Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: September 30, 2023

Citation: Oldoni, E., et al., 2023. It is time we got more personal with advanced therapies- How do we create the right ecosystem for more effective ATMP development in Europe? Medical Research Archives, [online] 11(9). https://doi.org/10.18103/mra.v11i9.4322

DOI: https://doi.org/10.18103/mra.v11i9.4322

ISSN: 2375-1924

RESEARCH ARTICLE

It is time we got more personal with advanced therapies- *How do we create the right ecosystem for more effective ATMP development in Europe?*

E. Oldoni[1], A. Ussi[1], A.L. Andreu[1], D. Morrow[1*]

[1]EATRIS, European Research Infrastructure for Translational Medicine.

[*]davidmorrow@eatris.eu

ABSTRACT

Over the past few years, Advanced Therapy Medicinal Products (ATMPs), especially cell and gene therapies, have brought about a remarkable transformation in the field of therapeutics. ATMPs have the potential to be tailored to individual patients based on their distinct molecular characteristics, making them a crucial aspect of personalized medicine (PM) strategies. Unlocking the full potential of ATMPs is crucial for them to become the treatments of the future. Despite their immense promise, their success is hindered by significant complexity, as evidenced by various systemic bottlenecks in the realms of science, clinical implementation, and regulation. Presently, ATMPs face challenges such as a limited understanding and predictability of in vivo cell fate specific to each patient, regulatory issues caused by rapid technological advancements, inadequate standardization in data acquisition, limited reproducibility during preclinical development, and insufficient knowledge exchange among key stakeholders. Addressing these aspects is essential to fully harness the benefits of ATMPs in healthcare. EATRIS, the European Research Infrastructure for Translational Medicine, is actively enhancing its capabilities in the field of PM through a series of key initiatives. These efforts aim to support also ATMP development and are focused on delivering novel and innovative scientific tools for the scientific community. The final aim is to create the right ecosystem for more effective ATMP development in Europe, by better serving academia and industry in the translation of ATMPs for patient benefit.

Advanced Therapy Medicinal Products (ATMPs), in particular cell and gene therapies for rare diseases and cancer, have transformed the therapeutic landscape over the last few years. Advanced Therapy Medicinal Products can be developed for the individual patient based on their unique molecular profile and are therefore regarded as personalised medicine (PM) approaches. They represent a unique opportunity to make the promises of PM a reality, through patient-tailored interventions that include novel and complex medicines based on genetic engineering and cell-based therapies for editing a patient's own cells, which help them fight a disease. This personalized approach in oncology, for example, can result in the patient's immune system being reprogrammed to recognize specific cancer cells as a foreign body and attack them as they would any infection. Every individual's cancer or the 70% of rare diseases of genetic origin, has its own genetic specificities. A major goal of PM is to look at developing novel ATMPs that can target these differences and thereby succeed where other classic therapeutic approaches have failed. Advanced Therapy Medicinal Products can be the treatments of the future, but only if we can unlock their full potential. With such great promise, however, comes great complexity as evidenced by the systemic bottlenecks in the science, clinical implementation, and regulatory field, that currently prevent ATMPs from attaining full success. This includes amongst others, a lack of understanding and predictability of *in vivo* cell fate dictated by the "individual patient," poor regulatory clarity due to the break-neck speed of technological advancement, lack of standardisation in data acquisition, a lack of reproducibility in the preclinical development phase and poor exchange of knowledge between the major players. The ability to modify and tailor the administration of ATMPs to maximise individual patient impact based on their unique biological signatures, and hence reduce the cost of these promising and often curative personalized treatments, resides in improving and consolidating our capacities in the field of PM. This includes, in particular, advances in developing and validating multimodal biomarker signatures that can allow clinicians to stratify patients into responders and non-responders, and to identify those with an increased risk of adverse side effects such as immunotoxicity, which can be inherent to several classes of ATMPs. Through improving and consolidating these technical capacities as a research community, only then will we have the ability to optimally stratify patients based on predicted response and hence have the promise at the clinic to offer new robust platforms that can function as early prognostic indicators for a specific patient and for a specific ATMP. To achieve these goals and overcome the hurdles related to making ATMPs a reality at the clinic, Europe needs to create a first of its kind ecosystem among research institutions, patients, health care practitioners, industry, regulators, and governments to exploit the growing range of resources including the necessary high-quality data to treat genetic diseases. European Research Infrastructures foster such efficient cooperation and collaboration in health care research by providing researchers access to not only the scientific expertise and facilities, but also the regulatory and health technology expertise to address the implementation and reimbursement aspects, and future sustainability expertise

where and when needed. The European Research Infrastructure for Translational Medicine (EATRIS)[1-5], through several key initiatives is now working to further its capabilities in the PM domain including the delivery of new innovative scientific tools in ATMP development[6-7]. The work of EATRIS in the ATMP field aims to fill the gap between basic research and clinical implementation by providing the high-quality services necessary for the scientific community actively translating their discoveries into clinical development. The overall goal is to be one of Europe's key research infrastructures in the PM domain for the advancement of this critical field, for the benefit of patients where ATMPs can represent the best chance of success. In this commentary piece, our objective is to describe some of the ways EATRIS is currently supporting researchers by facilitating the right collaborations as we strive to achieve this very important goal.

Making more effective, safer, and less costly advanced therapy medicinal products available for the individual – what are we missing?

Predicting patient response to cell and gene therapy has proved to be a major challenge for the field. There represents however, an urgent need for the right patient-tailored biomarker' signature that can offer clinicians the ability to stratify patients at the clinic into responders and non-responders. This allows us the ability to identify patients that have an increased risk of suffering from adverse side effects. With ATMPs a major adverse effect is immunotoxicity, an area where innovative standardised omics technologies - such as single-cell functional proteomics that can predict adverse responses – have high potential to succeed where previous technologies have failed[8]. In addition, possessing the ability and technologies to directly measure the function of immune cells in the patient is absolutely critical to predicting potency and persistence, thereby representing the patient response to ATMPs during clinical testing. The availability of the right technology platforms allows the researcher and the clinician the essential ability to evaluate the polyfunctionality of ATMPs, such as with CAR-Ts[8]. Such validated and harmonized platforms across ATMP developing institutes and companies can be used to develop better products with improved anti-tumour activity, increased persistence, and decreased exhaustion in the individual patient. Currently, considerable focus on the utility of non-invasive multimodal imaging to assess biodistribution, as well as in silico modelling to generate an "index" for each patient as an early-stage prognostic indicator of an ATMP, is garnering deserved attention[9-15]. For example, cell therapy localisation and proliferation can be evaluated through such imaging modalities, replacing the need for invasive biopsies. This technology - in a similar fashion to the right omics technologies - could be integrated with existing ATMP supply chains, with standardisation of data acquisition, analysis and reporting, and regulatory clarity to again stratify patients at the clinic for better success with these costly interventions. Additional stratification strategies are also being considered that look to reduce the toxicity effects, such as cytokine release syndrome (CRS), that are associated with some ATMPs[16]. This often-life-threatening complication occurs when cytokines associated with T cell engagement and proliferation, such as interferon-γ and IL-6 which

are systemically released, initiate an unchecked chain reaction of white blood cell activation and subsequent further cytokine release. A certain level of cytokine release is expected following immunotherapy administration as a consequence of T cell activation and is linked to product efficacy[16-18]. However, it is important to have strategies in place to monitor and manage CRS before severe complications emerge. This involves the need for the right quantitative prognostic tools that can aid clinical decisions[7]. The ability to time the need for potential additional treatments to offset the effects of CRS and to find the balance between the risk of relapse versus adverse response in patient A versus Patient B remains a major focus in the ATMP field.

These above examples are only a snapshot of some of the many areas of ATMP development that are being researched, in order to improve the development and tailoring of ATMPs for the right patient. By improving our ability to predict and account for individual differences in disease diagnosis and therapy response through the right PM approaches, we can diminish the duration and severity of illness and improve success rates. At the same time, we can support the reduction of often enormous health care costs by improving our ability to select quick, dependable, and effective ATMPs for a given patient, while minimizing the present excessive costs that are associated with ATMPs, not to mention the use of ineffective ATMP treatment, and avoidable adverse events. To overcome this existing barrier, we need to address multiple "systemic issues" in the ATMP development process. This includes amongst others, making the required changes in regulation and reimbursement pathways for ATMP development such as promoting the importance of the right biomarkers which are integral to all health care research - rather than merely optional. Central to this is also highlighting the critical need of artificial intelligence (AI) in boosting the use of multimodal biomarkers signatures in the ATMP domain. The "right CAR-T" for the "right patient" for example. In the right way, AI algorithms can be harnessed to deconvolute high-dimensional data from multi-omics data profiling and integrate them with imaging and clinical data to resolve molecular profiles that are indicative of treatment response and/or potential drug toxicity. In addition, some research groups are now developing automated AI-driven CAR-T cell manufacturing platforms to address the challenges in poor CAR-T design and patient results. Automation has shown the potential to increase the cost-effectiveness and robustness of manufacturing. Using AI to interpret the data collected on this newly developed platform can provide researchers valuable process insights and drive decisions for process optimization. This smart integration of automated CAR-T cell manufacturing platforms into hospitals enables the independent manufacture of more effective patient-specific, autologous CAR-T cell products[19]. To support researchers in the AI domain the European AI Act - Europe's first regulation on artificial intelligence - has been launched and represents the world's first comprehensive AI Law[20]. With this legal framework, the EU wants to regulate artificial intelligence (AI) to ensure better conditions for the development and use of this innovative technology. Artificial intelligence can create many benefits, such as better healthcare; safer and cleaner transport; more efficient manufacturing; and cheaper and more

sustainable energy. Taken together all of the above can help streamlining of the development process, allowing faster, more efficient, cost-effective delivery of ATMPs to the patient at the clinic when needed.

What about standardized technology platforms for ATMP development and the need for robust non-clinical and clinical standards? Whilst the concept of gene therapy, for example, is straightforward with nucleic acids being delivered to target cells to alter their function in a beneficial manner, the reality however, is a complex process comprised of multiple steps and components. This includes the demand for the right systems for delivering and trafficking nucleic acids into target cells, such as next generation vector approaches which are safer, or non-viral approaches such as nanoparticles or extracellular vesicles; the right DNA regulatory elements that control the amount, location and duration of gene expression, and the efficient production of proteins with appropriate activity to alter cellular function in the desired manner. Development of effective and safe gene therapies requires not only novel and innovative technology, but creative approaches to solving the technical challenges in the production processes such as robust and scalable manufacturing. This includes the need for defining and validating fit-for-purpose or simply good enough manufacturing-related analytical assays and technologies, and agreement on starting materials that sufficiently support viral or non-viral gene therapy manufacturing. Platform approaches and strategies have now become a more efficient and more common approach to address new treatment or diagnostics development including clinical trials. The advantage of developing a "platform" technology is its capacity of adaptation or customization to specific needs while being based on a set of standardized tools or techniques, allowing the streamlining of the development process, reduction of costs and increased efficiency[21]. These platform technologies, such as robust imaging technologies at point of care mentioned above, and during preclinical development, can help tailor ATMPs for the individual improving efficacy, increasing safety and of course support lower costs so that they remain a viable option at the clinic for the patients that need them. Standards are critical to ensure the highest level of quality and reproducible research. This remains a major challenge in the field. To achieve this in a relatively new and fast-changing field such as ATMPs, there is an urgent need to develop European and global networks of excellence that address these fundamental challenges in ATMP and PM development. A major goal of these would be to addressing these delays and bottlenecks in the progression of ATMPs into clinical development and manufacturing at scale[21]. The right ecosystem could support data access and the development and broad adoption of standards that improve quality, while promoting more reproducible research through better harmonization between developers. For example, the exchange of best practice procedures, QC protocols and processes are essential activities, necessitating close collaboration with policymakers and regulatory scientists across the EU to address the cost and delay drivers in the development pipeline.

To support this, and many of the challenges highlighted in this editorial, comprehensive cross-border education and training programs are also necessary to educate the "new ATMP

scientist" as the field currently suffers from a major skills gap in this growing field. Bringing together the most relevant stakeholders as well as competent ATMP-specialized research organizations - including clinical centers – would be a critical success factor in any educational effort. This ecosystem must include patient advocacy, regulatory and standards experts, pharma, med-tech, and manufacturing companies, all who are committed to delivering lasting impact on the ATMPs development landscape in Europe, driven by the individual patients' needs and empowered by cutting-edge technological advancements. Only then can the ATMP make an impact to more patients' lives. But where do we start and what role can research infrastructures play in this endeavour?

How can we consolidate our capacities and expertise in the field of personalised medicine in europe to better serve academia and industry in the translation of advanced therapy medicinal products?

Research infrastructures can play an even more prominent role in PM in addressing the main needs and challenges in the development and translation of better standardized, more effective, and safer ATMPs (Figure 1).

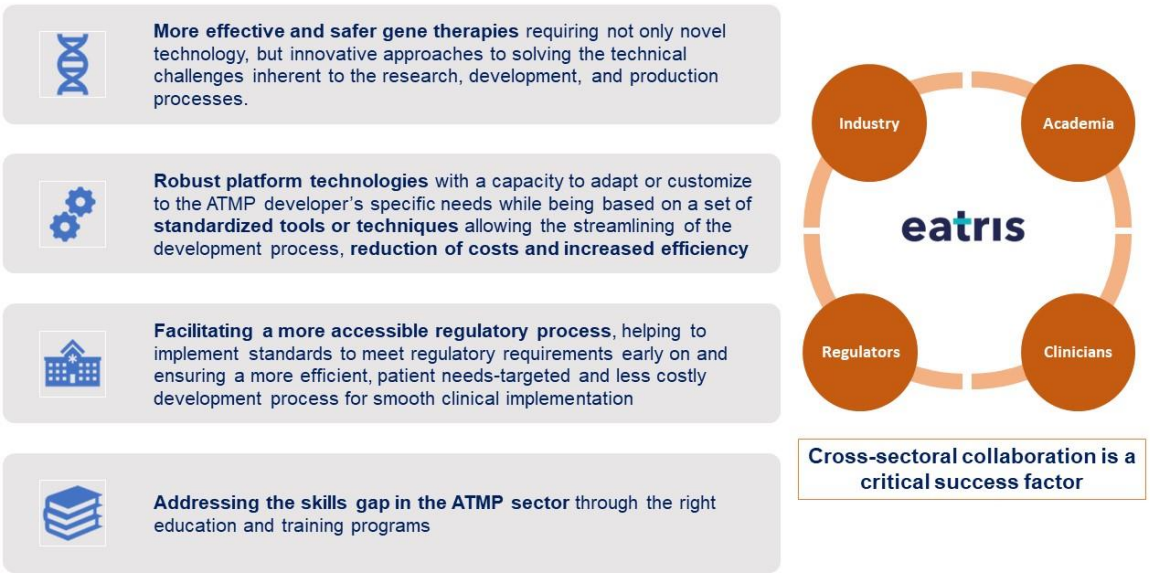

Figure 1: Addressing the needs in ATMP development for better translation to the clinic.

In particular, EATRIS, over the past 3 years with its flagship project EATRIS-Plus has worked, and continues to work, towards building EU capabilities to support the long-term sustainability strategies for PM. The main goals of the EATRIS-Plus project are to consolidate EATRIS capacities across the 150+ institutions within 14 EU countries in the field of PM (particularly omics technologies) to better serve academia and industry, and to augment the number of EATRIS Innovation Hubs with large pharma. The project also seeks to drive patient empowerment through their active involvement in the infrastructure's operations; and to expand strategic partnerships with research infrastructures and other relevant

stakeholders that can address the regulatory and developmental challenges at the research policy level. One such example is the Patient Engagement Resource Centre (PERC) which is a joint initiative between EATRIS, the European Patients' Forum (EPF) and the European Aids Treatment Group (EATG), funded through EATRIS-Plus. The PERC was developed to help academic researchers understand and practice meaningful patient engagement and co-creation in their research. The PERC is a repository of publicly available guidance, training and practical tools that support researchers with every stage of their patient engagement activity: planning, conducting, and evaluating.

Furthermore, as the efficient advancement of PM depends on the availability of validated patient-targeted biomarkers, at the core of this project is the drive to truly integrate multi-omics in the PM pipeline, which demands the facilitation of the process of generation of high quality data and the effective sharing thereof, federated data analysis and integration for other omics technologies. In this regard, EATRIS-Plus has been developing a multi-omics toolbox, a web-based tool containing standardised protocols, SOPs, reference materials, data analysis pipeline and more, to support such data integration and joint analysis of clinical samples. By providing such a toolbox to the research community, EATRIS-Plus can function as an engine to enable high-quality research in the context of patient stratification and accelerate the implementation of PM solutions[6].

The need, however, for the advancing this complex field of more effective, personalised ATMPs also demands the creation of an EU platform and forum that facilitates additional scientific and technology advances, such as those mentioned in the EATRIS-Plus project with a goal to bringing ATMPs to the patient faster. EATRIS is currently working with industry and public partners across the EU to develop a first of its kind Ecosystem for Rare Disease. The overall aim of such an ecosystem is to create a world class, sustainable network of interconnected centers of excellence that could be accessed by all involved in the development, production, and standardization of ATMPs. This first of its kind, European ecosystem, would represent the most promising and impactful technologies aiming to generate ATMP resources that the research community could use to streamline their development programs for rare disorders (genetic), making the process more efficient, and less costly. Such local ecosystems to support best practice ATMP development are increasing in number across the EU such as the DARE-NL project[22] in the Netherlands or the Saxocell[23] cluster from Fraunhofer in Germany. The overall aims are conserved due to the clear demands of the field, such as developing innovative approaches to targeted delivery, product stability for example, establishing more scalable, translatable, and sustainable manufacturing solutions, building analytical quality standards across the entire technology platform for development of these innovative modalities. Again, the aim is to develop a more streamlined and transparent development pathway including the regulatory concerns, to optimise and speed up the development and delivery of these gene therapy products. EATRIS represents a pan EU infrastructure that could join regional ATMP hubs across together to create a larger forum for the development of best practice, standardized ATMPs. For the development of

such an EU ecosystem, different funding strategies are currently being pursued but the needs are clear, the required solutions are clear and the willingness for the right partners in the ATMP development process are now fully engaged.

European research infrastructures such as EATRIS have the ability to create the right platform for the interaction of all necessary players in personalized ATMP development from the researcher in industry and academia, to the clinicians, the policymaker, the regulator, and the patient group, who together see the creation of such an ecosystem as a major priority. Taken together with our current flagship project EATRIS-Plus which aims to build further capabilities and deliver innovative scientific tools to support the long-term sustainability strategy, solidifies EATRIS as one of Europe's key research infrastructures for PM where we see the needs are clear and so, the mission.

Conclusion

It is now clear that Europe needs to create a new ecosystem among all stakeholders to exploit the growing range of data resources to treat complex disease of unmet medical need, such as rare diseases more effectively. Advanced Therapy Medicinal Products, a highly promising personalized medicine, represents a ground-breaking approach to altering the genetic composition of cells as a way to correct disease-causing mutations or to express proteins or RNA molecules that confer a therapeutic benefit for such diseases. Whilst the concept of ATMPs can be straightforward such as the delivery of nucleic acids to target cells to alter their function in a beneficial manner, the reality however, is a complex process comprised of multiple steps and components. Gaining a better understanding of the European setting for personalized ATMP development and it is delivery, by demonstrating our exceptional potential within European landscape to create disruptive ideas and technologies should be our goal. Secondly, the overwhelming complexity of the delivery of these ATMPs and the associated personalized treatment processes as part of the healthcare environment must also be addressed with equal rigour. EATRIS and its partners across the EU have made this a strategic priority. The real work now begins

Conflict of Interest Statement:

None

Funding Statement:

None

Acknowledgement Statement:

None

References:

1. van Dongen GA, et al. EATRIS, a European initiative to boost translational biomedical research. Am J Nucl Med Mol Imaging. 2013; 3: 166-174. www.ajnmmi.us /ISSN:2160-8407 /ajnmmi1301007

2. Gilliland CT, et al. Putting translational science on to a global stage. Nat. Rev. Drug Discov. 2016; 15:217–8. doi:10.1038/nrd. 2016.33

3. Ussi AE, et al. In Search of System-Wide Productivity Gains - The Role of Global Collaborations in Preclinical Translation. *Clin. Transl. Sci.* 2017; 10, 423–425. doi:10.1111 /cts.12498

4. Morrow D, et al. EATRIS: Providing the right tools, at the right time, for vaccine development in a pandemic. *Vaccine Insights.* 2022. 1(3), 131–137. doi: 10.18609/vac.2022. 022

5. Oldoni E, et al. European research infrastructure join forces to provide innovative cancer research services across Europe- how can they support the cell and gene therapy develop? *Cell & Gene Therapy Insights.* 2023; 9(7), 1003–1008. doi: 10.18609/cgti.2023.127

6. Oldoni E, et al. Tackling the translational challenges of multi-omics research in the realm of European personalised medicine: A workshop report. *Front. Mol. Biosci.* 2022; eCollection 2022. doi.org/10.3389/fmolb. 2022.974799

7. Fosse V, et al. Recommendations for robust and reproducible preclinical research in personalised medicine. *BMC Med.* 2023; 21(1): 14. doi: 10.1186/s12916-022-02719-0.

8. Marshall D, Sharpe M, Ward S. Cell & gene therapies, and the evolving role of personalized medicine. *Cell Gene Therapy Insights.* 2016; 2(2), 277-286. doi:10.18609/ cgti.2016.034

9. Koshkina O , Lajoinie G, Bombelli F. Multicore Liquid Perfluorocarbon-Loaded Multimodal Nanoparticles for Stable Ultrasound and 19F MRI Applied to In Vivo Cell Tracking. *Adv Funct Mater.* 2019; 29(19): 1806485. doi: 10.1002/adfm.201806485

10. Srinivas M, Mann C, Andreu AL, Ussi A, Morrow D. Broadly applicable imaging platforms are necessary for optimizing cell therapies in solid tumors. *Cell & Gene Therapy Insights.* 2019; 5(7), 629-638. doi:10. 18609/cgti.2019.071

11. Helfer BM, et al. Options for imaging cellular therapeutics in vivo: a multi-stakeholder perspective. *Cytotherapy.* 2021; 23(9): 757–773. doi: 10.1016/j.jcyt.2021.02. 005

12. Chapelin F, et al. Fluorine-19 MRI for detection and quantification of immune cell therapy for cancer. *J Immunother Cancer.* 2018; 6. 105. doi: 10.1186/s40425-018-0416-9

13. Ahrens ET, et al.Tracking immune cells in vivo using magnetic resonance imaging. *Nat Rev Immunol.* 2013;13:755–63. doi: 10.1038/ nri3531

14. Frangioni JV, et al. In vivo tracking of stem cells for clinical trials in cardiovascular disease. *Circulation.* 2004; 110:3378–83. doi: 10.1161/01.CIR.0000149840.46523.FC

15. Ashmore-Harris C, et al. Non-invasive reporter gene imaging of cell therapies, including T cells and stem cells. *Mol Ther.* 2020; 28:1392–416. doi: 10.1016/j.ymthe. 2020.03.016

16. Morris EC, et al. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol.*

2022; 22:85–96. doi.org/10.1038/ s41577-021-00547-6

17. Balagopal S, et al. Emerging approaches for preventing cytokine release syndrome in CAR-T cell therapy. *J. Mater. Chem. B.* 2022; 10:7491-751. doi: 10.1039/D2TB00592A

18. Cosenza M, Sacchi S, and Pozzi S. Cytokine Release Syndrome Associated with T-Cell-Based Therapies for Hematological Malignancies: Pathophysiology, Clinical Presentation, and Treatment. *Int J Mol Sci.* 2021; 22(14):7652. doi: 10.3390/ijms 22147652

19. Hort S, Herbst L, Backel N. Toward Rapid, Widely Available Autologous CAR-T Cell Therapy – Artificial Intelligence and Automation Enabling the Smart Manufacturing Hospital. *Front Med (Lausanne).* 2022; 9: 913287.doi: 10.3389/fmed.2022.913287

20. European Parliament. EU AI Act: first regulation on artificial intelligence. https://www.europarl.europa.eu/news/en/headlines/society/20230601STO93804/eu-ai-act-first-regulation-on-artificial-intelligence (Press Release) 08-06-2023

21. Iglesias-Lopez C, Agustí A, Vallano A. Current landscape of clinical development and approval of advanced therapies. *Mol Ther Methods Clin Dev.* 2021; 10(23): 606–618. doi: 10.1016/j.omtm.2021.11.003

22. DARE-NL- To accelerate clinical testing of novel oncological ATMPs to ensure timely and sustainable access to potentially curative treatment options for cancer patients. https://www.dare-nl.nl/

23. Saxocell https://www.saxocell.de/en/news-press-media/