcomes. Improving accessibility to treatment, retention at follow-up and management of other symptomatic domains, may be useful when trying to improve the clinical course of the illness. For instance, several authors have described the presence of other symptomatic domains rather than pure paranoid symptoms. In brief, four main factors have been identified: pure or paranoid, cognitive, depressive and schizoid. Treatment specifically targeting these four different clinical domains may improve the clinical course.

DD usually occurs in the middle-to-old age. Because of age-induced pharmacodynamic and pharmacokinetic disturbances, patients with DD may suffer from higher rates of medication side-effects and poor response to medications. Optimizing treatment according to these factors holds clinical promise. The combination of pharmacological and psychosocial/psychological interventions are recommended. Specific strategies in elderly patients include the consideration of physical comorbidities. Pharmacogenetics may play a role to target the clinical goals.

Galenic Pharmacy in the Past, Present, and Future

Paula DeVos

Galenic Pharmacy, the tradition that guided pre-modern pharmaceutical theory and practice in the west for almost 2 millennia, is relatively little known among historians of science and medicine - and when it is addressed, is usually disparaged as primitive, ineffective, and bizarre, if not downright dangerous. However, my research into this tradition has revealed it to be highly important not only to the western medical tradition, but to the development of matter theory and epistemology - the way that knowledge and truth are constructed - in the Scientific Revolution. In this paper, I will discuss the main components and developments of Galenic pharmacy and outline its significance to modern understandings of science and medicine, and the ways in which this tradition remains very much among us in the modern day, hidden in plain sight, and holds significant possibilities for the future.

The journey to a flexible care setting for high-dose monoclonal antibodies in oncology: Where do we stand and what comes next?

Beate Bittner

Today, with the increasing pressure on healthcare costs and resources and especially in light of the COVID-19 pandemic, the value of treatment management of cancer patients in a flexible care setting is broadly recognized. In such a setting patients and caregivers can choose the place of drug administration according to individual preferences and capabilities. Drugs may be administered in the clinic, a physician's office, a community center closer to the patient's home, or even, if permitted by the safety profile of the medicinal product, at the patient's home.

Inherent to the need for parenteral administration, at home dosing is particularly complicated for high-dose monoclonal antibodies in cancer care. While in the past, these biotherapeutics had been dosed intravenously only, the development of high-concentration formulations and the co-formulation of the dispersion enhancer recombinant human hyaluronidase have greatly facilitated subcutaneous dosing. Subcutaneous bolus injections have been shown to be broadly preferred over more invasive intravenous infusions by patients and healthcare providers and to reduce drug administration related expenditures in the clinic. Dosing volumes for approved monoclonal antibodies in oncology range from 5 to 15 milliliters and still need to be administered in a controlled treatment setting and under the supervision of a healthcare provider.

This presentation will summarize the pharmacokinetic-based development pathway for subcutaneous dosing alternatives to intravenous treatments for monoclonal antibodies in oncology and highlight the challenges that still need to be overcome to enable dosing in a flexible care setting. Key focus areas for multidisciplinary researchers and drug developers that are currently in development, such as automated high-volume on-body delivery systems and connected devices with adherence trackers, dosing reminders, electronic patient diaries, and tools enabling a remote contact between patients and the treating physician will be described. The opportunities and challenges underlying the application of these novel technologies to support home- and possibly even self-administration of high-dose monoclonal antibodies will be discussed.

Cryptolepine - A Lead Towards 'Green' Novel Antimalarial and Anti-Trypanosomal Drugs

Colin Wright

New antimalarial agents are urgently needed on account of increasing parasite resistance to currently available drugs. These need to be affordable to those who need them, and, bearing in mind climate change, should ideally be sustainable. The roots of the West African climbing shrub, *Cryptolepis sanguinolenta* are used traditionally for the treatment of malaria; its principal constituent, the alkaloid cryptolepine has been shown to have antimalarial properties and the synthetic analogue, 2,7-dibromocryptolepine is of interest as a lead to new drugs for the treatment of malaria and trypanosomiasis. In this presentation, a 'green' process for the extraction and isolation of cryptolepine from the roots of *C. sanguinolenta* and the preparation of semi-synthetic halogenated analogues as well as their

evaluation against Plasmodium and Trypanosoma sp. will be discussed. This study is shown that the development of sustainable and affordable antiparasitic drugs from *C. sanguinolenta* may be feasible.

Modelling the Innovative Potential of Companies in the Pharmaceutical Industry in Bulgaria **Stanimir Kabaivanov**

Successful Research and development is crucial for supporting high added value and innovation in the pharmaceutical industry. In our research we focus on a distinct feature of Bulgarian pharmaceutical companies - the fact that they are producing mostly generic drugs, and explore their capability to develop and benefit from creating brand-name medicine that allow for higher profit margins. We create a model that is able to capture different stages and efforts related to innovative research and verify if it is also suitable to handle extreme and unusual situations like COVID-19 pandemic. Calibration and validation of the model output is based on recent publicly available data of Bulgarian pharma companies.

If I am not wrong the original registration done for the event was with a different title - "Advanced data analysis for tracking and improving control over COVID-19 outbreaks", so I am providing also abstract for this paper (depending on which one remained in your program as a final one):

Nucleoside Phosphonate Prodrugs as Prominent Source of Hepatitis B Virus (HBV) Inhibitors **Groaz E., Herdewijn P.**

Small molecule oral treatments currently approved against hepatitis B virus (HBV) comprise nucleoside analogues [lamivudine, entecavir (ETV), and telbivudine] and acyclic nucleoside phosphonate prodrugs [adefovir dipivoxil, tenofovir disoproxil, and tenofovir alafenamide (TAF)]. However, these drugs are not effective for achieving HBV eradication, and chronic HBV infection remains endemic in many areas with an estimated 296 million people infected worldwide (2019, WHO) as well as the leading cause of end-stage liver diseases. Moreover, these figures can be expected to increase over the coming decade, particularly in low-income countries. Current efforts by our group are devoted to identifying novel nucleoside phosphonates that could completely inhibit the HBV polymerase to avoid accumulation of nuclear covalently closed circular DNA (cccDNA) molecules that are responsible for viral persistence and reactivation. To this end, we synthesized three series of nucleoside phosphonate prodrugs featuring either a cyclic (e.g., phosphonmethoxydeoxythreosyl) or acyclic [e.g., 3-fluoro-2-(phosphonmethoxy) propyl, 2-ethynyl-3-hydroxy-2-(phosphonmethoxy) propyl] sugar moiety connected to natural nucleobases, which exhibited potent in vitro anti-HBV activity. Effective synthetic routes were designed that allowed to gain access to multigram quantities of these compounds for

further in vivo studies. Selected prodrugs were demonstrated to effectively inhibit the replication of ETV-resistant HBV and significantly reduce HBV cccDNA in cell-based assays. An antiviral efficacy comparable to TAF was observed for these prodrugs in a hydrodynamic injection-based HBV mouse model.

Green LED light has anti-inflammatory effects on burns

Ronierly de Oliveira Costa, Maria Helena Chaves de Vasconcelos Catão, Cassiano Francisco Weege Nonaka, Ricardo Luiz Cavalcanti de Albuquerque Junior, Ivna Rafaela Ribeiro dos Santos Costac

Purpose: The aim of this study was to evaluate the effects of green LED light on inflammatory cells in skin burns: a histological study in rats.

Methods: In this study, 40 rats were randomly divided into 2 groups: G1 – Control (CTR) and G2 – Green Led (LED). Immediately after injury, green light (60 J/cm², 10 s, λ520 at 550 nm) was applied in a timely manner in the four coinciding points of the wound angles and at each point, the amount of 60 J/cm² with a time of 10s was delivered, totaling 240 J/cm² per session with 24 h intervals until the day before animal sacrifice at 3, 7, 14 and 21 days with a lethal dose of intraperitoneal anesthetic.

Results: In the histological analysis, animals treated with green LED, from 7 days, showed a significant decrease ($p < 0.05$) in inflammatory cells when compared to control group.

Conclusions: Green LED light provides an anti-inflammatory effect on skin burns of rats.

Drugs That Accelerate Wound Healing After Irradiation Combined With Wound Trauma

Juliann G. Kiang, Ph.D., Elih M. Velazquez-Delgado, Ph.D.

The future nuclear battlefield against near-peer adversaries brings the challenge of how to perform casualty evacuations. Combined radiation injury (CI), hemorrhage and burn injuries would be the dominant pattern in combat casualties in response to such events. CI has manifested more significant morbidity and mortality than radiation injury (RI) alone, with no U.S. FDA-approved drugs available for treating this type of combat injury. Previous studies in mice have demonstrated that countermeasures (Neupogen® and Neulasta®) for acute radiation syndrome showed no efficacy in mitigating the RCI-induced detriments, including the delayed wound healing. This report compared the animal body weight, survival, organ damage, and skin wound healing in a mouse model. B6D2F1/J female mice, 12-14 weeks old, were exposed to sham, puncture wounding (250-350 mm² on the dorsal area between 2 shoulder blades), RI, and R+W CI at 9.5 Gy total body ionizing irradiation (TBI) with a dose rate of 0.4 Gy/min. Mice were administered with mesenchymal stem cells (MSC, i.v. +24 hr), Ciprofloxacin (CIP, 90 mg/kg, p.o., +2 hr after that once daily up to +21 days), or Ghrelin (113 µg/kg, s.c., +24 hr, +48 hr, +72 hr), or their respective vehicles accordingly. After irradiation, we monitored animal mortality, body weight, and wound healing for 30 days. On day 30, post-irradiation, blood, serum, sternums, spleens, ileums, and femurs were collected; blood cell counts, serum cytokine array, and histological examination were performed. Our data show that 9.5 Gy was an LD_{50/30} for RI and LD_{70/30} for RCI. RCI at 9.5 Gy caused significant body weight loss and delayed wound healing from typically 14 days

to 30 days. Day 3 post-irradiation skin histopathology analysis showed a smaller healing bud in the epidermis with adipocyte atrophy in the dermis as compare to the ones without irradiation. MSC treatment accelerated wound healing by 7 days, increased survival, mitigated body weight loss, and ameliorated bone marrow injury. Ciprofloxacin treatment accelerated the wound healing starting on day 15, and the wound showed complete healing on day 21. In contrast, the wounds in vehicle-treated CI mice took another 7 days to complete healing. This treatment mitigated the CI-induced body weight loss, elevated RBCs and increased survival. Ghrelin treatment significantly increased survival, accelerated wound healing, mitigated body weight loss, and ameliorated leukocytopenia, thrombocytopenia, splenomegaly, and bone marrow injury. IL4 and IL-13 maintain skin health, whereas IL-18 is against skin homeostasis. Ciprofloxacin and Ghrelin effectively inhibited IL-18 while Ghrelin increased IL-4 and IL-13 in wounded mice and RCI mice. Our data support the notion that Ghrelin and Ciprofloxacin are potential therapeutics for accelerating wound healing that CI delays. (This study is supported by NIAID-AFRRI IAA Work Plan A; the views expressed do not represent NIH, AFRRI, USUHS, Department of Navy, or US DoD. The authors declare no conflict of interests.)

Bioavailability of a controlled release subcutaneous formula for tramadol hydrochloride **Shaimaa ElShebiney, Mostafa Mabrouk, Hanan Beheri, Asmaa Galal**

Background: Management of pain in chronic diseases such as cancer or neuropathy is essential to enhance quality of life for the patients. Tramadol is a potent analgesic of preference for such patients. However, it is a controlled prescription medication in most countries. We developed a polycaprolactone based biodegradable subcutaneous implant to facilitate its frequency and control the delivery of the drug. The implant showed sustained release for more than 45 days in vitro following the Korsmeyer-Peppas model without affecting the chemical integrity of the drug (Mabrouk et al.,2018). The current study investigated the in vivo kinetics of the drug.

Methodology: Ribbons of polycaprolactone polymer (T350, T650) or cyclodextrin-coated polycaprolactone (CT350, and CT650) were prepared and loaded with tramadol HCl in two quantities [350 and 650 mg]. In vivo pharmacodynamic and pharmacokinetic parameters were evaluated. Ribbons (1cm²) were implanted in skin layer of male Wistar rats and tramadol plasma level was monitored by HPLC/UV. Analgesic activity was observed by hot plate test. Liver function and general oxidative stress were evaluated at the end of the study.

Results: The CT650 loaded ribbons caused high mortality, thus were excluded from the study. The T350 loaded ribbons showed t_{max} of about 72 hours and C_{max} (91ng/ml), while the T650 loaded ribbon showed t_{max} at around 720 hours and C_{max} (83ng/ml). The CT350 achieved C_{max} (111ng/ml) at 720 hours. However, the pharmacodynamics study proved that analgesic efficacy of tramadol started once it was implanted and decreased along time. Examining liver functions revealed safety of introduced treatments where no alterations were observed. Serum oxidative biomarkers were of normal range.

Conclusion: Pharmacokinetic evaluation proved similar pattern to in vitro model and achieved sustained delivery over long period of time reached 45 days. However,

pharmacodynamics showed ineffectiveness in pain management due to sensitizing effect, an unprecedented observation. Other release models should be investigated.

Convection Enhanced Delivery of EGFR Targeted ADCs for Treatment of Glioblastoma

Jann N. Sarkaria, Kendra A. Porath, Michael S. Regan, Jessica I. Griffith, Sonia Jain, Sylwia A. Stopka, Danielle M. Burgenske, Nathalie Y. R. Agar, and William F. Elmquist

Background: EGFR targeting antibody-drug conjugates (ADCs) are highly effective against EGFR-amplified tumors, but poor distribution across the blood brain barrier (BBB) limits their efficacy in glioblastoma (GBM) when administered systemically. We studied whether convection enhanced delivery (CED) can be used to safely infuse these ADCs into orthotopic patient-derived xenograft (PDX) models of EGFR-amplified GBM.

Methods: The efficacy of depatuzumab mafodotin (Depatux-M) and Serclutamab talirine (Ser-T) was evaluated in vitro and in vivo. CED was performed in non-tumor and tumor-bearing mice following stereotactic catheter placement. Immunostaining was used to evaluate ADC distribution, pharmacodynamic effects, and normal cell toxicity.

Results: Dose-finding studies in orthotopic GBM6 identified single infusion of 2 μg Ser-T and 60 μg Depatux-M as safe and effective associated with extended survival prolongation (>300 days and 95 days, respectively). However, with serial infusions every 21 days, four Ser-T doses controlled tumor growth but was associated with lethal toxicity approximately 7 days after the final infusion. Limiting dosing to two infusions in GBM108 provided profound median survival extension of over 200 days. In contrast, four Depatux-M CED doses were well tolerated and significantly extended survival in both GBM6 (158 days) and GBM108 (310 days). In a toxicity analysis, Ser-T resulted in a profound loss in NeuN+ cells and markedly elevated GFAP staining, while Depatux-M was associated only with modest elevation in GFAP staining.

Conclusion: CED of Depatux-M is well tolerated and results in extended survival in orthotopic GBM PDXs. In contrast, CED of Ser-T was associated with a much narrower therapeutic window.

A bone remodeling model governed by cellular micromechanics and physiologically based pharmacokinetics

Miguel Tobias Bahia,

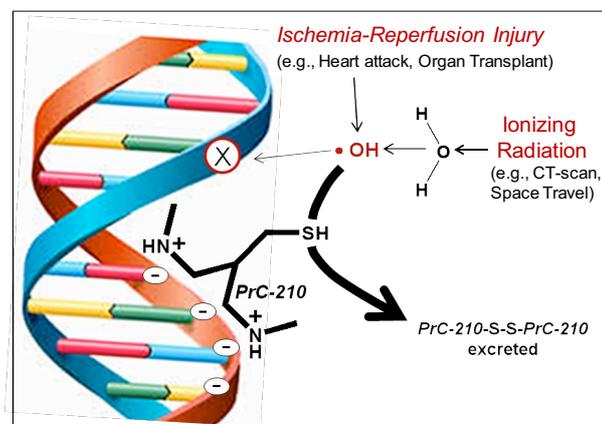
This study describes a mathematical model for bone remodeling that integrates the bone cells activities with the pharmacological dynamics for bone-seeking agents. The evolution of bone cells population involves the osteoblast-osteoclast signaling mediated by biochemical factors and receives both mechanical stimuli evaluated at the microscale and pharmacological regulation. A physiologically based pharmacokinetic model (PBPK) for bone-seeking agents was developed to provide the drug concentration on bone sites and feed the remodeling algorithm. The drug effect on bone was reproduced coupling three different strategies: modification of the RANKL expression, increase the osteoclast apoptosis and change in the rate of differentiation of preosteoblasts. Computational

simulations were performed in the PBPK model considering different dosing regimens. A 3D finite element model of a proximal femur was generated and the simulations of the bone remodeling algorithm were implemented in Matlab. The results indicate that the proposed integrated model is able to capture adequately the expected adaptive behavior of bone subjected to mechanical and pharmacological stimulus. The model demonstrated to have potential for use as a platform to investigate therapies and may help in the study of new drugs for bone diseases.

Suppression of Free Radical-Induced Radiation and Ischemia-Reperfusion Organ Damage Using the New PrC-210 Aminothiol Free Radical Scavenger

William Fahl

We designed and synthesized a new, immediate-acting, aminothiol, free radical scavenger, PrC-210. PrC-210 could potentially be used in more than 200 medical indications where oxygen free radicals generated by ischemic reperfusion injury or radiation exposure are the underlying cause. Many of these medical indications have no current medical treatment, and due to high mortality and enormous medical costs, there is a high medical need to find a treatment option; PrC-210 could become a viable treatment option for these diseases. PrC-210, an aminothiol, generates a protective envelope around DNA, proteins and lipids and thereby protects them from oxidation. PrC-210 captures Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) and eliminates them from mitochondria, nucleus and cytoplasm spaces. Two broad areas of human use include:



1. *Radiation Protection*: Increasing risks of radiological and nuclear accidents, such as Chernobyl and Fukushima, terrorist attacks, or a nuclear weapon are driving interest in developing radiation countermeasures to suppress injury from radiation exposure. There is no compound approved that is able to prevent Acute Radiation Syndrome when given ahead of a nuclear or radiation event, and compounds administered after radiation exposure have little efficacy. In rodent radioprotection studies, PrC-210 showed 100% survival in mice that received an otherwise 100% lethal dose of whole-body radiation (8.75 Gy) when administered ORALLY or by IP injection.

2. *Organ Transplant*: In rodent kidney and limb transplant studies, organ injury and damage from "cold-ischemia" (during storage) and "ischemia-reperfusion" (upon organ implant) are unavoidable consequences of kidney and limb transplants, and they are associated with a high rate of organ failure and patient mortality. The short-term clinical correlate of this damage, which is seen in up to 50% of human kidney transplant patients, is defined as "Delayed Graft Function (DGF)". Patients with Delayed Graft Function need dialysis during the first week after kidney transplantation to stabilize their kidney function. Delayed Graft Function is correlated with reduced organ survival and increased mortality of the organ

recipient. PrC-210 has been shown in animal experiments to suppress apoptosis in transplanted kidneys to the background level seen in untreated kidneys.

Parallel clinical development paths to enable PrC-210 use as both a human radioprotector and as a means to suppress organ transplant failure are being pursued by Obvia Pharmaceuticals, Ltd. (www.obviapharmaceuticals.com).

No Association Between Pharmacogenomics Variants and Hospital and Emergency Department Utilization: A Mayo Clinic Biobank Retrospective Study

Paul Y Takahashi

Background:

Pharmacogenomics is an important tool for clinical medicine. The application of pharmacogenomics in primary care has significant potential; however, it has some implementation challenges. The objective of this talk will be to discuss the potential advantages and challenges for pharmacogenomics in primary care. We will discuss strategies for implementation of pharmacogenomics including reactive and pre-emptive approaches. We will discuss in detail the RIGHT 10K study from Mayo Clinic which implemented pre-emptive pharmacogenomics in a primary care practice. We will discuss some of the primary findings from the study as well as other initiatives. For implementation, we will discuss some of the barriers faced including educational efforts, provider attitudes and some bioethical aspects of the pharmacogenomics. This talk will also broadly talk about other efforts to expand the evidence base for pharmacogenomics in practice. There will be an emphasis on use of pharmacogenomics for specific disease states.

Learning Objectives:

By the end of the session, all learners will be able to

- Discuss the common uses of pharmacogenomics in clinical practice
- Explain the inherent challenges that many in clinical practice face with pharmacogenomics
- Outline the use of risk prediction with pharmacogenomics in different models.

Novel HIV-1 fusion inhibitors targeting the membrane-proximal external region of Env spike **Tianshu Xiao**

Combination antiretroviral therapy (cART) has transformed HIV-1 infection, once a fatal illness, into a manageable chronic condition. Drug resistance, severe side effects and treatment noncompliance bring challenges to the cART implementation in clinical settings and indicate the need for additional molecular targets. Here we have identified several small-molecule fusion inhibitors, guided by a neutralizing antibody, against an extensively studied vaccine target- the membrane proximal external region (MPER) of HIV-1 envelope (Env) spike. These compounds specifically inhibit the Env-mediated membrane fusion by

blocking CD4-induced conformational changes. An NMR structure of one compound complexed with a trimeric MPER construct reveals that the compound partially inserts into a hydrophobic pocket formed exclusively by the MPER residues, thereby stabilizing its prefusion conformation. These results suggest that the MPER is a potential therapeutic target for developing fusion inhibitors and that strategies employing an antibody-guided search for novel therapeutics may be applied to other human diseases.

Methodical process digitization: The process-driven approach (PDA) in its application to the pharmaceutical sector

Simon Huff

The phenomenon of process digitization according to the PDA (Process Driven Approach) method plays a prominent role in all areas of human life in times of progressive digitization. Methodical process digitization based on the BPMN (Business Process Model and Notation) language and the most extensive automation of human work, leads to an increase in work productivity and a simultaneous reduction in CO₂ emissions in the newly designed and now IT-supported executable processes. The goal of this paper is to apply the PDA, which is globally applicable to any process, in the context of the pharmaceutical field and to present process-driven applications and platforms that have the potential to develop and also execute more sustainable and efficient processes in this field. By adding modern information technologies (e.g. process management systems, service-oriented architectures and cloud computing), innovative and globally competitive interactive application systems are created, that can be part of a new economic network (process app store).

During the project work, I have once again dealt more intensively with the conference and the topics covered there. I noticed that almost exclusively medical fields (cardiology, dermatology, etc.) were covered. To be on the safe side, I wanted to inform you that we are not medical doctors, so we do not have any exclusive knowledge in the field of medicine per se and cannot show any innovative research here. Rather, we operate in the field of software engineering and information technology. Although our contribution relates to the pharmaceutical field, the focus is clearly on the Process Driven Approach rather than on the medical topic.

An Overview of Bayesian Inference for Clinical Trials

Stephen J. Ruberg, PhD

The scientific and medical community has long embraced the use of Null Hypothesis Significance Testing (NHST) and the resulting p-values for assessing the significance of findings in research. The practice of NHST and the use of p-values has persisted despite their misuse, misinterpretation, and subsequent misunderstanding about the interpretation of scientific results. In response to these misgivings about p-values and to the ongoing concerns about the lack of reproducibility of scientific results, the American Statistical Association has written a consensus statement on p-values, organized a symposium on the

topic and published a special issue of *The American Statistician* containing 39 articles debating the use and interpretation of p-values.

Many in the statistical community prefer a Bayesian approach to statistical inference and to evaluating the veracity of a scientific hypothesis. While many have perhaps heard of Bayesian Statistics, few have a thorough understanding of how it differs from NHST/p-values (known as the Frequentist approach to inference). This talk will (a) review the fundamental difference between Bayesian and Frequentist inference, (b) show Bayesian inference is important in clinical trials (particularly related to drug development), and (c) make some recommendations for its use to improve our scientific understanding and interpretation of clinical trial results.

Point-of-care and utility in clinical trials: making quicker decisions to transform patient care and drug development

Sally Fischer

The increasing focus on personalized healthcare and patient convenience has placed greater emphasis on technologies with fast turnaround times (Point of Care) as well as technologies that enable home sampling, reducing the burden of visits to the clinic. Although Point of Care (POC) technologies have been around for years, their use has been limited to diagnostics purposes and has not been used as a tool for drug development. POC technologies have made great progress in the last decade and can provide near real time results with reliable precision and accuracy comparable with central labs. So appropriate technologies are available and can be used as tools for drug development. These technologies can provide immediate actionable results that have the potential to positively impact patient care and clinical trial timelines. Convenient home or microsampling technologies are also available that can improve patient convenience and participation, leading to faster clinical trial enrollment. Furthermore, these technologies can enable development of medicines for neonates and young children (<2 years of age), help with collecting samples from vulnerable populations, and increase diversity in clinical trials by making trials more accessible through reduction in clinic visits. Another area that has not yet been fully explored, is leveraging these technologies to increase our understanding of disease biology by providing longitudinal sampling and biomarker data during episodic diseases where patient sampling may not be possible without the availability of home sampling. The good news is that appropriate technologies are available and improving every day to address a clear need in patient care. The challenge is their uptake and implementation into our current healthcare and established clinical trial models. This talk will provide several case studies to illustrate the capabilities of these promising technologies

Using cyclopeptidic prodrugs for targeting proteases in prostate cancer

Norbert Lange

Cyclopeptidic chemotherapeutic prodrugs (cPCPs) are macromolecular protease-sensitive drugs synthesized from a cyclodecapeptidic scaffold, termed Regioselectively Addressable Functionalized Template (RAFT). In order to increase the chemotherapeutic potential of anticancer agents and limit their toxicity, we used a Cathepsin B (Cat B) and urokinase like

protein activator (uPA)- sensitive prodrug concept for its targeted release since these enzymes are frequently overexpressed in cancer cells. Copper-free "click" chemistry was used to synthesize cPCPs containing up to up to four anticancer moieties tethered to the upper face of the scaffold through a Cat B or uPA-cleavable peptidic linker. On the lower part, PEG 5, 10, 20 kDa and a fifth peptidyl DOX moiety were grafted in order to improve solubility, bioavailability and pharmacokinetic profiles of the compound. In vitro results on different human cell lines showed that cPCPs display a delayed action that consists of cell cycle arrest in G2 phase comparable to DOX alone, and increased cell membrane permeability.

Albumin as a biomarker of ocular insult: The blood-tear barrier breakdown from a clinical and pharmacological perspective

Lionel Sebbag

1. Regardless of the underlying etiology, ocular disease results in a key (yet poorly described) physiological phenomenon on the ocular surface: the breakdown of the blood-tear barrier.
2. Through vascular permeability and disruption of epithelial tight junctions, breakdown of the blood-tear barrier allows for plasma compounds (eg., proteins, xenobiotics) to diffuse at high levels into the tear compartment.
3. Albumin concentration in tears is generally low in healthy state but increases substantially in diseased eyes, as shown in dogs, humans, and other species. Increased albumin in tears has serious consequences on drug bioavailability, as any portion of drug that binds to albumin can be considered as 'lost' from a pharmacological standpoint. Clinical implications are broad, including:
 - Reduced bioavailability for intraocular targets: The inability of protein-bound drugs to penetrate the cornea lowers the amount of drug available inside the eye to exert its pharmacological action. This phenomenon was recently demonstrated for medically-relevant topical drugs in dogs (REF).
 - Reduced bacterial susceptibility to topical antibiotics: Albumin in tears reduces the efficacy of ophthalmic antibiotics as only the unbound portion of an antibiotic is microbiologically active. In one experiment conducted by our research group, albumin increased minimal inhibitory concentrations in a dose-dependent, bacteria-specific, and antibiotic-specific manner.
4. Systemically administered drugs can reach the ocular surface by active secretion from the lacrimal gland, or passive diffusion through the conjunctival vessels. The latter is enhanced when the blood-tear barrier is disrupted -allowing for selected systemic medications to treat ocular surface diseases - although the degree of drug diffusion varies given different physico-chemical properties.
5. Given the importance of the blood-tear barrier, our research group has recently established a robust in vivo model in dogs (histamine-induced conjunctivitis), a translational model that provides a unique opportunity for scientists to investigate the ocular surface in health and disease states.

Clinical Pharmacology and Safety of Trifarotene, a First-in-Class RAR gamma-selective Topical Retinoid

Nathalie Wagner

Trifarotene is a new drug with retinoic acid receptor activity and selectivity for retinoic acid receptor-gamma. Trifarotene 50 µg/g cream is approved for the treatment of acne vulgaris on the face and/or trunk in adult and adolescent patients. The clinical pharmacology program aimed at assessing the clinical pharmacology and safety of trifarotene. Systemic exposure to topically applied trifarotene up to 100 µg/g was investigated through 4 clinical studies: 2 studies were maximal usage pharmacokinetic trials (MUsT) conducted in subjects with moderate to severe acne vulgaris. The 2 other studies were conducted in healthy volunteers: 1 clinical drug-drug interaction (DDI) study and 1 thorough QTC study to assess the potential for cardiac repolarization delays. Considering the pharmacologic class of trifarotene and the class-associated potential teratogenicity, and because trifarotene is intended to be used by women of childbearing potential, a DDI study was conducted to assess the potential trifarotene effects on contraceptive steroids. Safety assessments included adverse event reporting and assessment of erythema, scaling, dryness, and stinging/burning using a scale from 0 = none to 4 = severe, as well as the evaluation of the systemic safety of trifarotene through routine laboratory testing. Systemic absorption of trifarotene 50 µg/g cream was generally unquantifiable in adults and adolescent patients with acne vulgaris, including patients with severe acne. Daily use of trifarotene was not associated with cardiovascular effects and did not reduce the systemic exposure to oral contraceptives such as levonorgestrel or ethinyl estradiol. Safety analyses did not show local or systemic safety concerns with trifarotene up 100 µg/g, a dose twice as high as the marketed dose. The present pharmacology studies confirmed that trifarotene 50 µg/g cream is well tolerated and safe, even when applied under maximized conditions in adults and adolescent patients with acne vulgaris.

In situ rheological testing of soft gel materials for pharmaceutical application**Univ.-Prof. Dr. Natalie Germann**

Soft capsules based on gelatin and other hydrocolloidal materials have attracted considerable interest in recent years in the field of pharmaceuticals and dietary supplements. They allow liquid and semi-solid fillings, are convenient single-dose forms, and have the advantage of being easy to swallow. Of great importance to capsule design is the significance of the complex interrelationship between capsule composition, manufacturing process, and release kinetics after pharmaceutical application. In this keynote, I will provide an overview of my advanced rheological tools for uncovering these aspects that are critical to developing soft capsules with tailored release kinetics. Using a custom-built experimental setup, it is now possible to study gelation kinetics under the conditions encountered during manufacturing. The same setup can also be used to study dynamic changes in capsule materials and drug release from capsules in the presence of enzymes, acidic pH or gastric juice. In the future, the setup will be optimized with a large number of holes and automated injections and combined with Raman spectroscopy for in situ chemical monitoring during rheological testing.

Concordance assessment of self-reported medication use with prescription data: the PharmLines initiative**Eelko Hak**

Background: In pharmaco-epidemiological study designs, self-reported questionnaire data are frequently the source of drug information. However, such information can be biased and accuracy may be modified by patient characteristics.

Objective: As part of the PharmLines Initiative, we assessed the concordance of self-reported drug use at entry to the Lifelines Cohort Study, a Dutch three-generation follow-up study that started in 2006 and included over 167,000 participants.

Materials and methods: All drug information reported by Lifelines participants were encoded using the Anatomical Therapeutic Chemical (ATC) coding scheme and linked to the prescription data of a representative pharmacy prescription database of the University of Groningen, IADB.nl. We conducted analyses at second level of ATC coding and estimated Cohen's kappa to measure the concordance for all Lifelines participants, and according to sex and age.

Results: Concordance levels between the two data sources largely differed according to the therapeutic class. Information on drugs for the cardiovascular system and diabetes, thyroid therapy, bisphosphonates and anti-thrombotic drugs showed a very good agreement ($\kappa > 0.75$). Medication as needed or prone to stigmatization bias showed a moderate agreement ($\kappa = 0.41-0.60$), whereas medications used for short a period of time showed a fair agreement ($\kappa = 0.0-0.4$). Concordance was similar for males and females, but younger adults tended to have lower concordance rates than older adults.

Conclusion: Self-reported questionnaire data appeared valid for capturing prevalent chronic drug use in a fixed period of time, but invalid for certain drug classes and short-term drug use. Sex differences were not observed and the influence of age was varying. The PharmLines initiative that started in 2019 enables optimization of accuracy on drug use information by a combination of self-reported and prescription data.

The Upper Nasal Space: An efficient route for systemic drug delivery Shrewsbury SB, Hoekman J.

One of the challenges in drug development is the limitations of today's administration systems. Oral delivery remains popular but variable absorption caused by gastrointestinal (GI) comorbidities or dysmotility, exaggerated by the underlying condition affect blood levels. Delay in gastric emptying, solubility or absorption limitations, and first pass effects can also reduce the systemic level of orally dosed drugs. Healthcare practitioners are required for intravenous (IV) administration (100% bioavailable) – the pharmacokinetic “gold standard”. Intramuscular (IM) and subcutaneous (SC) injection cause discomfort and risks needlestick injury while also providing variable bioavailability and delayed systemic levels.

More recently systemic delivery of drugs via the airways has become increasingly investigated, but delivery to the lung is technically challenging requiring in some cases drug formulated in propellant, and consistent, reproducible delivery of a “respirable fraction” to the alveolae. Nasal delivery has been predominantly reserved for topical nasal treatment and its use for systemic drug delivery has been limited by lack of advancements in delivery technology. Traditional nasal sprays tend to deliver a cloud of drug particles to the lower nasal space providing unreliable drug absorption and reports of bad taste.

Impel NeuroPharma has investigated delivery to the previously underutilized upper nasal space by the Precision Olfactory Delivery (POD[®]) system, which gently pushes a focused

plume of drug through the nasal valve to deposit on the vascular olfactory epithelium of the upper nasal space.

SNAP101 was a phase 1 PK and safety study comparing INP105 (POD-Olanzapine (OLZ)) to placebo and OLZ IM injections or OLZ orally disintegrating tablet. INP105 provided faster time (T_{max}) to similar maximum plasma OLZ concentration (C_{max}) than IM injection with a favorable safety profile at the same 5 mg OLZ dose.

STOP101 was a phase 1 PK and safety study comparing INP104 (POD-Dihydroergotamine (DHE)) to IV DHE and traditional nasal spray (Migranal[®]). INP104 provided systemic levels matching IV administration by 30 minutes, and faster T_{max} at 0.5 hours, compared to Migranal at 0.78 hours; 434% of C_{max} , and 285% of Area Under Curve (AUC), with less variability. POD delivery was well tolerated in this, and the 360-patient STOP 301 Phase 3 study and is now approved in the US.

Clinical programs with POD delivery of powder OLZ (a second-generation antipsychotic for the treatment of agitation) and liquid DHE (for the acute treatment of episodic migraine) to the upper nasal space have shown beneficial PK profiles and good tolerability.

PUBLIC HEALTH

Public health effects of vector-borne disease

Fadime Eroglu

Vector is defined as arthropods that transmit an infectious pathogen from an infected human or animal host to an uninfected human. The major global vector-borne diseases are malaria, leishmaniasis, trypanosomiasis, schistosomiasis, lyme disease, tick-borne encephalitis and west nile fever according to the World Health Organization. Although these vector-borne diseases account for 17% of all infections worldwide, they are included in the neglected tropical diseases. The epidemiology of vector-borne diseases is affected by interactions between vector, reservoir, host, and environmental factors. Most vector-borne pathogens are zoonotic and their potential for transmission by travel is high. Vector-borne diseases have re-emergence in many countries due to factors such as environmental factors and travels. The aim of the study is to provide information about the current changes in the epidemiology of vector-borne diseases and their effects on public health.

Anopheles mosquitoes are vector for malaria parasite Plasmodium while Aedes mosquitoes are vector for viral diseases such as dengue fever, zika, chikungunya and yellow fever. Malaria has been a major public health hazard for years and 200 million malaria cases have been reported in the world in 2018 years old. On the other hand, dengue fever was reported in only 9 countries in 1970 while more than 100 countries reported dengue fever in 2019. Tick-borne diseases one of the vector-borne diseases have increased in recent years. In the US, well over 600,000 human cases of vector-borne disease were reported during 2004-2016 with tick-borne. Leishmaniasis is an important vector-borne disease and it has been reported to be cutaneous leishmaniasis endemic in 92 countries and visceral leishmaniasis in 83 countries. According to the current data of the World Health Organization, an estimated 30,000 new cases of visceral leishmaniasis and more than 1 million new cases of cutaneous leishmaniasis occur annually.

Vector-borne diseases have been fatal to many people of all age groups in worldwide. Obtaining basic knowledge about the vector-pathogen-host relationship helps

to understand the spread of outbreaks and is useful for public health planning. Effective and sustainable vector control, including insecticide and non-insecticide based approaches, is needed to prevent vector-borne disease. In addition, new vaccines and drugs are needed to protect public health from vector-borne diseases.

Keywords: Vector-borne disease, Public health, Epidemiology

PULMONOLOGY

SPHK2-Generated S1P in CD11b+ Macrophages Blocks STING to Suppress the Inflammatory Function of Alveolar Macrophages

Dolly Mehta

Macrophages are the most abundant immune cells in many tissues, including the lung and have the vital task of restoring tissue homeostasis after triggering inflammatory signaling. Upon sensing pathogens, alveolar macrophages (AM), trigger host-defense through pro-inflammatory cytokine generation and neutrophil recruitment via a pathway involving activation of the transcription factor NF- κ B and by cell-surface Toll-like receptor 4 (TLR4) in the lungs. Additionally, STING (stimulator of interferon genes), a transmembrane homodimer located in the ER (endoplasmic reticulum) membrane, has emerged as a potent inducer of macrophage inflammatory signaling following tissue injury. Suppression of inflammatory signaling pathway by macrophages in a timely manner is critical for reinstatement of tissue-homeostasis. Impairment of this homeostasis leads to acute lung injury (ALI) due to the accumulation of protein-rich fluid and leukocytes in the alveolar space. Recent studies also indicate that the monocytes may replenish AM pool following lung injury. However, the mechanisms instructing reparative AM generation that rescue lung homeostasis remain elusive. Sphingosine 1 phosphate (S1P) and cyclic AMP (cAMP) are two well-known agents that repair lung barriers. We have demonstrated that monocyte derived M ϕ (CD11b+ M ϕ) recruited into the airspace upregulates AM ϕ anti-inflammatory function by suppressing their stimulator of type 1 interferon genes (STING) signaling. Recently, we have also shown that phosphodiesterase 4b (PDE4b) as the top LPS-responsive cAMP-regulating gene. Inhibition of PDE4 activity at the time of peak injury, using i.t. rolipram, increased cAMP levels, augmented the reparative AM ϕ pool, and resolved lung injury. In this talk I will summarize these findings as we believe understanding of these pathways will provide targets to promote reparative AM ϕ generation for lung repair.

Interventional Immunology in Early Life Diseases – Advancing Interleukin-1 Receptor antagonist to Prevent Inflammatory Disease in Preterm Infants.

Claudia Nold

Every year preterm birth exposes 15 million infants worldwide (WHO) to serious early life diseases. Fortunately, nowadays preterm infants with a gestational age (GA) as low as 22 weeks survive. Sadly, improved survival of preterm infants has come with a rising incidence of early life cardiovascular diseases with dire short- and long-term consequences. Bronchopulmonary dysplasia (BPD) is a severe inflammatory chronic lung disease, with an incidence of 35-68%. Pulmonary hypertension secondary to BPD (BPD-PH) occurs in 15-30% of BPD patients and is the most severe complication of BPD. BPD-PH and BPD all are inversely related to GA and birth weight and share common risk factors, all of which lead to

inflammation and underpin their pathophysiology. Inflammation is now accepted as the common pathogenetic pathway and thus the main culprit. This deranged cardiopulmonary physiology adversely impacts neurodevelopmental outcomes. For BPD systemic corticosteroids, primarily dexamethasone, are among the few anti-inflammatory drugs in clinical use but are associated with serious adverse effects and are therefore reserved as a rescue therapy. As a result, a safe and reliable therapy has yet to be found.

Preclinical studies by us and others have shown that blocking such inflammation, specifically the potent proinflammatory interleukin 1 (IL-1), early and effectively, holds great promise for preventing BPD and BPD-PH. Blocking IL-1's deleterious activities, using its endogenous IL-1 receptor antagonist (IL-1Ra, drug name anakinra) is a strategy with an excellent safety and efficacy record, which has been established via anakinra's clinical use in paediatric and adult medicine for 2 decades. In our preclinical program, which preceded our IL-1Ra clinical trial in preterm infants we tested IL-1Ra in a newborn mouse model of BPD and BPD-PH. The placebo group suffered from severe perinatal inflammation with consecutive BPD and BPD-PH, whereas the IL-1Ra-treated mice were nearly identical to healthy controls. Further pre-clinical studies determined optimal dosage and timing for IL-1Ra and proved that IL-1Ra also protects mice from BPD-PH and altered airway reactivity. Most important for translation of our findings, we demonstrated that early commencement of treatment is essential for efficacy.

Based on the success of our pre-clinical program we started an investigator-initiated Phase I/IIa clinical trial to pave the way to reposition IL-1Ra as a treatment for inflammatory early life diseases, including serious cardiovascular diseases, in preterm babies.

PSYCHOLOGY & PSYCHIATRY

New Herbal Treatment for depression and Anxiety Disorders with minimal side-effects

Ravid Doron, Motty Franko, Roni Toledano, Keren Nitzan, Moshe Rehavi

Anxiety and Depression disorders are prevalent and severe diseases with deleterious impacts on both patients and society. Selective serotonin reuptake inhibitors (SSRIs) were shown to be effective in treating a wide spectrum of anxiety and depression disorders. Despite their therapeutic actions, SSRIs are associated with a wide variety of side effects such as weight changes, insomnia, gastrointestinal disturbances, and sexual dysfunction. Furthermore, recent studies show that their success rates are not high, reaching 50% at most. Therefore, there is a clear need to explore alternative treatments for anxiety and depression disorders. We have recently produced a novel herbal mixture for the treatment of anxiety disorder. The novel treatment displayed anxiolytic and antidepressant-like effects in treated mice previously exposed to stress. The present study aimed to examine whether the novel treatment induces two common side effects normally induced by the conventional treatment with the SSRI escitalopram, namely, sexual dysfunction and weight gain. Mice were treated with either: (a) herbal treatment, (b) one of the four herbal components, (c) escitalopram; or (d) control group. Following treatment, sexual behavior and weight gain were evaluated in the different groups, as well as changes in prefrontal cortex serotonin transporter levels. We have found that the novel treatment has not altered sexual behavior and did not cause a weight gain, while escitalopram did lead to these two side effects. Interestingly, serotonin transporter levels in the prefrontal cortex of the escitalopram treated group was significantly lower compared to the other treatment groups. The BDNF level in the hippocampus increase after escitalopram and herbal treatment. These results

suggest that the novel treatment may have the same behavioral anxiolytic and antidepressant efficacy as SSRIs while causing fewer side effects, possibly due to different biological mechanisms. Further studies are now conducted in order to explore the underlying biological mechanisms through which the novel treatment leads to the behavioral anxiolytic and antidepressant effects.

Key words: SSRI, sexual behavior, herbal treatment, weight gain, mice

Bipolar Disorders, a Yet to Describe Thyroid Disease?

Andy Zamar

Bipolar disorders (BPS) are a highly prevalent range of conditions affecting 4.4% of the US population, with a global prevalence of some 2.4%. They carry a high mortality rate of up to 56%, predominantly due to early cardiovascular mortality, as well as suicide and accidents. The disability ratings of BPS exceed those all forms of cancer, heart disease and major neurological disorders. Bipolar disorders are characterised by mitochondrial dysfunction, which are postulate are most likely due to inefficient cerebral transport and/or activation of thyroid hormones in the brain. To review this hypothesis, we will discuss our findings of genetic mutations affecting Deiodinase1(DiO1, peripheral converting enzyme of T4 to T3) and Deiodinase 2 (DiO2, brain/ placental activating enzyme of T4/T3) and the SLCO1C1 cerebral protein transporter. We will also correlate these findings to treatment response with supra physiological doses of Levothyroxine combined with neuromodulation namely repetitive transcranial magnetic stimulation (rTMS). The intervention aims at targeting the inducing mitochondrial function in the brain, whilst benefiting from Deiodinase 3 enzyme activity to protect against peripheral side effects, via reverse T3 (rT3). A significant number of studies have shown that, as a population, these patients not only tolerate high doses of thyroid hormones with little or no side effects, but show sustained substantial improvement with a marked reduction in disability and morbidity. We will examine this concept in light of Evidence based medicine levels.

Rapid Evidence Assessment of Mental Health Outcomes of Pandemics for Health Care Workers: Implications of the COVID-19 pandemic

Susan Giles

Healthcare professionals often work in high-pressured and demanding environments. This can impact upon their mental health and coping strategies. In this presentation, I summarise findings from two reviews. First, a rapid evidence assessment (RAE) that examines what is currently known about short- and long-term mental health impacts of pandemics on health care workers (HCWs) Second, an international review aimed at determining the pooled prevalence of hazardous, harmful, dependent and frequent binge drinking in HCWs.

Study 1: - A RAE was conducted on 41 studies published in the past two decades. Literary synthesis highlights common MH outcomes across pandemics, including increased stress, distress, burnout and anxiety in the short term and post-traumatic stress and depression in the long term. Findings also show the key role that organisation and public health bodies play in promoting adaptive coping and reducing health worries and the emotional and psychological distress caused by this. Evidence highlights particular groups at risk of developing MH issues and time points where risk may increase. However, inconsistencies in measures, analysis and reporting all create limitations for pooling data.

Study 2: - A meta-analysis was conducted on 43 studies published 2003-2021. The pooled prevalence was 19.43% [95% CI: 14.23% - 25.11%] for hazardous alcohol use (K = 32), 14.04% [95% CI: 7.15% - 22.75%] for frequent binge drinking (K = 10), and 1.93% [95% CI: 0.07% - 3.59%] for harmful drinking (K = 5). Meta-regressions identified no study (year of data collection, geographical location) or participant characteristics (age, gender) that were associated with variance in prevalence estimates. Only two studies reported prevalence estimates in the context of the COVID-19 pandemic. The level of alcohol use observed in healthcare professionals is comparable to general population estimates.

Findings from study 1 can be used by researchers to provide a knowledge framework to inform future research that will assist HCWs in responding to pandemics and by policy makers and service planners to provide an evidence-led brief about direction and evidence base for related policy initiatives, interventions or service programmes. Further research is needed to determine the impact of the COVID-19 pandemic on healthcare professionals' alcohol use, to ensure that targeted support is provided.

Quality of life Among the Elderly: Understanding the Effect of Loneliness, Mobility, and Health Service Satisfaction

Shani Bachar-Avnieli

Background: The numbers of elderly are increasing globally, and the growth is expected to continue. As more people are living in their late years, ensuring the quality of life of the elderly has become an increasingly important focus.

Method: Four hundred and seventy-one participants, aged 60 and older in Israel, completed self-reported measures of loneliness, health service satisfaction, mobility and quality of life. Structural equation modeling was used to analyze data.

Results: Older adults' people who had a higher sense of loneliness reported lower quality of life. The results also showed that mobility health service satisfaction had a partial mediator role in the relationship between loneliness and life quality.

Conclusions: Loneliness, mobility and health service satisfaction were important factors related to low quality of life measures among older people in Israel. The findings indicate that reducing loneliness, improving mobility and health service may help to improve the quality of life for older people.

Key Words: Aging, Quality of life, Loneliness

RADIOLOGY

Lipids MS Imaging Differentiates bTBI and CCI Brain Injury and Validate Remedial Therapy.

Amina S Woods

Traumatic brain injury (TBI) is a serious public health problem and the leading cause of death in children and young adults. It also contributes to a substantial number of cases of permanent disability. As lipids make up over 50% of the brain mass and play a key role in both membrane structure and cell signaling, their profile is of particular interest. In this study, we show that advanced mass spectrometry imaging (MSI) has sufficient technical accuracy and reproducibility to demonstrate the anatomical distribution of 50 mm diameter microdomains that show changes in brain ceramide levels in a rat model of controlled cortical impact (CCI) 3 days post injury with and without treatment. Adult male Sprague-Dawley rats received one strike and were euthanized 3 days post trauma. Brain MS images

showed increase in ceramides in CCI animals compared to control as well as significant reduction in ceramides in CCI treated animals, demonstrating therapeutic effect of a peptide agonist. The data also suggests the presence of diffuse changes outside of the injured area. These results shed light on the extent of biochemical and structural changes in the brain after traumatic brain injury and could help to evaluate the efficacy of treatments.

REHABILITATION

EWGSOP and EWGSOP2 Prevalence of sarcopenia depending on Physical Performance Assessment Method

Sara Garcia Isidro

Introduction: Childhood overweight and obesity are a worldwide problem whose prevalence is increasing according to data from different studies. There are different methods to diagnose overweight and obesity in childhood, the most widely used being the body mass index (BMI) based on percentile graphs for the age of the children. There are several reference tables to establish emitters are the indicator parameters of overweight and obesity, without agreement on which graphs should be used. This disagreement must be resolved since there are great differences when diagnosing childhood overweight and obesity according to the reference growth chart. The objective is to establish the prevalence of obesity and overweight and concordance between the diagnostic tables for BMI and R-BMI in children and adolescents of the Community of Madrid

Methods: The subjects studied included children and adolescents from the Community of Madrid, Spain. BMI was calculated from weight and height measurements measured under standardized procedures. Additionally Relative-BMI was calculated and included in the analysis. Six international references (IOFT, WHO, Carrascosa and Orbegozo Foundation 1988, 2004 and 2011) were used as cut-off points for overweight and obesity. BMI and R-BMI results were categorized in order to calculate obesity and overweight prevalence. Kappa concordance tests were used to analyze agreement between means of diagnosis. Pearson chi-square was also used to relate dichotomous and categorical variables in a transversal analysis. In all cases, a $P < 0.05$ value and a 95% confidence interval were used for the degree of statistical significance.

Results: A total of 957 study subjects were obtained, with a mean age of 13.37 (1.07) years. The classification that found more subjects in normal weight and less obese was that of Carrascosa (96.87% of children in normal weight, 2.82% overweight and 0.31% obese). The one that found the most obese children was the Relative-BMI according to the WHO tables (62.9% of children in normal weight, 17.87% overweight and 19.23% obese). It was found that there was always a relationship between the Relative-BMI and its corresponding reference table ($p < 0.05$), however, a concordance between poor and slight was found between both classification methods ($K = 0.1-0.4$). Regarding the agreement between different percentile tables, It was between slight and very good in all cases ($k = 0.23-0.9$). When studying the concordance between the different Relative-BMI, kappa between 0.4 and 0.87 was found (agreement between low and very good).

Conclusions: The prevalence of obesity according to percentile tables ranges between 3.66% and 0.31%, and that of overweight between 2.82% and 8.05%. The prevalence of obesity between relative-BMI ranges between 9.3% and 19.23%, and that of overweight between 10.66% and 17.87%. The tables that offered the most agreement for BMI were those of Orbegozo 2011 and IOFT2000. For R-BMI the best agreement was between

Carrascosa and IOFT 2000, and Orbegozo 2004, and Orbegozo 2011. There is a low concordance between IMCR and percentile tables

Smartphone-Based Clinical Outcome Measures for Evaluating Functional Changes in Lower Limb Amputees

Vibhor Agrawal

Unilateral lower limb amputees show subtle variations in movement kinetics and kinematics during the rehabilitation process. These variations can be detected using laboratory-based equipment, which are expensive and are not feasible for clinical use. This presentation will discuss two smartphone-based Applications (Apps) for assessing movement kinetics and kinematics in a clinical setting, i.e. S.E.W (Symmetry of External Work) and G.A.I.T (Gait Assessment and Intervention Toolbox) respectively.

The S.E.W App is based on the SEW measure and assesses the kinetic symmetry between the non-amputated limb and the prosthetic limb. SEW values between the two limbs are calculated by integrating vertical ground reaction forces (or center of mass acceleration) from each limb and determining percentage of symmetry between them. The SEW measure is a reliable and valid measure for assessing amputee movement kinetics and is correlated with selected clinical measures. Its test-retest reliability ranges from 0.84-0.94 for the functional activities of level walking, incline walking, decline walking, ascending stairs, descending stairs, sit-to-stand and stand-to-sit. There is good to excellent correlation between the SEW values for level walking and other clinical outcome measures. SEW values are also sensitive to the variations in the designs of prosthetic feet. The S.E.W App is a thus viable method for detecting kinetic differences in lower limb amputees and represents a resource-effective alternative to traditional gait laboratories and expensive equipment.

The G.A.I.T. App can assist clinicians in identifying kinematic differences through observational analysis. This App is perceived to be more useful than traditional (paper-based) methods of kinematic analyses, by a sample of clinicians and students. The App is also highly rated for "Ease of use" when compared to the traditional methods. The G.A.I.T. App thus has greater clinical efficacy and is more suitable for tele-health applications.

In conclusion, as healthcare transitions to online and virtual delivery methods, App based outcome measures are becoming a necessity in the clinics. The S.E.W. and G.A.I.T. Apps are not only viable methods for amputee rehabilitation but are also preferred by the tech savvy Millennials and Gen-Z generations, who are clinicians of the future.

Death and grief: A Complex Thought Point of View

Author: Luz Marina Cano M. MD.MsC. Ph.D.

The ultimate goal of Palliative Care is to alleviate the suffering of both the patient and his family, through the proper understanding, detection and control of physical, psychosocial and spiritual symptoms experienced by patients at the end of life, regardless of diagnosis. . But, while it is true that death is a natural phenomenon, the process of dying is treated as a disease, and today we are experiencing the medicalization of death. As a consequence, many people die in hospitals in the most extreme loneliness and pain. In other cases, service provision models have been dichotomized to the point of providing aggressive curative treatment and establishing palliative measures in the face of therapeutic failure. The consequence of this reality is that patients and families are left in the middle of an economic and social conflict, since they do not find a team that allows them to understand

the nature of the disease, the diagnosis and the prognosis, this being a crucial aspect for the decision making at the end of life. Total pain, conceived as the sum of physical pain, psychological pain and spiritual pain, constitutes one of the origins of suffering. The most relevant triggers in addition to physical pain are: the process of dying itself, loss of autonomy and resignification of life. The foregoing requires a transdisciplinary team with relevant training to intervene in these realities of patients and family members in palliation. Palliative patients need to develop a closure and forgiveness mechanism to die in peace.

As death approaches, symptoms require extreme palliative strategies. Likewise, as interventions intensify, service delivery processes must be strengthened. It should be clarified that care at the end of life does not end with the death of the patient, after which the efforts of the team in charge are oriented towards the family and the elaboration of grief.

The world that occurs in the framework of complexity, with a Western culture based on tradition and orthodox values, is at the gates of an Emerging Society with varied and new lifestyles, transformation of values and less universal visions. This turn brings with it new challenges and obstacles such as coexistence in divergent, multicultural settings, identity modification, marginalization and social, ethnic, religious, sexual, professional and academic exclusion (Tho, 2012).

The validation of complexity in biopsychosocial processes forces educational institutions to train new professionals with a high degree of comprehensiveness, with programs that allow reality to be constructed from multidimensionality, with clear and innovative ideas, objective judgments, assertive decisions, metacognitive skills with which can articulate the previous knowledge with the new one and understand the multiplicity in the unit (morin, 2000). This implies a wide-ranging reconstruction of the curricular structure.

On the other hand, the art of caring is an action whose destiny is the good of a human being and his family in a society. Although physicians dedicate much of their training and assistance to the reproduction and maintenance of life, the end of life is relegated to a few pain specialists and spiritual practices that allow patients and their families to accept and resign the death process. And it is precisely to the person, to the human being and his family to whom palliative care is directed, care at the end of life (Torralba, 2007).

The foregoing means that for an effective implementation, a deep knowledge of human reality is required, not only in its somatic or biological aspects, but of all the environmental, psychological, social and spiritual dimensions of the individual. Additionally, death constitutes one of the fundamental themes of philosophy, psychology and medicine. Questions about the meaning of death, its reason for being, and the other questions that arise around it, are a constant topic in human history. But beyond death, one of the most studied and least multidisciplinary intervened aspects is the meaning of suffering.

Caring for a human being means: accompanying him, being with him, ensuring his autonomy and assisting him in his vulnerability. Palliative Care is a specific way of applying this care. Likewise, from the transdisciplinary point of view that the work of caring for a patient can acquire, we can refer to the fact that it is about accompanying the human being in their process of illness and death. Here death not only becomes a problem, but life itself, therefore, it entails a series of bioethical and multidimensional issues.

When the human being lives in the vicinity of death, he feels and perceives it with greater impetus. He becomes aware of his radical and challenging character. Therefore, in the care of a person at the end of life, the perception of death must be considered very seriously,

since this perception, the sense or nonsense of it, is directly related to the person's state of mind dying. For this reason, before being with this class of patients, it is pertinent and responsible to theoretically confront one's own death, and that of close beings, in order to intervene around it.

This scenario is the engine of this research work. Within the course of life, we do not choose to die, but we have the fundamental right to decide how we will die. Therefore, a qualified team is required to provide comprehensive, loving and compassionate care at the end of life.

Responsibility and Compassion in Prehospital Support to Survivors of Suicide Victim - Professionals' Experiences

Christina Nilsson, Anders Bremer, Karin Blomberg, Mia Svantesson

Summary of introduction: Death is not only an ending: it is also a beginning for the survivors of the suicide victim. In order to improve the support for them, there is a need to understand the experiences of the involved professionals in the acute situation.

Aim: To describe experiences of facing and supporting survivors of suicide victim from the perspectives of Emergency Medical Services personnel, police officers and general practitioners.

Method: Six focus group discussions with Emergency Medical Services personnel, police officers and general practitioners. Data were analysed using content analysis.

Result: The Emergency Medical Services personnel, police officers and general practitioners described the situation as being characterised by feelings of inadequacy as they faced the survivors' emotional storm and despair. They made attempts to shield themselves and also the survivors. Focus was on the survivors, to give time, to be accessible and to find a person who could continue providing support. The professionals experienced a deep sense of uncertainty about their responsibility and feeling torn in their professional role and a frustration over lack of guidelines.

Conclusion: This complex situation involves not only the ethical conflict of 'should I stay or should I go', i.e., whether to take responsibility or not, but also each professional's capacity and courage to give both compassion and support.

Vaccines As an Alternate Treatment Agent for Opioid Use Disorder

Agnieszka Sulima, Oscar B. Torres, Rodell C. Barrientos, Essie Komla, Rashmi Jalah, Eric W. Bow, Joshua F. G. Antoline, Connor Whalen, Gregory H. Imler, Mariia Makarova, Alexander V. Mayorov, Jeffrey R. Deschamps, Zoltan Beck, Arthur E. Jacobson, Gary R. Matyas, Kenner C. Rice

Prescription opioids are powerful pain reducing medications used to treat variety of pain from acute to end-of-life care and many people rely on prescription opioids to manage their pain. However, opioids also produce a high level of positive reinforcement that can lead to dependence, addiction, overdose, and death. Opioid use disorder (OUD) is defined as a chronic use of opioids that causes significant impairment and it is a growing problem worldwide. It was declared an epidemic in the United States in 2017. Effective treatments for OUD are available, however, only a fraction of people with opioid use disorder receive adequate treatment. For this reason, the need for novel treatments for OUD is urgent and opioid vaccines may represent a clinically viable strategy. We developed an improved

synthesis of our lead heroin hapten, 6-AmHap, that incorporates a hydrolytically stable amide group at the C-6 position of the morphinan core and a linker at the C-3 position for conjugation to a carrier protein (tetanus toxoid, TT). We have also developed a fentanyl hapten, para-AmFenHap, that incorporates the intact fentanyl scaffold. Preclinical studies with anti-heroin and anti-fentanyl vaccines developed by our groups have demonstrated their efficacy. Immunization blocked heroin and fentanyl psychoactive effects and reduced heroin and fentanyl potency by ~4 and 8-fold, respectively. This talk will present these findings and discuss future directions.

Study Providing Normative Data of Objective Upper Extremity Strength Measured with a Handheld Dynamometer

Wanda VanHarlinger, OTT/L; John L. Merritt, MD

Background: Muscle strength is the most important predictor of function, mobility, independence in activities of daily activities and quality of life. Manual muscle testing systems, such as the modified

Kendall scale, are tools most used in clinical settings. But these scales provide only descriptive and cardinal, nor ordinal data. Such limitations impact their usefulness in objective and statistical assessments of the impact of muscle strengthening rehabilitation programs. However, tools are available that can provide objective, ordinal data for measuring key upper extremity muscle group strength. Here we provide an initial database for one such system, readily available in a clinical setting.

Method: Using the Nicholas Manual Muscle Tester (NMMT), muscle strength of 11 upper extremity muscle groups, right and left, were measured in 180 healthy subjects, 90 men, 90 women, 20-65 years old, using standardized methodologies. Data was recorded for each muscle

group bilaterally in each subject.

Results: Data confirmed some expected patterns: in all muscle groups men have significantly higher strength than women, and the dominant side is stronger in men and women. A potentially clinically relevant finding included a decline in shoulder external rotator strength with age in men.

Conclusion: This study provides a normative database for clinicians and researchers who evaluate injured or impaired patients and monitor their progress. Means, standard deviations, and ranges are categorized by age, gender and hand dominance. This research provides an initial database for this handheld system. There remains a need for further and expanded database studies, for this and other dynamometer systems.

Growing up & Growing Older with a Physical Impairment: The Paradox of Normalization through Rehabilitation

Laura R. Moll, MSW, RSW, Cheryl A. Cott, B.P.T., M.Sc., Ph.D.

The purpose of this presentation is to describe key findings from a study on growing up & growing older with a lifelong physical impairment. A qualitative methodology was utilized

consisting of narrative inquiry informed by the Life Course Perspective. The life course perspective is a dynamic approach that encompasses multiple theories including sociology, human development, and aging highlighting how social, historical, and cultural contexts shape peoples' lives. Narratives are storied ways of knowing and communicating that people use to organize events in their lives and make sense out of their experiences. Nine community-dwelling individuals (3 men; 6 women), aged 26-70, with mild to severe Cerebral Palsy were recruited using a combination of purposive and snowball sampling. Multiple (3-4), in-depth interviews were completed with each participant in order to co-construct their life stories. The data analysis was iterative. NVIVO 8 was used to organize the data supporting a systematic comparison of emerging themes and categories, as well as the central plot that weaves the participants' experiences together. "Normalization" emerged as a key recurring theme in the participants' life stories. The focus of rehabilitation on "normalizing" movement, particularly walking, during childhood can lead to social psychological challenges as well as problems later in the life course as people encounter increasing fatigue and decreasing functional abilities but no longer have access to rehabilitation services. The impact of attempts to normalize participants' physical performance throughout the rehabilitation process during childhood and adolescence on experience in adulthood will be highlighted.

Distal tibia peri-implant fracture with an intramedullary nail: a case report.

Johanna M. Reyes Cabrera

Peri-implant fractures after intramedullary nailing are rare. A case with distal tibia peri-implant fracture with an intramedullary nail is presented and the possible factors that influence in such result are analyzed. There have been published two cases in the world literature at the time of this publication associated with tibial fracture. However, a review article and a case series have been published since then and are taken into account in this presentation.

STEM CELLS

Epithelial Stem Cells, a Real Tool for Effective Regenerative Medicine Treatments

Graziella Pellegrini

Regenerative medicine has generated many efforts to explore new therapeutic potentials of both somatic and pluripotent stem cells with many possibilities envisaged for therapeutic applications. Hematopoietic and epithelial cells are extensively adopted for tissue regeneration, due to their high proliferative capacity and their accessibility. 30 years ago, the method for producing epidermis was discovered by cultivation from a small skin biopsy, allowing life-saving treatment of thousands severely burned patients in the following years. The importance of stem cell content was proven for tissues or organs in different pathologies. For instance, recent developments in cell-based therapy for ocular burns provided support for improvement and standardization of the cure for this disabling disease-causing depletion of limbal stem cells. Indeed, biopsies taken from the healthy eye, or other autologous source as oral mucosa in bilateral blindness, can be used for their content of stem cells. Few of these therapies overcame the hurdles related to medicinal product regulation and became available to patients.

The combined use of cell and gene therapy represents a further scientific approach for the treatment of congenital diseases. This approach was proven on hematopoietic cells and has

recently been established using genetically modified epidermal cells for life-saving treatment on severe genetic diseases, as epidermolysis bullosa.

Next Generation Stem Cells - Ushering in a New Era of Cell-Based Therapies

Erin Kimbrel

Pluripotent stem cells (PSCs) are a key starting material for the development of off-the-shelf cell-based therapies to help treat patients with high unmet medical need. The marriage of gene editing technologies with PSC technology is helping to create the next generation of engineered cell therapies that go above and beyond what naturally-occurring cells of a patient's body can do. Engineering can be used to help overcome issues with immunogenicity and rejection of allogeneic cell sources as well as endow cells with improved specificity, functionality, and responsiveness. Various examples of next generation PSC-based therapies in development will be discussed.

SURGERY

How technology can improve ophthalmologic surgical decisions

Ana Sofia Travassos

Surgical decisions must be based on objective data for the safety of the patients. It is possible to get images from most of intraocular structures, if cornea, aqueous and vitreous humor are translucent. Several exams can be used to program surgical procedures and to anticipate severe problems.

Removing an intraocular faquic lens (for correction of ametropia) before corneal decompensation can be decided based on endothelial cells counting with specular microscopy.

Prevention of a sudden angle closure crisis in a narrow iridocorneal angle (avoiding severe pain episode, loss of cornea transparency and damage of pupil diaphragm and optic nerve) is possible by measuring the angle with topography of the anterior chamber and anticipating the time of cataract surgery, to gain space in the anterior chamber.

Vitreomacular tractions and epiretinal membranes can be asymptomatic, but they can cause vision distortion if retinal external layers are damaged. Central vision can be lost if macular tractions develop a macular hole. Anticipating these problems with OCT tracking and OCTA allows the surgeon to decide the best opportunity to perform a vitrectomy and release these tractions.

Vascular diseases that can cause ischemia in the macula or in peripheral retina can be documented with 30 ° and 200° angiography , it can detect neovessels with higher risk of bleeding. Hemovitreous can be prevented with vitrectomy, removal of fibrovascular tissue and lasertherapy in ischemic areas. If ischemia is very severe, vitrectomy and panphotocoagulation with laser can reduce significantly the risk of neovascular glaucoma.

Asymptomatic retinal tears, with or without peripheral retina detachment, can be found in 200° retinography. Vitrectomy, with gas tamponade in case of detachment, can prevent central vision loss.

Serous macular detachment associated with optic nerve pit can be treated with a new technique. After vitrectomy a scleral plug was used to tamponade the hole in the optic nerve, without a foreign body reaction and with a good resolution of the serous detachment.

It is possible to decide the best procedure for each patient after analyzing information from different exams, with much better functional results.

Endoscopic Extrabursal Excision of Olecranon Spur

Vikas Singh

Olecranon spur is a common underlying clinical problem with inflammatory conditions such as triceps tendonitis, olecranon bursitis and gout which may also be associated or occur in isolation with chronic repetitive elbow strain reflective of occupation, strength training and/or sporting involvements. It is often managed non-operatively. Conventionally, symptomatic olecranon spurs that have failed the non-operative management are excised along with the overlying bursa using an open surgical technique. We describe an endoscopic extrabursal technique, where the spur is dissected out and excised in its entirety under endoscopic vision. Using this technique, a satisfactory view is achieved with less morbidity compared with the open excision; it also avoids a wound on the sensitive skin over the olecranon process.

Total Hip Arthroplasty "The Operation of Century": How Far We Have Come, Where We Stand, and Where We Need to Go

Rupesh Tarwala

The treatment of hip arthritis has evolved from rudimentary surgery to modern total hip arthroplasty (THA) over the past three centuries. Initial treatment included excision arthroplasty, which developed into interpositional arthroplasty and further advanced into a prosthetic replacement in the 1900s. Sir John Charnley introduced low-friction total hip arthroplasty in the 1960s. Since then, researchers and clinicians have worked endlessly towards advancing the THA in terms of bearing surfaces, implant designs, and surgical technique, which has improved implant survival, wear resistance, mechanical stability, and clinical outcomes. THA is considered one of the most successful surgical interventions ever developed and is named an "operation of century." It provides highly satisfactory results and restores the quality of life of patients crippled with end-stage hip arthritis. This review aims to focus on the evolution history of THA, current trends and techniques, and future directions to improve this procedure further.

Keywords: Total hip arthroplasty or replacement, implant design, bearing surfaces, surgical techniques

Surgeon-Performed Ultrasound for Primary Hyperparathyroidism

Schenk WG MD, Smith PW MD, Hanks, JB MD

The role of pre-operative parathyroid imaging in the US continues to evolve. The accepted surgical approaches to nonfamilial primary hyperparathyroidism (1°HPTH) in the US is *either* four gland exploration or image-guided adenoma excision. With the image-guided approach the standard in the US is two concordant imaging studies. This study evaluated whether surgeon-performed ultrasound (U/S) obviates the need for other imaging studies and leads to a focused excision with a high degree of surgical success. From July 2010 to February 2012, 200 patients presenting with (1°HPTH) underwent neck U/S in the surgeon's office. The U/S interpretation was classified as Class 1 if an adenoma was identified with high confidence, Class 2 if a possible, but not definite, enlarged gland was imaged, and

Class 0 (zero) if no adenoma was identified. The findings were correlated with subsequent intraoperative findings. There were 144 class 1 U/S's (72 %); Of 132 patients electing surgery, 131 of 132 (96.2%) had surgical findings concordant with pre-op U/S and all had apparent surgical cure. 29 patients (14.5%) had Class 2 U/S; 20 of 29 had concordant findings on dynamically enhanced CT scan (4DCT) and all had concordant findings at surgery. Most of the 9 false positives were colloid nodules. 14/27 with Class 0 U/S underwent surgery after an adenoma was identified on 4DCT. All 166 of the 200 patients consenting to surgery were apparent cures after a minimum ten year follow-up. Surgeon-performed U/S is expedient, convenient, inexpensive, and accurate. A clearly identified adenoma can safely lead to a focused limited excision without additional imaging 72% of the time.

"DIGITS" An Augmented Reality Remote Hand Telerehabilitation Solution for Small Joint Range of Motion and Dexterity Assessment

H. Dong, A. A. Kuchtaruk, H. Shin, R. Eagleson, C. Symonette

Hand telerehabilitation is limited by the ability to accurately assess small joint range of motion (ROM) and dexterity data. Augmented reality (AR) and computer vision have the potential to address this challenge. However- previous generations of AR solutions have been limited by upfront cost and accessibility. DIGITS is a novel web-based application, developed from open-source MediaPipe Hands pipeline, which uses AR to remotely measure small joint ROM and dexterity data. The advantage of our approach is the simple equipment needs of a device with a front-facing camera and an internet connection. The objective of the current research program is to validate our approach to remotely collect small joint ROM data against the gold standard of in person goniometry. Our secondary objective is to develop a remote evaluation of finger dexterity using a finger-tapping exercise. Participants (ages 5-80) with a history of hand pathology and an age-matched control group were recruited to participate. Small joint angle ROM data (600 entries) of the whole hand was collected for each person using DIGITS at a sampling rate of 15 Hz. The DIGITS application tracks 21 landmarks on the hand (**Figure 1a**) and records their coordinates, which are then used to calculate the angle across each joint of the hand: metacarpophalangeal (MP), interphalangeal (IP) joints of the thumb and MP, proximal IP (PIP), and distal IP (DIP) joints of digits 2-4. Separate datasets were recorded for hands at various positions outlined in **Figure 1**. One set of flexion-extension measurements of the affected digit or the index and small finger from each control participant was also recorded by a trained hand therapist in the clinic. Equivalence testing, two one-sided test (TOST) is performed. For the finger-tapping dexterity assessment, speed and accuracy were assessed. Interim analysis revealed an overall average of the difference between DIGITS and in person goniometry measurements from this control population is 8.9°. TOST test results have a p-value of 0.32, and a 90% confidence interval of (-2.85,8.58). Average standard deviation of individual datasets recorded through the DIGITS webapp is 8.5°. The finger tapping exercise was able to provide high fidelity data regarding speed and dexterity. Future directions of our work include developing a remote assessment of swelling.

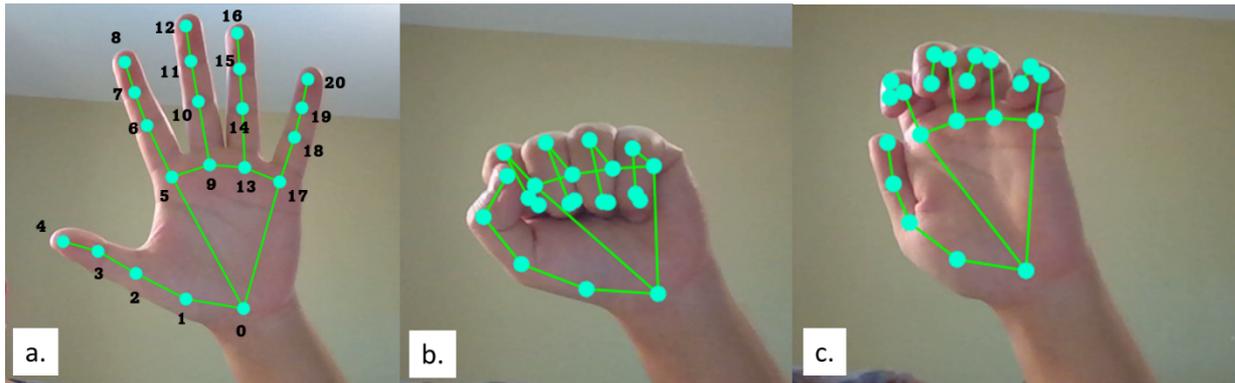


Figure 1. A demonstration of the 20 landmarks tracked by the DIGITS webapp with tracking at three hand positions: a. Full Extension, b. Full flexion & c. Intrinsic minus

Robotic Assisted vs. Traditional Video-assisted Thoracoscopic (VATS) Surgery for Lung Cancer

John C Lin MD

Background: Robotic assisted thoracoscopic lung cancer surgery has been popularized in the last 5-10 years. Prior to that, minimally invasive video-assisted thoracoscopy (VATS) has been popular following decades of traditional thoracotomy. Also in the last 5 years, new guidelines have been introduced in the lung cancer literature using lymph node harvest volume as a way to assess adequacy of surgical resection

Aim: We reviewed retrospectively the use of robotics assisted VATS for lung cancer surgery in the last 3 years in comparison to traditional VATS in the 3 year period prior in a single surgery practice.

Methods: Patient baseline information, pathology, staging, hospital stay days, morbidity/mortality were compared between the two surgical techniques. Lymph node harvesting volume in the mediastinum and the hium were interrogated as well.

Results: Baseline patient characteristics were comparable between the two cohorts. Robotic arm had 70% stage 1, VATS arm had 60%. Hospital stay was comparable, but there were prolonged bronchopleural fistula in the robotic arm. VATS lymph node harvesting average was below 10, while robotics provided at least 50% increase.

Conclusion: Robotic assisted VATS lung cancer surgery is being rapidly adapted by thoracic surgeons in the USA. Improved visibility and dexterity are some of the rationale for the adaptation. Objectively, increase in lymph node harvesting using the robotic approach will also help satisfy the new oncology guideline for satisfactory surgical standard.

The Role of Balloon Dilation of The Eustachian Tube in The Pediatric Population

Marc Dean

Objectives: Obstructive Eustachian tube dysfunction has been classically treated with indirect methods targeting the tympanic membrane or adenoids. Balloon dilation of the Eustachian tube (BDET) is a recent technique that targets the Eustachian tube pathology directly and has been shown to normalize middle ear pressures and improve symptom scores, however its role in addressing chronic otitis media with effusion in the pediatric

population has not been extensively evaluated extensively in children. The objective of this study is to report the safety and efficacy of BDET in children with COME.

Study Design: This is an IRB- approved retrospective review of patients under the age of 18 who underwent balloon dilation of the Eustachian tube for COME greater than 3 months at a tertiary referral center

Main outcome measures: Tympanometry data was collected before and after BDET, and success was defined as resolution of effusion both on physical exam and tympanogram.

Results: Sixty-one Eustachian tubes were dilated in 44 patients, aged 1-18 years for COME. All patients had previously undergone TT insertion and adenoidectomy. Patients undergoing BDET cleared their effusions within 6 weeks of the procedure in 89% (38/44) of cases. There were no complications.

Conclusions: BDET appears to be safe and effective in patients with COME.

Key words: Eustachian tube dysfunction, otitis media, otitis media with effusion, Eustachian tuboplasty, balloon dilation, tympanostomy tube

The Society of Thoracic Surgeons Thoracic Surgery Practice and Access Task Force-2019 Workforce Report

John Ikonomidis

Background. The Society of Thoracic Surgeons (STS) has intermittently surveyed its workforce, providing isolated accounts of the current state of thoracic surgical practice.

Methods. The 70-question survey instrument was received by 3834 STS surgeon members and responses gathered between September 16 and November 1, 2019. There was a 27.9% return rate.

Results. The median age of the active US thoracic surgeons is 56 years. Women comprise 8.4% of the responders, constituting 6.2 % of adult cardiac, 10.6% of congenital heart, and 12.6% of general thoracic surgeons. The majority of practicing US surgeons (83.5%) graduated from medical school in the US. Survey respondents had 7(21.8%), 8(25.0%), 9(22.1%) or ≥ 10 (29.2%) years of post-MD training before entering practice. Educational debt was increased compared to previous years, as was salaries.

Overall career satisfaction was 54.1% (very or extremely satisfied), and overall average hours per week worked has decreased compared with past surveys. However, 55.7% of surgeons had symptoms of burnout and depression. STS Database participation was high (90.5%), with the most common reason for not participating being cost (32.6%). Operative volume over the past 12 months

decreased for 23.7% of surgeons. 46.9% of responders plan to retire between the age of 66-69 years and a further 25.6% at age 70 or greater.

Conclusions. These data provide a current, detailed profile of the specialty. Ongoing challenges remain length of training and educational debt. Case volumes, scope of practice, and career satisfaction have remained relatively constant: however, symptoms of burnout and/or depression are common.

Empirical Findings of a 300 TMI Arthroscopic Surgeries

Marijus Leketas PhD, DDS, MD

Objectives: To present the achievements of a 7-year clinical experience along with conducted research in the field of TMJ arthroscopy.

Materials and methods: Clinical experience of 7 years, case-control studies, RCTs, and systematic reviews in a single institution were summarized.

Results: Clinical practice of TMJ arthroscopy has started in our clinic by performing first arthroscopic surgery in 2014 October. Since then, more than 300 successful TMJ arthroscopies were performed.

The scientific work in the TMJ field has begun by conducting a case-control study of 520 patients evaluating the frequency of oral behaviors in patients with temporomandibular disorders (TMD) compared to the control group. This study revealed that holding, tightening, or tensing muscles, grinding teeth, and sustained talking are associated with TMD disorder.

Later, a systematic review comparing different intraarticular injection substances (PRFG and HA) followed by TMJ arthroscopy. The results showed a tendency towards the superiority of PRFG over other treatments in pain management. However, a lack of randomized controlled trials (RCTs) that compared both substances made it hard to conclude which substance enhances recovery and effectiveness the most, therefore this was followed by a RCT that compared the effect of HA and PRGF injections on the early postoperative period after TMJ arthroscopy in 77 patients.

Lately, the object of interest has become the most advanced procedure in TMJ arthroscopic surgery – discopexy. A systematic review was carried out evaluating the effectiveness of different TMJ arthroscopic discopexy techniques.

Conclusion: TMJ arthroscopic surgeries have proven themselves to be a successful way of helping particular TMD patients. Despite that, to this day, the scientific field of TMJ arthroscopy has shown us that this procedure is not extensively researched.

Keywords: temporomandibular joint, TMJ, arthroscopy, discopexy, PRGF, hyaluronic acid.

Treatment Of Unilateral Laryngeal Palsy: Early Hyaluronic Acid Medialization and Long-Term Fat Medialization Results

C. Finck, MD, PHD

Unilateral laryngeal palsy(ULP) is associated with dysphonia, dysphagia and aspiration. Several techniques are available to restore laryngeal function depending on the importance of functional deficit, etiology and prognosis of palsy aswell as time elapsed since palsy installation: early and temporary medialisation procedures, fat medialisation, thyroplasty and re-innervation procedures.

In this presentation, we present the results of 30 early medialisation procedures with hyaluronic acid (HA) under local anesthesia (in-office procedure) aswell as the discussion of technique choice for long term functional restoration(fat injection, Montgomery implant or laryngeal re-innervation).

In a second part, we present the long term results of 18 fat injection procedures under general anaesthesia, using the following variables: Voice Handicap Index (VHI), GRBAS scale, mean phonation time (MPT), Mean Flow Rate (MFR), jitter %, Shimmer %, and glottic closure. The median follow-up was 19 months (12-58 months). Shimmer %, and glottic closure. The median follow-up was 19 months (12-58 months). Single fat injection shows to be a safe technique with long term excellent stability of functional results.

Key words: laryngeal palsy, laryngeal paralysis fat injection, laryngeal medialization, Hyaluronic acid injection

Resilience and Renewal: Strategies for Faculty Engagement and Education

Steven E. Raper

Introduction: The purpose of this presentation is to describe how, when faced with a professional catastrophe, one can learn resilience. In particular, my experience with a research subject death led me to earn a law degree and re-frame my academic career. Recent efforts have included a series of risk reduction initiatives focused on educating Department of Surgery faculty on topics directed at mitigating malpractice risk.

Methods Twelve years' worth (2009 – 2021) of risk reduction initiatives were reviewed for faculty education updating some of the data I presented at last year's ESMED General Assembly. This work has continued to be successful with three elements that seem to be important: 1) Choose topics that matter to surgical faculty; 2) Embed faculty champions within each division so that the planned initiatives are perceived to arise from within rather than imposed from without; and, 3) use positive reinforcement rather than negative.

Results: Forty-seven total initiative were directed at faculty surgeons (Table). The most numerous created procedure-specific informed consent documents comprising >350 individual forms (data not shown) covering all ten Department of Surgery divisions (Cardiac, Colorectal, Endocrine and Oncologic, Emergency/Critical Care, GI, Plastics, Thoracic, Transplant, Urology, Vascular). Another major effort is to track read results through provider pools and keeping pools up to date in terms of onboarding and off-boarding faculty and other clinicians. Ten faculty courses have been given on topics including medical malpractice, informed consent, inpatient and outpatient communication, and proper disclosure of medical error. Much of this work has been published. With rare exception, these initiatives have been successfully completed

Faculty Initiatives	N
Procedure-specific informed eConsents	13
Improved documentation and results review	11
Faculty Courses	10
Report select morbidity and mortality events to risk management	3
Upgrade Faculty On call Scheduling	2
Other	6
Total	46

Summary and Conclusions: We also published data showing a decrease in malpractice claims and premium costs associated with our on-going program of risk reduction initiatives. To this end, our Department has been able to receive rebate dollars from our malpractice premiums as an incentive to further our work.

Robotic Hair Restoration

Paul T. Rose

The technique of hair transplantation has evolved greatly over the years. The technique became popularized by dermatologists using biopsy punches of hair bearing tissue from

the donor area which were then placed into smaller sites. The punches were harvested with manual punches and later mechanized drill were used. The punches left round, hypopigmented scars usually 4-5 mm in diameter.

Since that time surgeons refined the techniques by excising ellipses of tissue which could then be cut down under a microscope to create follicular unit grafts. This technique became the predominant technique for many years.

In the past twenty years another technique based on the original technique of using punches to harvest grafts has become popularized. That technique is referred to as Follicular Unit Excision. The technique involved considerable training and was found to be quite arduous when using manual punches or motorized punches.

In response to the difficulties to perform FUE manually it was suggested that this repetitive process might be amenable to the use of a robotic device.

In approximately early 2011 the robotic device ARTAS became commercially available. The robotic device at that time was capable of harvesting several hundred grafts per hour which was significantly better than the vast majority of the surgeons performing the technique. The device was approved for use in males with dark hair. Since that time there have been further iterations of the robot.

In this lecture we review the use of the robotic device, benefits and limitations.

Nasal Decolonization: What Antimicrobials are Most Effective Prior to Surgery Ed Septimus

Background: Surgical site infection (SSI) is one of the most common healthcare associated infections. *Staphylococcus aureus* remains the most common etiologic agent causing SSIs. Studies confirm *S aureus* carriage increases the risk of *S aureus* SSIs. The purpose of this presentation is to review the strategies to reduce SSIs due to *S aureus* focusing on nasal decolonization. **Results:** Published studies indicate screening patients for *S aureus* nasal carriage and decolonizing carriers during the preoperative period decreases the risk of *S aureus* SSIs in cardiac and orthopedic surgery. Mupirocin remains the best topical agent at eradicating nasal *S aureus* however, concerns over resistance have led to development of alternative agents. Nasal povidone-iodine, alcohol-based nasal antiseptic, and photodynamic therapy are promising new interventions, but more studies are needed. **Conclusions:** Short term nasal mupirocin is still the most studied and effective topical agent in eradicating *S aureus* nasal colonization. However, increasing mupirocin resistance remains an ongoing concern and newer agents are needed. Currently, preoperative *S aureus* decolonization often uses combination chlorhexidine gluconate bathing and nasal mupirocin considering that colonization of multiple body sites is commonly seen

Conservative Treatment of Closed Subtalar Dislocation: A Case Report and 2 Years Follow-Up Nerantzoula Goutsiou

We report a case of a closed subtalar dislocation without any related fractures treated with closed reduction and conservative treatment with a cast immobilization. Pure subtalar dislocation without any fractures is extremely rare and hardly reported in the literature. Such injuries are more likely to be open and associated with fractures of the surrounding foot bones such as malleoli, talus or fifth metatarsal fractures. In the examined case, closed

reduction was followed by cast immobilization for 3 weeks. Six months post-injury, the patient had a full range of motion without any pain while there were no signs of residual instability or early post-traumatic osteoarthritis. Subjective clinical testing using a valid health instrument revealed an excellent outcome. We discuss in details the mechanism of such an injury and highlight the importance of prompt closed reduction and early mobilization to ensure a satisfactory long-term outcome.

Surgical Evaluation of Laparoscopic Pelvic Lymphadenectomy in the Treatment of Gynecological Neoplasms

Alvaro Gorostiaga Ruiz-Garma

Nowadays, surgical approach and definitive staging of gynaecological malignancies need pelvic lymphadenectomy, though in some cases of early stages the sentinel node technique has become a feasible alternative. Laparoscopy has become the surgical gold standard to perform it.

Its surgical results and applicability are shown in the presentation as well as data related to technical aspects and possible complications of the surgery. These surgical procedures by laparoscopy are safe and feasible when the surgeon has an adequate training and knowledge of the anatomy and when a strict surgical protocol is applied. The surgical aspects and the data related to surgical outcomes are clearly exposed.

Anaerobic Threshold and Surgery

Adrian Hall

Outcome following major surgery is influenced by patient-specific risk (mainly functional capacity or cardiopulmonary reserve) and surgery-specific risk (related to the extent and duration of procedure). It is known that functional capacity is an important prognostic factor in healthy asymptomatic individuals and in those at-risk of or with diagnosed disease.

When evaluating a surgical population the sensitivity and specificity of single-organ cardiac or respiratory tests are low and risk factors do not reliably identify those with sub-clinical disease. Bias or variation is implicit in subjective assessments.

Decreased functional capacity or cardiopulmonary reserve means decreased ability to transfer oxygen to metabolising tissue. It may be measured by Cardiopulmonary Exercise Testing (CPET) using respiratory gas analysis and expressed in terms of anaerobic threshold (AT), peak oxygen uptake or oxygen uptake/work rate relationship.

Anaerobic threshold is relevant to the peri-operative state because it relates to sustainable aerobic metabolism. Although expressed in terms of oxygen uptake, the AT defines a point of increased carbon dioxide elimination, not from increased metabolism of oxygen, but from onset of anaerobic metabolism and acidosis. Further, when measured using CPET, the AT is objective, non-volitional, reproducible, occurs at a submaximal work rate, and is the basis for analysis of other important physiologic parameters.

CPET provides more useful information than self-reported physical activity scales, tests performed at rest and exercise testing without respiratory gas analysis. Using such tests may deny intervention to those at low risk or expose others to intervention at significant risk.

CPET is an integrated and dynamic functional assessment. It identifies the cause of exercise intolerance and detects subclinical abnormalities not recognised during conventional assessment. CPET may be applied to individuals with either high patient-specific or surgery-

specific risk profiles to accurately stratify risk; to allow collaborative decision making, to guide post-operative care, or to assess the effects of neo-adjuvant therapy and medically prescribed exercise programmes.

Functional capacity may attain 'vital sign' status in future clinical practice. Individuals with low functional capacity have the most to gain from risk reduction strategies. CPET reliably detects all patients at increased risk and, perhaps more significantly, those who have low operative risk with major surgery. Accurate risk assessment is both a medical and an economic imperative. CPET should be considered as a desirable and valuable new standard.

The Effects of Bone Morphogenetic Protein-7 and Interleukin-1 on the Biomechanical Properties of Meniscus Explants

Victor Taylor II

Introduction: The meniscus is a wedge, C-shape fibrocartilaginous tissue situated between the femoral condyle and tibia plateau of the knee. Meniscus is an essential for the normal biomechanical function of the knee because it withstands different forces, shear, tension, and compression developed during normal motion. It also plays a crucial role in load-bearing, load transmission, shock absorption, and joint lubrication. The meniscus has proven to highly stabilize the knee because the wedge shape of the tissue serves to convert vertical compressive forces to horizontal hoop stresses. In addition, the shear force is developed between the collagen fibers while the meniscus is deformed. Tears in the meniscus are a common knee injury and most frequent surgical procedure performed by orthopedic surgeons. Damage to the meniscus leads to degenerative changes and loss of function mechanical function of the knee. Degenerative changes include hypocellularity, loss of collagen fiber organization, and increase water content. Ultimately, these changes lead to osteoarthritis. Cytokines like interleukin-1 can inhibit repair process. However, anabolic factors like bone morphogenetic protein-7 may help aid in the repair process. The goal of this project is to observe the effects of BMP-7 and IL-1 on the biomechanical properties of the meniscus using microindentation test. It is hypothesized that BMP-7 will have an anabolic effect by increasing the elasticity of the meniscus tissue, and IL-1 will have a catabolic effect by decreasing the elasticity of the meniscus tissue.

Methods: Porcine lateral menisci were collected from female pigs approximately three-years-old from a local abattoir. Six-millimeter explants (cut to 3mm thickness) were collected using a biopsy punch from four different regions of the lateral meniscus: posterior horn (PH), posterior body (PB), anterior body (AB), anterior horn (AH). Explant tissues were cultured in DMEM with 1% fetal bovine serum (FBS), penicillin/streptomycin (100ug/mL), amphotericin B (2.5ug/mL), and gentamicin (5ug/mL). Explants were cultured without treatment (control group) or treated with BMP-7, IL-1, and or combined with BMP-7 and IL-1 alpha. Microindentation experiments were performed to test the biomechanical properties of the culture and uncultured explant tissues. Explants were pre-loaded to a force of 0.15N for 20s, then indented 500 μ m at a speed of 5 μ m/s using a Bose ElectroForce 3200 (ElectroForce®, Eden Prairie, MN). Sixteen samples were test (four samples in each group). Microindentation curves were fit to the Hertz contact model (Fig. 1), which assumes an infinitely hard sphere indents a flat, linear elastic, infinite half-space: $F = \frac{4}{3} E \sqrt{R} \delta^{3/2}$; where F is the measured force (N), E is apparent Young's modulus (Pa), δ is

Poisson's ratio, and R is the spherical indenter radius ($R = 0.0005\text{m}$), and δ is the indentation depth (m). Hertz contact model was used to determine the Young's Modulus, also known as the elastic modulus. Young's modulus is used to characterize the elastic deformation behavior of a solid material, and it is directly proportional to the stiffness of the material. Higher the force, higher the Young's modulus, the stiffer the material will be. Since biological tissue is nearly incompressible at the indentation rates used in the present study, the Poisson's ratio (ν) was assumed to be 0.5. Since meniscus is viscoelastic in nature and the Hertz model assumes linear elastic behavior, only the first $100\mu\text{m}$ of indentation were used to fit the Hertz model (red in Figure 1). Each explant was indented at 4 different locations. Statistical tests were performed using SPSS (International Business Machines Corporation, Armonk, NY 10504 USA). Statistical differences were calculated using Analysis of Variance test. Differences were considered significant at $p < 0.05$.

Results: The Hertz contact model between the four culture groups is shown in Figure 1. The Young's modulus for the explants treated with BMP-7 (2.480 MPa) were significant compared to explants treated with either IL-1 alpha (1.501 MPa; $p=.001$) or both BMP-7 and IL-1 alpha (.866; $p \leq .000$). This indicates BMP-7 and IL-1 have a significant effect on the meniscus biomechanical properties. BMP-7 increase the Young's modulus (but not significant) compared to the control explants (2.072 MPa; $p=.065$), while IL-1 significantly decrease the Young's modulus ($p=.017$). In addition, the Young's modulus of explants treated with BMP-7 and IL-1 alpha significantly decrease compared to explants that were only treated with IL-1 alpha ($p=.011$). The statistical results between the four groups are shown in Figure 2.

Discussion: This data shows that BMP-7 has the potential to exert an anabolic effect on cultured meniscus explants reflected by the presence of increased mechanical compression properties. As a result, the meniscus explant tissues that were cultured with BMP-7 became more elastic after being cultured for seven days. In addition, meniscus cultured with IL-1 alpha or a combination of BMP-7 and IL-1 alpha became less elastic. Future experiments will continue testing the effect of these two treatments.

Significance: This research will help improve our understanding BMP-7 signaling variable pertinent to the environment of the osteoarthritic and injured knee and provide the foundation for future studies aimed to restore the efficacy of anabolic therapies for acute and degenerative meniscus injuries.

Single-incision laparoscopic appendectomy versus conventional 3-port laparoscopic appendectomy for appendicitis: an updated meta-analysis of randomized controlled trials Chaorong Xue

To investigate the application of single-port laparoscopy in acute abdomen, we analyzed the clinical data of 117 cases with acute abdomen undergoing single-port laparoscopic surgery from September 2020 and September 2021. Among them, 96 cases were acute appendicitis, 7 cases were inguinal hernia, 4 cases were adhesive ileus. We will discuss the indications, case selection, surgical techniques, precautions and prospects of single-port laparoscopic surgery.

New Anatomical Locking Plate for Displaced Intra-articular Calcaneus Fracture: The Journey from Design to Application.

Yanyu Chen

Introduction: The treatment of displaced intra-articular calcaneal fractures (DIACFs) is controversial. There are several problems in contemporary screw-and-plate implants for calcaneus, such as no one is truly anatomical, and need to bend intra-operatively. We reported our experiences of developing an anatomically shaped calcaneal locking plate with several innovative features for DIACFs.

Materials and Methods: The plate was made of titanium alloy and anatomical based on CT image data base of over 3000 people. It is trimmed from a titanium alloy block, allowing the 3-D configuration of the plate. There are 3 special fins to facilitate fracture reduction. There are also predesigned locking screws to support the posterior facet of subtalar joint, the tongue-type fracture, and the sustentaculum tali.

The design of the plate was proposed by a senior foot and ankle surgeon in a committee composed of orthopedic surgeons, engineers, and implant manufacturers. The concepts and the utilities of the implant were repeatedly discussed and modified until the prototype came out. After a preliminary clinical trial under the supervision of IRB committee, the implant was finally commercialized 3 years after initial proposal.

Results: Over 2000 plates has been used for DIACF patients by far with high satisfaction rate from the surgeons and patients. The second edition of the implant, which is lighter and thinner enabling minimally invasive surgery has been released 10 years after the first implant came into market.

Conclusion: There are always unmet demands in clinical works. We have built a platform of communication between orthopedic surgeons, engineers, and implant manufacturers to efficiently and comprehensively deal with these unmet needs.

Principles of managing mutilating injuries of the hand

Amitabha Lahiri, MBBS,MCh,FRCS, MRes.

Mutilating injuries of the hand is a serious problem in industrialised the world. It is a heterogeneous group of injuries that includes a wide spectrum of presentations. Every injury has a distinct combination of tissue damage. Because of this, it is extremely difficult to create an objective classification or a rigidly protocolised management system. The management needs to be tailored for each patient based on fundamental surgical principles. It requires an understanding the principles of bone and soft tissues reconstruction and surgical techniques. This presentation aims to equip the surgeon with the key principles and the knowledge that are essential for effective management of mutilating injuries of the hand.

Extra-articular endoscopic excision of symptomatic popliteal cyst with failed initial conservative treatment

ChienSheng Lo, MD

To reduce the damage to posteromedial knee capsule, we developed a direct extra-articular arthroscopic approach for excision of symptomatic popliteal cysts. This study aimed to demonstrate the surgical technique and present the 2-year follow-up results.

Cystectomy is performed by extra-articular surgical approach through a high posteromedial portal. Twenty-one consecutive patients diagnosed of symptomatic popliteal cysts with failed initial conservative treatments were included. At a median follow-up of 29.4 months, all knees had improved clinical function assessed by Rauschnig and Lindgren knee classification ($p < 0.001$). The cysts were either disappeared (95.2%) or reduced in size (4.8%). Only one (4.8%) patient had recurrent cyst., which was solved after ultrasound-guided aspiration. This direct extra-articular arthroscopic technique could be a feasible alternative for treatment of symptomatic popliteal cysts.

Objectives: Popliteal cyst combined with intra-articular lesion can be treated using arthroscopic techniques. However, damage of posterior knee capsule and difficult identifying the cyst orifice were the major concerns. We demonstrated a new technique with extra-articular endoscopic approach to excise the cyst. It has the advantages of preserving the posterior capsule, decreasing the meniscus injury and better orifice recognition.

Methods: Between January 2008 and July 2012, 26 consecutive patients received extra-articular endoscopic cyst excision for symptomatic popliteal cysts with failed initial conservative treatments. During operation, posteromedial portal and high posteromedial portal were used for excision the cyst. We used Rauschnig and Lindgren classification for pre- and post-operative clinical evaluation. Sonography was used for evaluation of possible recurrence at postoperatively 1-year and 2-year follow-ups.

Results: Preoperatively, 19 patients had Rauschnig and Lindgren grade 3 (90.5%) and two patients grade 2 (9.5%). Postoperatively, 11 patients had grade 0 (52.3%), 9 patients grade 1 (42.9%), and one patient grade 2 (4.8%). After an average of 29.4 months following, all knees had relieved symptoms. Sonography revealed 95.2% patients free from cyst recurrence. Only one patient had recurrent cyst which resolved after aspiration.

Conclusions: We demonstrated that the symptomatic popliteal cysts can be excised via direct extra-articular endoscopic approach with promising short-term and long-term outcomes. It is an attractive alternative surgical method with all-endoscopic techniques.

An Inexpensive Support for Prone or Lateral Decubitus Elbow Arthroscopy and Open Elbow Surgery

Klaud Miler M.D.

This will be a presentation of the construction and utilization an inexpensive radiolucent elbow support for arthroscopy and open elbow surgery.

Day-surgery and surgical waiting time

Paula Maria Caldinhas

Introduction: In this work we investigated what are the effects of mobility of health professionals in EU countries on vocational training and development, as well as the performance and organisational culture of health institutions.

Methods: quantitative and qualitative studies were conducted, using primary and secondary data.

Results: It was observed, at national level, a positive notion of professionals about "access to opportunity, information, professional support and collaboration between peers" but a negative perception about "access to resources" and "creativity and innovation". The performance of analyzed health institutions did not reveal significant changes in relation to the use of external health professionals and services.

Conclusions: Health Professionals mobility between European countries is referred to as an enriching professional experience, and there is also a notion of better performance, organization and quality of health services abroad.

We highlight the need for optimization of information collection to monitor these flows of professionals and how this affects performance and quality of health services.

The creation of common *guidelines* contributes to the integration and standardization of professional practices, and facilitates the comparison of health outcomes between countries.

TOXICOLOGY

Therapeutic Ultrasound for Treatment of Secretory Defects in Pancreatic Islets

Aleksandar Jeremic, Lydia Burnett, Mallory Brayer, Andrew Chen, Ivan Suarez Castellanos, Tania Singh and Vesna Zderic

Pancreatic beta cells secrete hormones, primarily insulin and amylin, to work as the primary mediators of glucose homeostasis. Insulin regulates blood glucose levels by increasing glucose uptake by peripheral tissues, while simultaneously decreasing liver gluconeogenesis. In patients with Type 2 Diabetes Mellitus (T2DM), both the typical pattern of insulin secretion is disrupted, and peripheral cell insulin sensitivity is decreased. Our recent published studies show that treatment with ultrasound can induce insulin secretion from both human pancreatic islets and rat insulinoma INS 832-13 cells. Specifically, ultrasound applied at frequency of 800 kHz and intensity of 0.5-1 W/cm² for 5 min was effective at stimulating insulin release from rat pancreatic insulinoma (INS 832-13) pancreatic beta cells (n=6, p < 0.05, Student's t-test) with no adverse effects. Similarly to this *in vitro* findings, our recent *in vivo* ultrasound studies performed in non-diabetic mice demonstrated effectiveness of sonication on secretory processes: ultrasound treatment (1MHz, 1 W/cm², 5 min) of the whole non-excised pancreas caused a statistically significant (n < 6, p < 0.005, Student's t-test) increase in insulin serum concentration immediately after the five-minute stimulus was ceased as compared to control mice. Thus, understanding the mechanism of ultrasound induced insulin secretion could lead to targeted, noninvasive therapies for T2DM patients. Increased intracellular calcium has been implicated in insulin secretion and can be stimulated by activation of mechanosensitive channels, namely transient receptor potential vanilloid (TRPV) and Piezo channels. Isoforms of these channels have also been implicated in glucose stimulated insulin secretion. However, very little is known about the possible regulatory effect of ultrasound on expression and function of mechanosensitive channels in secretory tissues and glands such as pancreas. In this study,

using INS 832-13 cells as a model secretory system, we examined the expression of TRPV isoforms 1-6 and Piezo 1 & 2, and the possible sonogenetic effect of ultrasound on expression of these mechanosensitive genes. Using RT-qPCR, we found that INS 832-13 cells predominately express TRPV1, TRPV2, and Piezo1 channel isoforms. We then treated the INS cells with continuous ultrasound application for 5 min at a frequency of 800 kHz and intensity of 0.5 W/cm^2 to stimulate insulin release from these cells. However, this short-term ($\leq 1\text{h}$) ultrasound stimulation had no significant effect on gene expression (mRNA) levels of any of the three channel proteins. Interestingly, metabolic fuels such as glucose also did not show a modulatory effect on the expression of these channels, despite its significant ($p < 0.05$, $n=3$, ANOVA followed by Tukey post-hoc test) stimulatory effect on expression of metabolically-responsive TXNIP gene. In contrast to gene expression studies, protein expression analysis revealed an increase in intracellular insulin levels following INS cell stimulation with high (20 mM) glucose or ultrasound treatment although this did not reach significance ($p > 0.05$, $n=3$, ANOVA followed by Tukey post-hoc test). Thus, our current data suggest that, at least in short term, ultrasound and glucose stimulated-insulin release do not depend on the change in expression levels of these genes, implying involvement of post-transcriptional and/or secretory mechanisms in acute ultrasound-stimulated insulin release. Additional protein expressional and functional studies will be needed to confirm or refute involvement of TRPV1, TRPV2, and Piezo1 channel isoforms in ultrasound-stimulated insulin release from pancreatic islets. Understanding the mechanism and role of mechano-sensitive channels in insulin release may reveal new therapeutic strategies in treating this metabolic disease.