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RESEACH ARTICLE

The Emerging Role of Photobiomodulation in COVID-19 Therapy Part II: Whole Organ PBM Case Studies for Acute & Long COVID

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ABSTRACT

Purpose: To assess the utility of photobiomodulation (PBM) in the treatment of acute and long COVID-19 guided by a mechanistic analysis of the photochemical effects of pulsed light on SARS-CoV-2 infections and disease progression.

Background: COVID-19 comprises a coronavirus severe inflammatory disease infecting tissue populated by angiotensin-converting enzyme 2 (ACE-2) receptors of the upper and lower respiratory tract and airway epithelial cells causing an overexpression of pro-inflammatory cytokines. Once in the lungs, viremic spread and cytokine profusion progresses into multi-organ hyperinflammation of visceral epithelium; vascular endothelium; neurons of the central, peripheral, and autonomous nervous system; and the brain with long-term sequelae. In response to an oxidative state, red and near-infrared (NIR) PBM down-regulates proinflammatory cytokines, activating M2 macrophages and Th2 helper cells to increase anti-inflammatory immune response in accordance with a biphasic dose response. Published reports confirm efficacious therapy of COVID-19 using conformal LED pads or scanned lasers.

Case Studies: To further explore the impact of pulsed red and NIR light on SARS-CoV-2 infection, two acute COVID case studies comprising 69 ambulatory (stage 1-to-5) and five stage-6 hospitalized patients were preformed using whole-organ deep-tissue PBM comprising algorithmically-pulsed conformal light-emitting diode (LED) pad optical delivery methods. Using the same PBM regimen, approximately 200 acute cases were subsequently performed, along with therapy of 150 cases of long COVID using a modified PBM protocol targeting the lungs, nerve tissue, and the brain. Disease case presentations comprised 60% acute COVID-19, 20% metabolic and respiratory long COVID, and 20% neurological long COVID. No digestive or reproductive symptoms were observed in long COVID cases.

Results: A total of 62/62 patients in the ambulatory study exhibited acute symptomatic recovery from two 64-84 min PBM sessions within three days. Full recovery occurred within four sessions for 100% of PBM patients (all but two cases resolved within one week). Prophylactic benefits were recorded in 17/17 asymptomatic-to-mild (stage 0-1) patients exposed to symptomatic infected family members. Recorded PBM outcomes of long COVID symptoms include resolution of dyspnea, ability to maintain blood oxygen saturation (SpO_2) above 97% without oxygen supplementation, relief from digestive distress, elimination of brain fog, improved memory recall, restored executive function, and symptomatic improvement in emotional deficits. Chest X-rays and blood tests also showed a reduction in tissue and systemic inflammation. Unresolved cases totaling 0.25% include two cases of severe long COVID anxiety and nosophobia where PBM was found to deliver only short-term palliative relief.

Conclusion: Using protocols targeting tissue with a preponderance of ACE-2 receptors, whole-organ deep tissue PBM in the treatment of acute and long COVID-19 have been demonstrated to provide symptomatic relief of disease symptoms while shortening patient recovery times. Acute COVID-19 patients receiving PBM therapy shown significant reduction in tissue inflammation as evidenced by marked improvements in chest X-ray ground-glass opacity, patient discomfort, reduced inflammatory markers (such as CRP), and elimination of the need for oxygen supplementation. Both scanning lasers and conformal LED pads demonstrate favorable outcomes. LED pads deliver higher fluences than scanned lasers in the same session times. Further studies of the prophylactic benefits of PBM are indicated.

Keywords: COVID-19, photobiomodulation, anti-inflammatory cytokines, M2 macrophage, conformal LED pads, scanning laser, c-reactive protein (CRP), chest X-ray lung opacity, SpO_2, long COVID.

Photobiomodulation Therapy of COVID-19

Photobiomodulation (PBM), the local and systemic application of non-ionizing electromagnetic radiation in the optical and near infrared spectrum to affect the biochemistry of living cells, tissue, and organs, is rapidly emerging as a new and promising modality in the battle against COVID-19 and other pathogenic inflammatory diseases.

Why PBM and Why Now?

The COVID-19 pandemic and its horrendous death toll was a wake-up call to the world that despite all the miracles of modern medicine, the state-of-the-art of present day medical technology remains woefully inadequate to combat unknown pathogens. Current therapeutic strategy requires first isolating and identifying a disease, then designing a therapeutic agent or vaccine to counteract it. This process is time consuming, requiring months-to-years of work for each newly encountered contagion. Unfortunately, while a response is being prepared a new infectious disease has ample opportunity to spread, mutate, injure, and kill.

But what if an efficacious immune defense to a new pathogen could be mounted not by focusing on the invader, but by boosting the immune defense of the infected (or even by resisting infection in the first place)? A variety of evolving medical technologies seek to customize immune response [1], learning new survivor skills from cells previously exposed to contagion or by adapting pluripotent cells. They include bone marrow mesenchymal stem cells (BMSCs) [2], monoclonal antibodies [3], convalescent plasma [4], and synthetic immunology [5,6]. Recruited in the battle against COVID-19 with mixed success, these nascent biotech modalities share a common weakness – they all rely on promoting human adaptive immune response to selectively target a known (and identifiable) pathogen.

Rather than attempting to program specific immunity, another altogether different approach to combating disease is to change the bioenergetics [7,8] of immune response – giving cells extra fuel they need to rapidly counteract infection using innate immune mechanisms perfected over millions of years of survival. To that effect, the sciences of photobiomodulation and photodynamic therapy represent the use of energy, not chemistry, to confer immunity.

In photobiomodulation (PBM), the molecular targets absorbing energy are naturally occurring light sensitive molecules called chromophores present within cells. These chromophores are able to absorb and metabolize photons photochemically (generally in the red and near infrared spectrum), stimulating otherwise inactive biochemical processes. In the case of photodynamic therapy (PDT), inert pharmacological agents introduced into a patient are activated by light into a chemical active state [9]. In this sense, PDT may be considered a pharmacological intervention and will not be discussed further here. Regardless, light activation of metabolic processes is unaffected by genomic mutations virions employ to deceive host immune defenses. As such, PBM can be deployed rapidly as a first line of defense to protect public health and contain contagions.

As evidenced by innumerable physiological and cytological changes, the rapidity of photobiomodulation is impressive. Transpiring within minutes of commencing treatment, the biological impact of PBM manifests measurable and significant changes in cellular metabolism. The metabolic changes affect mRNA gene transcription [10]; protein and enzyme synthesis [11]; nitric oxide signaling [12,13]; tissue pH [14]; SpO_2 and O_2Hb levels [15,16]; and tissue oxygen [17]. Quantifiable physiological effects of PBM include modulation of pro- and anti-inflammatory cytokines [18]; blood viscosity [19,20]; inflammatory markers (e.g. C reactive protein (CRP) and D-dimer levels) [21,22,23]; nerve transduction velocity [24,25], nociception [26,27]; edema [28,29], pulmonary infiltrates [30]; and angiogenesis [31]. Brain PBM also confirms improved cerebral blood flow [32]; increased neural connectivity [33]; neurogenesis [34]; and modulation of EEG brainwaves [35].

Observed improvements in general patient health from PBM include enhanced mobility [36,37]; reduced muscle fatigue and cramping [38,39]; reduced pain and inflammation [40,41,42]; improved breathing with reduced bronchoconstriction [43]; improved cardiovascular performance [44]; amelioration of digestive distress [45,46,47,48]; accelerated wound healing [49,50,51]; reduced mental stress [52,53]; improved sleep quality [54], enhanced brain waste removal [55]; and an heightened sense of overall wellbeing. Although the enumerated PBM indications extend beyond acute COVID etiology, as a multisystem inflammatory disease long COVID involves all of the aforementioned mechanisms.

As confirmed in randomized clinical trials, controlled case studies, and in evidence-based medicine studies described herein, health benefits of medical-grade PBM are repeatable across all demographic groups (age, biological sex, genetic origin, comorbidities). The consistency of reported beneficial results has also improved commensurately with progress in biophotonic technology used in PBM optical delivery.

Moreover, no significant adverse effects of PBM have been reported for more than four decades of PBM studies. Although PBM apparatus are considered Class II devices by the US FDA, the technology of PBM is considered 510(k) exempt.

PBM of Mitochondria

In photobiomodulation, non-ionizing radiation in the red and near infrared spectrum is delivered transdermally from arrays of LEDs or scanned low power lasers into visceral organs through cutaneous tissue. Contained within the tissue of target organs are wavelength-specific light-absorbing transmembrane proteins called chromophores [56,57] including most notably those of the cellular organelle mitochondria. To produce a therapeutic or homeostatic effect, photons of the right wavelengths must reach the target chromophores in sufficient number over time (measured as fluence) to stimulate a photochemical (not photothermal) effect. The properties of light transport (including optical scattering and absorption in intervening layers of tissue) and the thermodynamics and quantum photochemistry occurring within a target organ are a topic of Part I of this paper and will not be repeated here.

Pragmatically speaking, transdermal deep tissue PBM of visceral organs (and transcranial PBM of the brain) needed to treat COVID-19 induced tissue dysfunction and to protect organs against damage involves meeting strict criteria to deliver light into pleural, abdominal, pelvic, and cranial cavities in an appropriate range of doses. Most light therapy devices by contrast, are not suitable for use in deep-tissue PBM (even if they are effective for skin therapy).

The effects of PBM on cells and various organelles within them is well established. Among these organelles, mitochondria is considered a primary cellular target in photobiomodulation. In particular through the action of cytochrome-c [58,59,60,61] and reportedly through membrane bound water [62] the molecular biology and physiology of mitochondria is altered, i.e. modulated, by certain wavelengths of light.

Photochemical mechanisms include mitochondrial involvement in cellular respiration and metabolism [63,64]; gene expression [65,66,67]; immune function [68,69,70,71]; and tissue regeneration [72]. As such, mitochondria represent an important target of photobiomodulation-based cardiopulmonary [73,74,75,76]; immunotherapeutic [77]; neuroprotective [78,79]; and homeostatic regimens – modalities beneficial in the treatment of SARS-CoV-2 infections and COVID-19 disease therefrom. The pervasiveness of mitochondria occupying every organ and tissue type infected by coronavirus renders PBM the perfect nemesis to the SARS-CoV-2 virus and its genomic variants.

Mitochondria vs COVID-19

During infection and incubation, the SARS-CoV-2 spike protein attaches itself to the angiotensin-converting enzyme-2 (ACE-2) receptor as its primary molecular target for infection [80,81,82]. The ubiquity of the ACE-2 receptor present within tissue spans every physiological system. It is COVID's affinity for ACE-2 that gives the virus its unique ability to concurrently infect and inflame multiple organs throughout the human body – a condition referred to as multisystem inflammatory syndrome (in adults called MIS-A [83,84], and in children MIS-C [85]).

The diverse presentations arising from a multi-organ infection like COVID-19 greatly complicate conventional pharmacological regimens, forcing a patient to ingest a spectrum of medicines (including anti-inflammatories, antivirals, antibiotics, antipyretics, mucolytics, and analgesics), a concoction referred to in the popular press as a "pharma cocktail". Other meds are needed to protect the stomach, kidneys, and liver from drug toxicity. The frequent emergence of COVID-19 viral variants further complicates matters by evading human adaptive immune response, putting even previously infected or vaccinated patients at risk for reinfection.

By contrast, photobiomodulation of mitochondria disrupts COVID viral replication and inflammation at the molecular level, not by a specific chemical action. Therefore unlike pharmacological agents, photobiomodulation is applicable to all organ and tissue types enabled photochemically through reactive oxide species (ROS) and biologically by stimulating innate immune response locally and systemically. PBM efficacy is thereby unaffected by viral variants.

So despite the ability of SARS-CoV-2 to infect any organ hosting ACE-2 receptors, mitochondria too is present wherever the virus attacks – but in far greater numbers. An average human hosts 100,000 trillion mitochondria, with critical organs such as the liver and heart muscles containing from 3,000-to-5,000 mitochondria *per cell*, respectively. Mitochondria are tenacious survivors living approximately 100 days and replenishing at a rate of two billion per second [86].

Even in the absence of PBM activation, mitochondrial function is fundamental to innate immune defense, adaptive immune response, and cell death (apoptosis, autophagy, pyroptosis, oncosis, and necrosis) [87,88,89]. Among these

mechanisms, pyroptosis uniquely acts as a failsafe to prevent sequester of healthy cells by pathogens. Triggered by proinflammatory signals and oxidative stress [90,91] during pyroptosis, pores open in a cell's lipid membrane causing cytoplasmic swelling until the cell bursts. Cytoplasmic releases from cell bursts include inflammatory factors (IL-1β, IL-18, and HMGB-1) and NLRP3 inflammasomes. These tissue factors are present in lung inflammation observed in acute COVID-19 [92] and ARDS [93] patients.

So, in this sense, even though they are not considered immune cells, mitochondria perform important immune functions at the subcellular level. Mitochondria also function as sentinels governing cytotoxic response to ROS stress and hypoxemia [94], conditions common in epithelial bronchi during early phase COVID-19 infection [95]. In addition to promoting immune response in epithelium and endothelia, mitochondria also populate immune cells [96]. Although mitochondria are crucial in immune response, paradoxically they also may contribute to causing hyperinflammation, cytokine storms (aka cytokine release syndrome), and sepsis.

The hypoxic sensing ability of mitochondria naturally activates production of proinflammatory cytokines in an attempt to contain and eliminate pathogenic intruders. While inflammation is fundamental to immune defense and wound repair, too much inflammation is dangerous. This careful balance is dynamically and homeostatically regulated through intricate feedback mechanisms involving T-cells, cytokines, and macrophages. Such immunological components occur as pro-inflammatory and anti-inflammatory agents functioning in diametric opposition, the relative magnitude of which depends on oxidative stress arising from infection and inflammation, a process referred to as immune cell polarization. Macrophage polarization refers to the transformation of an undifferentiated macrophage into one of two distinct functional phenotypes, either M1 or M2. Similar polarization mechanisms exist for naïve T-lymphocytes.

Immune Cell Polarization

To understand the unique ability of photobiomodulation to limit inflammation during immune response we must examine the origin of inflammation itself. The immune system comprises a complex array of interacting cellular and molecular components arranged into two broad categories – lymphocytes involved in antigen-specific *adaptive* immune response and phagocytes supporting *innate* immune system mechanisms [97]. Both lymphocytes and phagocytes produce a combination of pro- and anti-inflammatory cytokines, proteins including interferon, interleukin, and growth factors involved in cell signaling, immune response, and inflammatory regulation.

Lymphocytes of the adaptive immune system comprise three major types, namely T-cells, B-cells, and NK (natural killer) cells. Born of mesenchymal stem cells in bone marrow, naïve T-cells migrate to the thymus where they mature into pathogen-specific cytotoxic (killer) T-cells used to kill invading pathogens and into helper T-cells stimulating antibody production both short-term and post-infection. However, because they are programmed to identify specific protein markers on a pathogen's surface, the adaptive immune system is ill equipped to combat the high mutation rate of single-strand RNA viruses such as SARS-CoV-2.

Phagocytes (including monocytes, macrophages, neutrophils, dendritic cells, and mast cells) are components of the innate immune system, defensive mechanisms not specific to any particular antigen. Monocytes develop in bone marrow and mature in the blood, entering tissue or organs within a couple of days where they transform into macrophages – immune cells capable of both cytotoxic and cytoprotective phenotypes. Specifically, M1 type macrophages are catabolic proinflammatory agents beneficial in destroying pathogens while M2 macrophages are anabolic anti-inflammatory cells important to tissue repair and wound healing. The two types of macrophages operate in balance to provide necessary but not overly aggressive immune response.

The cytotoxic type macrophage responds to endogenous cellular sensing of a molecules indicating a disease state. For example, exposure of naïve monocytes to tissue necrosis factor (TNF); lipopolysaccharide (LPS); granulocyte-macrophage colony-stimulating factor (GM-CSF); and interferon IFN-γ (a Th1 cytokine) *polarizes* macrophages into the M1 type [98]. The M1 macrophages, once activated release proinflammatory cytokines including IL-1, IL-6, G-CSF, IFNs (α, β, γ), and tissue necrosis factors TNF-α and TNF-β.

These cytokines promote a variety of pathogenic and antiviral mechanisms including pyrogenicity; B-cell, T-cell, and granulocyte activation; monocyte & neutrophil recruitment; and phagocytosis. M1 macrophages also release nitric oxide (NO) or reactive oxygen intermediates (ROI), initiate immune response, and phagocytize invading pathogens. Proinflammatory T-helper cells including Th1 and Th17 [99] detect the presence of a disease state and produce more *cytotoxic* cytokines, a positive-feedback biochemical control mechanism akin to inflammatory cytokine amplification.

Concurrently, detection of a disease condition also stimulates production of *cytoprotective* immune response. For example, exposure of naïve monocytes to toll-like-receptor molecules (TLR), interleukins IL-4, IL-6, IL-13, and adenosine stimulate M2 polarizations [100]. Once activated, M2 macrophages produce a variety of anti-inflammatory cytokines including IL-1ra, IL-4, IL-10, IL-12, and TGF-β and others. Released cytoprotective cytokines activate inhibitors of T-cells, B-cells, TGF-β factor, and regulation of phagocytes and NK cells, facilitating negative-feedback regulation of inflammation. Anti-inflammatory T helper cells including Th2 [101] detect the presence of disease conditions to produce more cytoprotective cytokines, a positive-feedback biochemical control mechanism involving amplification of anti-inflammatory cytokines.

Although both classes of cytokines demonstrate elevated concentrations during infection, the relative concentrations of cytotoxic-to-cytoprotective cytokines change ratiometrically as an infection progresses step-by-step. Considering time (chronicity) in the *sequential* process of anti-infective wound healing, the M1 type macrophage appears first during the inflammatory and proliferative phases, while the regenerative M2 macrophage predominates the differentiation and remodeling (maturation) phases. The relative activity of M1 and M2 macrophages are correspondingly controlled through the aforementioned pro- and anti-inflammatory cytokines [102,103] in accordance with a cell's oxidative stress, also known as the redox state of the cell.

Reactive oxide species (ROS) are naturally present within a cell's cytoplasm. ROS and their ROI reactive intermediaries include superoxide ($O_2^{-\bullet}$); singlet oxygen ($^1O_2$); the hydroxyl radical ($OH^\bullet$ or $^\bullet OH$); perhydroxyl radical ($HO_2^\bullet$); hypochlorous acid (HOCl); hydrogen peroxide (H_2O_2); and nitric oxide (NO). Reactions of nitric oxide with superoxide may also produce peroxynitrite ($ONOO^-$), formally classified as a reactive nitrogen species (RNS). Reactions between ROS and thiols also produce reactive sulfur species (RSS). As they are derived from ROS, both RNS are RSS are still considered variants of reactive oxygen species, performing important tasks including cell signaling, gene expression, apoptosis, and ion transport. In excess, ROS (especially hydroxyl radicals) can exhibit deleterious effects damaging nucleic acids (RNA, DNA); lipids; proteins; amino-acid side chains; and double bonds in unsaturated fatty acids.

In healthy cells, reactive oxygen, nitrogen, and sulfur species are homeostatically regulated and balanced by endogenous antioxidant molecules. Cellular antioxidants neutralize free radicals through electron exchange to eliminate unpaired electrons [104,105]. Examples include ascorbic acid $AscH^-$ (vitamin C); alpha-tocopherol $C_{29}H_{50}O_2$ (vitamin E); glutathione; uric acid; phenol; polyphenols; and complex natural compounds including flavonoids (catechin, epicatechin, resveratrol), carotenoids, steroids, ginsenosides, glycosides, and thiols [106]. Disruptions in this sensitive balance, either from an accumulation of excess ROS or depletion of antioxidants, results in oxidative stress. The oxidative stress in turn modulates immune response and inflammation.

In the case of severe COVID-19 infections, homeostatic regulation and redox signaling malfunction, mismanaging the inflammatory response process and triggering hyperinflammation [107,108]. In cases of severe or chronic inflammation, autoimmune disease may result with the potential for permanent organ damage or organ failure. The lungs comprise a primary site of hyperinflammation, generally expressed in the form of bilateral interstitial pneumonia [109]. It is hypothesized that liver impairment may play a central role, especially in severe clinical presentations of COVID-19 [110,111]. Persistent long-term inflammation in post COVID patients is also commonly observed in the brain and in the intestines. In essence, the immunopathology of the SARS-CoV-2 virus is its ability to provoke excessive cytotoxic inflammation, sacrificing its early viral replicants for the greater long-term cause of weakening or damaging host defense.

Another unique (if not insidious) feature of COVID-19 is its ability to infect *immune cells* and disrupt their function. Recent studies show that the virion can infect at least two types of immune cells normally engaged in sentinel functions, namely macrophages in the lungs and monocytes in the blood. Once infected these first-responder immune cells die by pyroptosis scattering inflammatory alarm signals and further fueling hyperinflammation [112]. The surprising feature of this attack is that monocytes don't carry ACE-2 receptors and macrophages are only minimally populated by them. Instead COVID-19 uses antibodies in its spike protein to help attach to the CD16 receptor present on the monocyte's surface. The stronger an adaptive immune response is, the more antibodies are formed helping the virus to infect and kill monocytes, in turn releasing pro-inflammatory mediators further exacerbating hyperinflammation [113].

PBM Regulates Inflammation

Given the diabolical mechanisms of COVID-19 to over-stimulate the immune system into

hyperinflammation, it would be reasonable to assume that anti-infective PBM might further exacerbate the problem, when in fact just the opposite is true. The effect of photobiomodulation on local and systemic immune response is not simply to boost immunoresponse to infection but to photochemically promote a balancing of pro-inflammatory cytokines and anti-inflammatory cytokines [114,115].

Although the exact mechanisms for PBM regulating these anti-infective and inflammatory factors are not fully understood, mitochondria are known to be sensitive to oxidative stress. Specifically, photobiomodulation of normal cells activates NF-kB (the immune transcription factor for stress response genes) and concurrently causes a burst of ROS [116] producing a biochemical cascade beneficial in ridding infected tissue of pathogens. In tissue under oxidative stress, however, PBM invokes a countereffect of reducing ROS levels and suppressing the transcription of pro-inflammatory cytokines. So photobiomodulation does not simply elevate all cytokine production, it selects which types of cytokines are produced depending on the redox state of the cell, essentially down-regulating cytotoxic immune levels in tissue exhibiting signs of hyperinflammation.

Limiting the over-expression of inflammatory cytokines by reacting to changes in cellular redox represents a *state-based* immunoregulatory form of negative feedback. As shown schematically in **Figure 1**, the interaction between photobiomodulation and an infected cell's oxidative state, as mediated by macrophages and T-cells, controls the expression and relative ratio of pro- and anti-inflammatory cytokines.

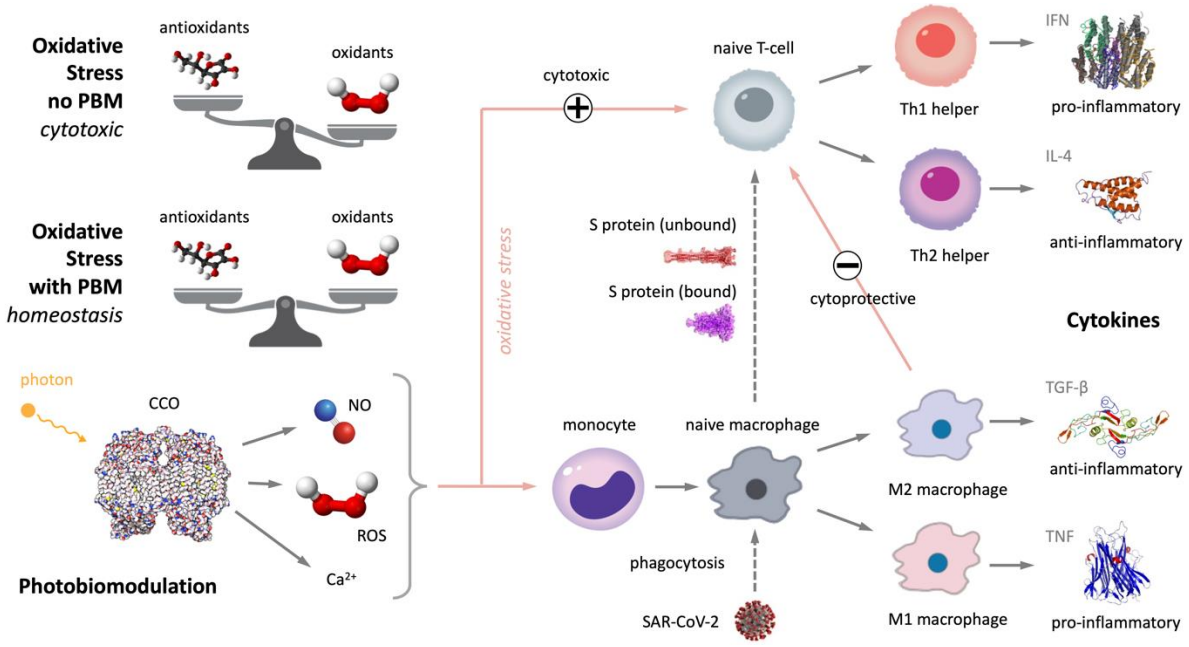

Figure 1. The role of oxidative stress in photobiomodulation of COVID-19. In the absence of PBM increased NO, ROS, and Ca^{2+} released from mitochondrial CCO produces oxidative stress causing increased production of pro-inflammatory cytokines by macrophages and T-helper cells at the risk of hyperinflammation and a cytokine storm. In the presence of red and NIR light, CCO photobiomodulation increases the production of anti-inflammatory cytokines and through negative feedback to T-cells, down regulates cytotoxic cytokine production promoting immune homeostasis. Attribution: CCO and cytokine images courtesy of Wikipedia.

Represented symbolically, a COVID-19 infection imbalances the homeostatic ratio of oxidants and antioxidants, creating oxidative stress detected by mitochondria resulting in a responsive burst of ROS, NO, and Ca^{2+}. The oxidative stress stimulates an increase in cytokine production from phagocytes and T-helper cells, predominantly expressed by pro-inflammatory components. Photobiomodulation of cells in oxidative stress produces a countereffect reducing the production of ROS and the release of NO, rebalancing the scales and in turn increasing the fraction of anti-inflammatory cytokines in the immune response. Also depicted is the process of phagocytosis of a SARS-CoV-2 virus extracting the spike protein signatures in both pre-fusion and post-fusion [117] conformal topologies. These molecular messages program naïve T-cells with the ability to recognize viral surface proteins, enabling albeit for a limited time (at least until the virus mutates) an adaptive host immune response.

Another mechanism of PBM in treating COVID-19 is its ability to accelerate the inflammatory phase of wound healing through enhanced biokinetics resulting from PBM-induced ATP generation. By accelerating the body's antiviral response from weeks to days, the severity and chronicity of COVID-19 disease can be minimized, thereby limiting the opportunity for the infection to damage organs or produce sequelae causing chronic inflammation or autoimmune disease, i.e. long COVID. Limiting the over-expression of inflammatory cytokines by shortening the duration of the inflammatory phase in wound repair thereby comprises a *time-based* regulatory mechanism. Functioning together with *state-based* regulation PBM is able to promote a robust anti-infective response to COVID-19 without being tricked into hyperinflammation.

Other mechanisms moderating inflammation involve the NIR activation of ion gates such as transient receptor potential channels (TRPs) – transmembrane proteins present in mitochondria [118], on stem cells, and on certain immune cells (such as mast cells). The photochemical activity of ion channels present on the surfaces of immune cells (including T-cells, T-memory cells, B-cells, and NK cells) may be highly charge-mass specific, or alternatively may indiscriminately accommodate transport of an entire range of cations and anions. Ion transport affecting cellular function involves an impressive range of charge states, atomic dimensions, and masses.

Common ion transporters include Ca^{2+}, Na^{+}, K^{+}, Mg^{2+}, Zn^{2+}, Cl^{-}, I^{-}, Br^{-}, GABA, TRPM, TRPC, TRPV, P2X, P2R, and H^{+} (also known as proton or pH channels) [119,120]. At the present time the optical absorption properties (and corresponding action spectra) of many of the ion transporters remains largely uncharacterized. Dysfunction of ion channels is also implicated in vascular disease [121] and may play a role in PBM's beneficial effects on blood perfusion, thrombosis, and cardiovascular health during patient recovery from acute COVID-19. More research is required to isolate the direct effect of light on biodiverse transmembrane ion channels and transporters, and the therapeutic potential of PBM in treating respiratory and cardiovascular inflammatory disease.

Whole-Organ PBM of COVID

PBM Optical Delivery. The preponderance of ACE-2 receptors determines the primary targets of COVID-19 infection (and likewise the primary tissue and organ targets for photobiomodulation). As shown in **Figure 2**, organs infected by the SARS-CoV-2 virus are located throughout the body, underscoring the virion's multi-organ nature [122]. In the treatment of COVID-19, affected organs may be treated separately in sequential order, or concurrently. The key criteria of any anti-infective therapy is to ensure that the treatment of an infected organ covers the entire organ, otherwise pathogens in untreated areas will multiply and repopulate treated tissue freed of the contagion. This therapeutic modality is referred to as "whole organ" PBM because no portion remains untreated to reinfect the rest. To cover large areas, whole-organ PBM therapy requires either a laser scanner or reconfigurable conformal LED pads to cover the entirety of infected organs, treating areas ranging from as little as 200 cm^2 to as much as 1,200 cm^2.

As depicted, organs are arranged in physiological order by the head and face, neck and throat, and the upper, middle, and lower torso. The face and head zone includes mucosal membranes of the eyes, sinuses, oral cavity, and tonsils treated transdermally across the nose and face using both red and NIR light. Oral cavity treatment may also utilize under-chin LED pads. For eye safety, PBM of facial tissue, sinuses, and eyes should avoid laser optical delivery methods.

Transcranial treatments (using predominantly NIR light) involve three delivery configurations depending on COVID-19 clinical presentations – over the face, around the head (headband), and over the top. As the most basic configuration for treating neurological conditions of long COVID, the conformal LED headband covers the anterior forehead and posterior cerebellum, reaching the prefrontal cerebral cortex, motor cortex, and limbic system as well as the hindbrain and upper spinal cord. Placing LED pads over the face provides the most direct path for photons to reach the cranial neuroendocrine glands comprising the hypothalamus-pituitary-pineal axis. Top-of-head therapy is used to reach the corpus collosum when balancing hemispheric activity and improving cross-brain connectivity, valuable in treating COVID mental health issues.

Using a special collar-shaped LED pad circumscribing the throat, PBM of the neck concurrently treats the pharynges, airway epithelial cells (AEC), trachea, esophagus, lymph nodes, thyroid, and parathyroid glands. The upper torso region includes the lungs, heart, thymus, and sternum on the anterior portion and the lungs, spine, and spinal cord on the posterior side. The spine, sternum (and femur) are especially valuable in immune PBM as they contain significant quantities of bone marrow. The middle torso contains the stomach, liver, pancreas, spleen and gallbladder, accessible from the anterior upper abdomen; and the spine, spinal

cord, kidneys, and adrenal glands from the posterior backside. The lower torso or gut contains the intestines as well as the genitourinary tract including the urinary bladder, urethra, and genitalia of the pelvic cavity. The lower back and hips also importantly contain neurovascular connections to thighs and legs including the femoral and sciatic nerves and the femoral and gluteal arteries.

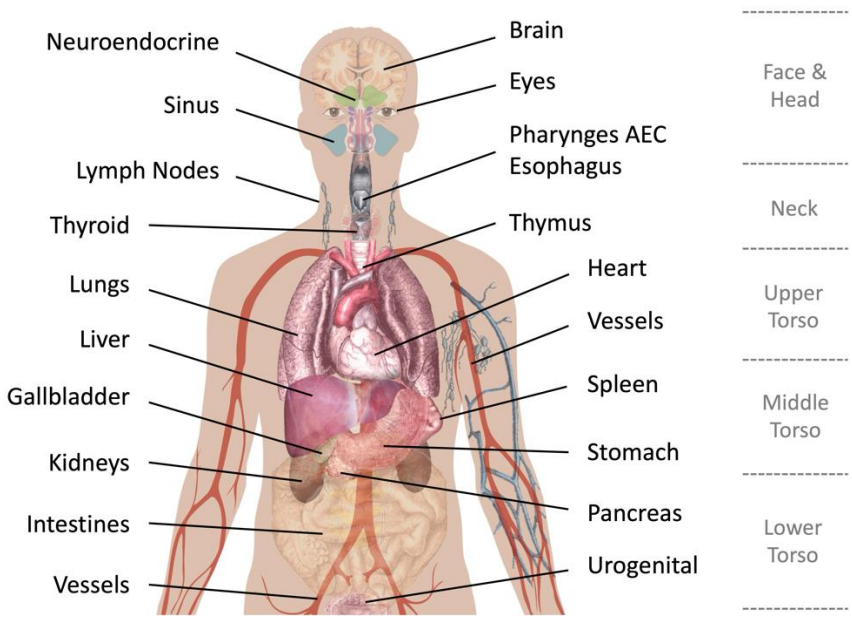

Figure 2. Anterior view of organs with preponderance of ACE-2 receptors subject to SARS-CoV-2 infection and representing therapeutic targets for photobiomodulation. Treatments are subdivided into PBM target zones comprising the face and head; throat and neck; upper torso (including lungs, heart, and thymus); middle torso or abdomen (including stomach, liver, spleen, pancreas and kidneys); and lower torso of the abdomen and pelvic cavity (containing intestines, urinary bladder, urethra, gonads (testes, ovaries), and uterus). Skeletal bones, muscles, soft tissue, along with tissue innervation and most vascularization are removed for the sake of image clarity. Anatomy representations used under public domain licenses (adapted from Mikael Häggström).

PBM Targets. As a multisystem inflammatory syndrome (MIS), COVID-19 is capable of manifesting symptoms in any organ or tissue with ACE-2 receptors in any of these identified regions. The corresponding disease presentations of acute COVID-19 and long COVID [123] are described in **Table 1**. ACE-2 populated organs thereby represent the primary tissue target candidates for PBM therapy. PBM targets are arranged in descending order by upper respiratory tract including mucosa of the sinus, nose, and eyes [124,125,126,127]; AEC of the oral cavity and tonsils [124,125,128,129,130,131]; passageways of the neck including the pharynx, larynx, trachea, and esophagus [126,132,133,134,135]; and the lower respiratory system including the lungs, bronchia, and cilia [124,125,126,127,128,129,136,137,138,139].

Non-respiratory organ involvement includes the heart and cardiac muscles [125,126,129,132,140,141] and the digestive tract including the stomach [124,125,129,142,143]; liver and bile duct [124,125,126,129,132,142,144]; gall bladder and appendix [126,129,132,142,145]; spleen [124,144,146,147]; and pancreas [125,126,142,148,149]. Excretory PBM organ targets of the gastrointestinal (GI) tract infected (or affected) by COVID-19 include the kidneys and ureter [124,125,126,129,132,150,151]; the small intestines (duodenum, jejunum, ileum), large intestines (cecum, colon, rectum) and potentially the diverticula [124,126,129,132,142]; along with the urinary bladder and urethra [130,152,153,154]. COVID is also implicated in impacting the microbiome of the gut disrupting the healthy blend of bacterial fauna now known to exert wide ranging systemic physiological effects (even on the brain).

COVID infection also occurs in reproductive organs of the genitourinary system in both biological males and females including the gonads (ovaries, testes) and glands. Other affected organs suspectable to COVID-19 induced hyperinflammation include the uterus and prostate glands, even if the organ itself is not infected. Possible adverse effects (presenting similar to STDs) include pain, edema, cramping, unusual bleeding, hormonal

deregulation, sexual dysfunction, and in severe cases, sterility [124,125,128,129,132,153,155]. COVID also manifests a variety of presentations throughout the body's largest organ – skin. Symptoms range from discoloration and itching to rashes and pustules [156,157,158,159,160,161,162].

Although not consistently expressed, COVID-19 also presents a diverse spectrum of musculoskeletal effects especially in long COVID. Symptoms include muscle weakness; joint stiffness; myalgia, myositis, myopathies, and sometimes polymyositis; along with arthralgia and arthritis [124,163,164,165,166,167,168,169,170]. Other non-localized expressions of both acute and long COVID-19 involve multi-organ multi-systemic disorders [124,156,171,172,173,174,175,176]. PBM is performed atop affected organs, along the upper spine, or transcranially over the face to treat the CNS (brain) and neuroendocrine system (via hypothalamus-pituitary axis).

Targeting COVID induced vascular inflammation [124,126,171,177,178,179,180,181] requires treating organs functioning as significant blood reservoirs, primarily concurrent PBM of the heart-lungs and/or the liver and spleen. Immune dysfunction [182] in acute and long COVID typically presents severe- or hyper-inflammation [183] and in more extreme cases autoimmune disease [184] or chronic conditions [185,186,187]. PBM targeting major organs of the immune system include the thymus, lymph nodes, bone marrow, spleen along with epithelium comprising the skin and mucous membranes of the sinuses, airway epithelial cells (AEC), and bronchia of the lungs. The liver also performs key immune functions to capture, damage, and clear blood borne pathogens, combatting viremic dispersal. Although PBM may be performed separately, for efficiency sake the major organs can be treated concurrently on the body anterior side across the face (sinuses) and along the Schell central core (from under the chin along the sternum to the stomach).

As COVID-19 exhibits significant involvement of the central and peripheral nervous system and the brain [188,189,190,132], a number of different protocols are required to treat nerve dysfunction along the spinal cord [171,175,191], cranial nerves of the autonomous nervous system (ANS), and spinal nerves of the peripheral nervous system (PNS) [192,193,194,195,196,197]. PBM may be performed locally targeting COVID impaired sensory nerve receptors [198,199,200,201,202], over-active nociceptors [203,204,205], ganglions [206], or to manage pain transduction along the spinal cord and peripheral nerves [207,208].

Transcranial PBM is required to treat cognitive deficits, physiological, and psychological effects commonly expressed by long COVID infections of the brain [124,132,171,208,209,210,211]. Numerous ACE-2 receptors populate glands of the endocrine [212] and neuroendocrine [211] systems causing organ deregulation affecting homeostasis and unbalancing hormone levels. PBM therapy may be performed on the affected glands; directly on the brain [213,214]; and over the face penetrating the hypothalamus-pituitary-pineal axis [215].

Table 1: PBM treatment targets of COVID-19 based on ACE-2 receptors including requisite treatment area

PBM Target	Treatment		Presentations		Refs
	Location	Area (cm^2)	Acute COVID-19	Long COVID	
Sinus & Eyes	Face, nose, eyes*	400	Rhinitis, sinusitis, anosmia (smell loss) conjunctivitis, eye infection, runny nose secondary infection	Chronic sinusitis, impaired vision, nasal congestion, sneezing, blurry vision, bacterial infection	124 -to- 127
Oral cavity AEC	Facial cheeks or under chin*	400	Ageusia (taste loss) sore throat, URTI, headaches, tonsilitis, oral lesions, Kawasaki-like syndrome	Sore throat, URTI, tooth pain, facial pressure, headaches, canker sores, oral lesions	124, 125, 128 -to- 131
Pharynx, larynx, trachea, esophagus	Surrounding neck (collar)	250	Sore or scratchy throat, swallowing difficulty, pharyngeal erythema	Sore throat, dry cough, gagging, tonsilitis, acid reflux, esophageal hypersensitivity	126, 132, -to- 135
Lungs	Transverse anterior chest (upper torso) or posterior	400 – 600	Dyspnea, sputum, choking, fibrosis, pneumonia, cough, co-infection, alveolar damage, pulmonary	Cough, shortness of breath, chest pain, arrhythmias, asthma oxygen requirements, ARDS, COPD, reduced	124 -to- 129, 136 -to-

	upper back		infiltration, paroxysmal cough	DLCO, pulmonary hypertension, reduced alveolar volume	139
Heart	Anterior transverse chest	200	Myocardial injury, acute coronary synd, cardio distress, cardio inflam, palmus, chest cardiac thrombosis, pain, arrhythmias, myocarditis	Cardiomyopathy, palpitations, chest pain, arrhythmias, myocarditis, pericarditis, heart attack	125, 126, 129, 132, 140, 141
Stomach	Transverse anterior abdomen (mid torso)	400 – 600	Diarrhea, cramps anorexia, nausea, abdominal pain, vomiting, acute colonic pseudo-obstruction	Diarrhea, stomach pain, food intolerance, gaseous distention, nausea, gut dysbiosis, GERD, peptic ulcer GI distress, bloating,	124, 125, 129, 142, 143
Liver & bile duct	Transverse anterior abdomen (mid torso)	400	Elevated liver transaminases, transaminitis, high creatine, acute liver injury	Elevated liver transaminases, liver-spleen dysfunction	124, 129, 132, 142, 144
Gall bladder & appendix	Transverse anterior abdomen (mid torso)	200	Cholelithiasis, acute cholecystitis, appendicitis, GBP (perforation)	Chronic cholecystitis gallbladder thrombosis	126, 129, 132, 142, 144
Spleen	Transverse anterior abdomen (mid torso)	200	Splenomegaly, microthrombosis, hematopoietic suppression, splenic infarction, atraumatic	White pulp atrophy, neutrophil/plasma cell infiltration, splenic fibrosis, corpuscular atrophy, liver-spleen	124, 144, 146, 147
Pancreas	Transverse anterior abdomen (mid torso)	200	Acute pancreatitis, multi-organ dysfunction	Insulin deficiency, type 1 diabetes (T1D) hyperglycemia, chronic pancreatitis	125, 126, 142, 144, 149
Kidneys	Oblique abdomen (mid torso or mid back)	400 – 800	Proteinuria, hematuria (stool blood), acute kidney injury, acute renal failure	Chronic kidney failure, drug interactions, dialysis, comorbidities	124 -to- 126, 129, 132, 149, 151
Intestine	Transverse anterior low abdomen (lower torso)	600 – 1,200	Cramps, ileus, Crohns, hemorrhagic colitis, ischemic colitis, infectious colitis, mesenteric ischemia	Chronic mesenteric ischemia, inflam bowel disease, diarrhea, cramps, constipation	124, 126, 129, 132, 142
Urinary Bladder	Transverse anterior low abdomen (lower torso)	200	Hematuria (urine blood), pyuria (pus), cystitis, pain	Changes in frequency, urgency, nocturia, incomplete emptying, chronic cystitis	129, 152 -to- 154
Repro	Transverse anterior low abdomen (lower torso)	400 – 600	Hormonal imbalances, hypogonadism, ED (erectile dysfunction), spermatogenesis impairment, prostatic hyperplasia	Hormonal imbalances, menstrual changes, early menopause, reduced fertility, cramping, bleeding low testosterone	124, 128, 129, 132, 153, 155
Skin	Over affected tissue	200 – 1200	Impaired wound healing, neurogenic issues,	Petechiae, rosacea psoriasis, eczema acne, pustules	156 -to- 162

			immune-complex dysfunction		
Musculo-skeletal	Atop affected muscle	200 – 600	Myalgia, arthralgia cramping, fever, muscle soreness, aches, osteonecrosis, heterotopic ossification (HO)	Muscle joint pain, arthritis, myositis, twitching, muscle weakness, stiffness, post exertion fatigue, elevated macrophages	124, 163 -to- 170
Multi-organ multi-sys	Atop organs, upper spine, hypothalamus-pituitary axis (transcranial)	600	Fever, malaise fatigue, aches, thrombosis, lymphopenia	Malaise, post exertion malaise, fever, ischemic heart disease, embolism	124, 156, 171 -to- 176
Vessels & Blood	Anteriorly atop heart-lungs, and/or spleen-liver	600	Vasculitis, viremia, hypokalemia, thrombosis, lymphopenia, alveolar-capillary dysfunction, myocardial infarction, increased viscosity, thrombotic risk, deep vein thrombosis, endothelial dysfunction	Chronic vasculitis, microangiopathy, microvascular coagulopathy, hypoperfusion, increased viscosity, thrombotic risk, deep vein thrombosis, endothelial dysfunction, low SpO_2, supplemental oxygen	124, 126, 171, 177 -to- 181
Immune & lymph	Anterior Schell core (thymus, sternum) or posterior spine	200 – 600	WBC modulation, lymphopenia, increase in monocytes, thrombocytopenia, bone marrow damage, hyperinflammation	Immune system dysregulation, fever, autoimmune disease, SIRS, multi-organ failure	124, 128, 171, 182 -to- 184
CNS, PNS	Spinal cord *or* vagus nerve	400 – 600	Polyneuropathy, Guillian-Barre syndrome, stroke (thromboembolic), muscle weakness, myoclonus, dizziness, nausea,	Synaptic hypoxemia, hypocapnia induced hyperventilation, neuromuscular disorders	132, 171, 175, 188 -to- 197
Sensory Perception	affected organ (e.g. eyes, nose, tongue)		Change/loss of smell (hyposmia, anosmia), change/loss of taste (ageusia, dysgeusia)	Inflammation, TRP/ion channel dysfunction, impaired signal transduction	198 -to- 202
Nociceptors	affected organ	200 – 600	Hypersensitivity, chronic pain, irritation, allodynia, paresthesia	Hyperinflammation, TRP/ion channel dysfunction	203 -to- 205
Neurologic Pain	spinal cord or peripheral nerve	200 – 600	Chronic pain, soreness, shooting pain, burning, numbness, paresthesia	Hyperinflammation, nerve hypoxia, allergy, pharyngodynia	206 -to- 208
Brain	headband (Transcranial brain)	450 + 200 (650 total)	Headaches, stroke, cerebral hemorrhage, confusion, seizures, ataxia, encephalitis, brain inflam, anosmia, ageusia, accelerated neurodegeneration, memory impairment	Headaches, brain fog, cognitive deficits, despair, dizziness, change in taste or smell, ADEM, AD risk, paresthesia, synaptic hypoxemia, meningitis, delirium, depression, sleep disorder, anxiety	124, 132, 171, 208, 209 -to- 211
Endocrine & Neuro-Endocrine Glands	affected organ *and/or*	400	Pituitary apoplexy, platelet dysfunction, hypercoagulability, elevated fibrinogen, and D-dimer levels,	Hormonal imbalances affecting sleep, mood, energy, metabolism, mental health, attitude	211, 212 -to- 215

transcranial brain (face)	corticosteroid insufficiency, cortisol dysregulation

* not amenable for scanned laser optical delivery
URPI: upper respiratory tract infection
GERD: gastroesophageal reflux disease
ADEM: acute disseminated encephalomyelitis
SIRS: systemic inflammatory response syndrome
DLCO: diffusing (lung) capacity of carbon monoxide

PBM Treatment Areas. The above table specifies the recommended surface area for treating various organs infected with active COVID-19 or with sequelae therefrom. Coverage areas apply to both the raster area of a laser scanner or the pad area for conformal LED pads. Light is assumed to impinge upon the skin nearly perpendicular to the surface. Although a number of glands and organs are smaller than 200 cm^2 in surface area, it is neither practical nor efficient to sequentially treat each organ separately. Instead, a larger treatment area between 400-to-600 cm^2 is beneficial for *multi-organ* therapy of the sinuses, lungs, stomach-liver, kidneys, reproductive organs, major immune system organs (Schell central core), the spinal cord, and the brain. Moreover, concurrent therapy of the entire middle and lower abdomen (intestines) or the upper middle torso (heart-lungs, stomach and liver-spleen) requires a treatment area between 600-to-1200 cm^2. While it is possible to raster light over large areas with a laser scanner, conformal LED pads uniformly deliver energy to the entire area contemporaneously.

Post-acute COVID-19 Sequalae. The aforementioned discussion of PBM targets considers all organs irrespective of whether the treated condition involves an active infection (acute COVID-19), a recent post-acute recovery (short-term sequalae), or one-or-more chronic conditions developing over time (long COVID). Compared to limited geography of organ involvement in early phase SARS-CoV-2 infections contained within the upper and lower respiratory tracts [216] and with regimens primarily focused on preventing a cytokine storm [217], the protocol and treatment areas required to manage long-term effects of mild [218] and severe [219] COVID-19 infections are far more diverse [220].

The spectrum of presentations of long COVID is further complicated by prolonged delays between the original infection and a post COVID diagnosis, typically a lag of over 8 months. More specifically, the long-term impact of long COVID on an individual's health depends not only on the severity of the infection but on various risk factors and comorbidities. Factors include hypertension, chronic lung disease, obesity, diabetes, depression [221] along with anxiety; asthma; eczema; hay fever [222]; and smoking [223].

Another complex topic in long COVID is myocarditis, inflammation of the heart muscle. Myocarditis is well established to be a consequence of a post-acute SARS-CoV-2 infection [224]. More recently it has been discovered that the COVID vaccine can also give rise to the condition [225,226] but at a significantly lower incident rate [227,228]. Complicating the discourse is the fact that asymptomatic SARS-CoV-2 infections can still cause long COVID symptoms [229] and even can lead to heart damage [230,231].

Regardless whether the source of myocarditis is sequalae of an acute symptomatic COVID-19 infection, from an undiagnosed asymptomatic SARS-CoV-2 infection, from a COVID vaccine reaction, or some combination thereof, the anti-inflammatory PBM regimen for recovery of injured organs is the same – a pro-circulation anti-inflammatory wound healing protocol. In this regard, PBM is agnostic to the cause of the heart damage.

Survey of COVID PBM Reports

As an emerging modality in the treatment of inflammatory disease such as acute and long COVID-19, photobiomodulation today remains a relatively nascent technology and fledgling industry. Widespread PBM adoption faces diverse challenges including lack of awareness and proper medical training on the topic; inconsistency among therapeutic protocols; disagreement in optical sources (lasers vs LEDs); diverse and confusing delivery methods (conformal pads, rigid panels, wands, and probes); and limited peer-reviewed case studies.

Challenges notwithstanding, a search of published works on the topic "photobiomodulation of COVID-19" yields over 150,000 results, the vast majority of which are overwhelmingly favorable. Survey results can be broken into several categories (i) meta-analysis of anti-inflammatory PBM studies, (ii) SARS-CoV-2 human cell cultures studies, (iii) animal studies, (iv) organ specific COVID-19 studies, (v) case studies in PBM of human acute COVID-19, and (vi) PBM case reports of human long COVID. Pragmatically, the literature survey described herein is necessarily limited in scope, concentrating on the insightful analytical papers or historically impactful case studies.

Anti-inflammatory PBM Studies. A number of review papers consider the suitability of PBM for COVID-19 therapy using mechanistic and phenomenological arguments of prior studies involving inflammatory disease such as ARDS, COPD, pneumonia, and arthritis. As described previously in this paper and related presentations [232], the mechanisms and anti-inflammatory benefits of PBM (and the molecular biology thereof) are well established.

Published studies include PBM's effect on tissue inflammation [233,234]; cellular metabolism [235]; cytokine regulation [236,237]; blood perfusion [238,239]; cardiopulmonary function [240,241]; tissue oxygenation and SpO_2 [242,243]; immunomodulation [244,245]; and inhibiting neurodegeneration [246].

In light of PBM results treating inflammatory disease, meta-analysis and systematic review papers [247,248] categorically agree on the "high potential" or "probable positive effects" of photobiomodulation as an adjunctive treatment for COVID-19. Interestingly the works refer to PBM in the future tense as an prospective coronavirus therapy. What is not widely recognized is that PBM has been used extensively in treating of COVID-19 since early 2020, and with great success. Reasons for this reporting asynchrony vary but include the fact that many studies delay publishing till certain milestones are reached, sometimes remaining unpublished for over a year.

In Vitro Studies. Various studies on the effect of PBM on SARS-CoV-2 infected cell lines have been performed in vitro. One red light laser study [249] compared infected and uninfected HEK293/ACE-2 cells, the stable ACE-2 line of HEK293 immortalized human embryonic kidney cells. Results showed PBM preferentially caused membrane damage in infected cells but exhibited no adverse effects on healthy cell viability and cytotoxicity.

Another experiment [250] studied the effects of PBM on HEK293 cell lines expressing the human TLR4 reporter gene alkaline phosphatase (SEAP). Regulated by NF-κB and AP1 transcription factors, the TLR4 receptor is implicated in COVID-19 induced hyperinflammation and acute lung injury as expressed throughout lung tissue alveolar cells, alveolar macrophages, and lung fibroblasts. An inflammatory mediator comprising bacterial lipopolysaccharide (LPS) dissolved in phosphate buffered saline was employed to emulate coronaviral inflammation. Assays of pro-inflammatory cytokine IL-6 show infrared PBM illumination reduces secreted cytokine levels by 75%.

Animal Studies. Animal studies, especially mammalian, are also insightful in understanding COVID-19 disease trajectories and anticipating PBM effects on impeding viral infection, viremic dispersal, and hyperinflammation. For example, a study of twenty-four Wistar rats [251]compared lung injury with-and-without PBM to normal healthy animals (control group). Intended to emulate COVID-19 inflammatory injury, surgical lung injury was induced in 2/3rd of the study population (administered with anesthesia), half of which also received infrared (808 nm) PBM. Three days after surgery, all animals were euthanized individually by anesthetic overdose and a lung tissue sample of each animal removed for analysis. Pulmonary evaluation included histopathological (morphometric) analysis, lung injury scoring, inflammatory cell assays, and expression of pro-inflammatory cytokine interleukin 1β (IL-1β). The study concluded PBM greatly reduced the magnitude of inflammation of lung tissue. Most notably inflammatory IL-1β cytokines were reduced by 30%.

The anti-inflammatory effects of PBM on lung inflammation were investigated in a meta-analysis of animal studies [252] comprising ten publications involving rats and three studies on rabbits. Results confirm PBM therapy reducedthe pro-inflammatory cytokines TNFα, IL-1β, IL-6 and the inflammatory enzyme myeloperoxidase (MPO) while it increased the anti-inflammatory cytokines IL-10.

Despite encouraging test results, adapting animal PBM studies to human therapeutic regimens is challenging in part because of differing immunopathology of species, and because of biphasic dose-response factors. Pragmatically, scaling is the greatest challenge in interpreting and adapting PBM for human subjects. Specifically a laser spot size of 10 mm (having an area of less than $1cm^2$) may cover the entirety of a mouse lung but represents less than 1% of a human lung. To adapt animal lab results to human whole-organ PBM therapy requires a different optical delivery technology, either a conformal pad containing large area LED arrays or a scanning laser.

Human Organ Studies. Several studies have focused on PBM therapy of COVID-19 in specific organs in the human body, mostly involving orofacial mucosal membranes and bronchial epithelium. Case studies [253,254] report significant clearance of COVID-19 oral lesions on the lips following a PBM regimen of 3-to-4 daily treatments. Other studies confirm successful PBM relief of COVID-19 induced taste dysfunction [255] and olfactory desensitization [256].

Another study [257] analyzed the effect of NIR (1064-nm) laser PBM on immunomodulatory markers including the effect of separate treatments to the lungs (450 cm^2 per lobe), tonsillar fossae (20 cm^2 per side), trachea (150 cm^2), and sinuses (20 cm^2). Using a high-power class-IV laser scanner, lung PBM was administered in a 12 min interval. Other areas involved the use of handheld laser probes. Therapy was administered at a fluence of 8 J/cm^2 on all locations. Total time for all seven locations was 84 min. Although analysis showed improvement in CRP levels, oxygen partial-pressure, and urea, only weak correlations to PBM treatments were observed. Even after multiple PBM sessions immunological improvements were unremarkable. For example, post therapy CRP levels remained extremely high at 72 mg/dL, seventy times healthy levels for C reactive proteins [258].

Table 2: Review of published PBM studies of human COVID-19

						PBM Regimen		
Author & Publication	**Dates**	**Genomics**	**Topic, scope**	**Presentation**	**Therapist, Facility**	**Photonics**	**Treatment, Dose**	**Outcome**
Williams et al *J Biophotonics.* [259]	Study: 2020 Mar-May. Pub: 2021 Oct	Ancestral SARS-CoV-2 (Wuhan strain)	50 patient whole organ PBM of lungs and sinus	Acute COVID-19 of resp, circ distress, fever, conjunctivitis, no mech ventilation or suppl O_2	Raimondo et al [1] ambulatory care (San Antonio, TX)	Algorithmic multi-λ (650/850nm) multi-freq pulsed, conformal cl-II LED pads: Applied BioPhotonics (US & TW) classic model	84 min anterior lungs (600 cm^2), sinus (400 cm^2), 55 Jcm^{-2} 1 sess every other day	50/50 acute recovery in 3 days (1-2 sess), 50/50 full recovery in 18 days (1-5 sess), no supp O_2 req post PBM
Vetrici et al *J Inflam Res .* [263]	Study 2020 Mar-May, Pub: 2021 Mar	Unreported, likely ancestral SARS-CoV-2 (Wuhan strain)	10 patient stage 5-6 COVID	60% admis to ICU & vent. 40% mortality ctrl group, SMART-COP 5.4 , BCRSS 4.0, CXR RALE 8.0	Sigman et al [1] Lowell General Hosp (Lowell Mass)	Multi-λ (808, 905 nm) uni-freq (1.5kHz) Cl IV laser scanner. Multiwave Locked Sys (MLS) Therapy Laser (ASA Laser, Italy)	4 sess daily, 14 min per lung, 7.2 Jcm^{-2}	0% mortality in PBM grp no vent or ICU admission improved resp indices SMART-COP 1.4, BCRSS 0.4, CXR 5.2
de Marchi et al *J. Inflam Res* [266]	Study: 2020 May, Pub: 2021 Jul	Unreported, likely ancestral SARS-CoV-2 (Wuhan strain)	30 patient PBM-sMF random trial of neck and lung muscles	Severe resp COVID, mech ventilation, high CRP 152 mg/dL, high O_2 demand	Tacchini et al [2] Hosp Tacchini (San Paolo, Brazil)	Handheld cluster probe: 8 LED (850nm, 250Hz), 8 LED 633nm, 2Hz), 4 LD (905nm 250Hz), MF 110mT	8 min on six sites, lower thorax muscles, 2 sites neck 1 Jcm^{-2}, total of 264 cm^2, 60 min total	No reduction in hosp day improved ventilatory parameters CRP to 72, TNF decreased by 30%, reduced mortality rate
Sigman et al *Am J Case Rep.* [264]	Pub: 2000 Aug	Unreported, likely ancestral SARS-CoV-2 (Wuhan strain)	57 yo M single patient study	Severe acute COVID-19 dyspnea O_2 req 2-6 LPM, 80% SpO_2 on RA, renal failure	Sigman et al [2] Lowell General Hosp (Lowell Mass)	Multi-λ (808, 905 nm) uni-freq (1.5kHz) Cl IV laser scanner. Multiwave Locked Sys (MLS) Therapy Laser (ASA Laser, Italy)	4 sess once-daily 14 min per posterior lung (600 cm^2), NIR_1 7.2 Jcm^{-2}, NIR_2 0.1 Jcm^{-2}	Improved SpO_2 from 94% to 100%, reduced inflam, restored unaided breathing
Sigman et al *Can J Respir Ther.* [265]	Pub: 2000 Sep	Unreported, likely ancestral SARS-CoV-2 or alpha variant	32 yo F obese single patient study	Acute resp COVID-19, BMI=50, RALE=8, SpO_2 88% on 5 LPM, inflam: ferritin=359 ng/ml CRP=3 IL6=45	Sigman et al [2] Lowell General Hosp (Lowell Mass)	Multi-λ (808, 905 nm) uni-freq (1.5kHz) Cl IV laser scanner. Multiwave Locked Sys (MLS) Therapy Laser (ASA Laser, Italy)	4 sess once-daily 14 min per posterior lung (600 cm^2), NIR_1 7.2 Jcm^{-2} , NIR_2 0.1 Jcm^{-2}	SpO_2 improved to 97-99% at 1-3 LPM O_2. reduced inflam RALE=33, IL-6=12, ferritin=175 hosp stay 7 days
Pelletier-Aouizerate et al *Clinical Case Rep* [267]	Study 2020 Feb-Mar Pub: 2021 Mar	COVID tests inconclusive or neg: if COVID likely ancestral SARS-CoV-2 (Wuhan strain)	2 multiorgan inflam cases F69 & 53 F unconfirmed etiology	Case 1 respiratory distress, febrile, CXR opacity, ageusia Case 2 respiratory distress, febrile, hypoxia, psoriasis	Case 1 Pelletier-Aouizerate et al [3] Toulon France, Case 2 UK home therapy under quarantine	3 rigid panels of 8 NIR LED (808, 905nm) 1000 cm^2 at 7cm gap derma CW op TriWings LLS® Biophoton (France)	15 min, 50 Jcm^{-2} Case 1: 3-sess/wk 12 tot Case 2: 2-sess/wk 6 tot	Reduced dyspnea, reduced inflam signs, long COVID symptoms
Lin et al *Intl Paramedic Summit & AI Forum* [260]	Study: 2021 May. Conf: 2022 Aug	Alpha variant of SARS-CoV-2 (2021 May Taiwan surge) COVID positive	5 patient hosp study, whole organ 2 ctrl, 3 PBM	Respiratory distress, CXR opacity, high CRP, low SpO2, supp O_2 2-5 LPM	Hung TS, Wu TH physicians [1], Wei-Gong Mem Hosp Taiwan	Algorithmic multi-λ (650/850nm) multi-freq pulsed, conformal cl-II LED pads: Applied BioPhotonics (US & TW) Mark II model	64 min anterior lungs (1,200 cm^2), 42 Jcm^{-2} 1 sess daily, 4 dys	3/3 acute symptoms resolved in 2 days, discharged from hosp within 4 days, no suppl O_2 or post COVID
Pereira et al *Int J Devel Res.* [257]	Study: 2020 Dec–Feb, Pub: 2021 May	Variant unknown	20 patient hosp random trial PBM vs control	Respiratory distress >1 LPM O_2, no mech ventilation	Pereira et al [2] Hosp Meridional Serra (Serra-ES, Brazil)	BTL-6000 Class IV laser scanner BTL Indus Inc (Mexico City)	laser scanning lungs, hand probe of sinus, trachea, tonsils 12 min/site, 8 Jcm^{-2}	Improved breathing, lower CRP and urea but above normal healthy range
Marashian et al *Front Immunol.* [261]	Study: 2021 Aug, Pub: 2022 Jul	Delta-plus variant of SARS-CoV-2 likely in fall 2021 surge	52 mild-to-mod COVID hospitalized patients, PBM vs ctrl	Respiratory distress, febrile, $SpO_2 < 90\%$, dyspnea,	Marashian et al [3] Masih Daneshvari Hosp (Tajrish, Iran)	8 LED per pad 625 nm direct contact with sanitary barrier: Xbiotec NeolysPlus model	5 pads anterior lungs + neck, concurrent 6 min every 12 hours for 3 days, 45 Jcm^{-2}	Lower inflam cytokines IL6 –83%; IL8 –54% TNFα –83%, improved IL6/IL10
PereiraJ et al *Photochem Photobio B: Bio* [262]	Pub: 2023 Jan	Omicron variant of SARS-CoV-2 most likely	30 patient moderate COVID patients	Respiratory distress, no mech ventilation, RA or $O_2 \leq 3$LPM	PereiraJ et al Resp Syndrome Ward [4] Santa Casa de Itajubˊa-MG, Brazil	custom 300 LED vest (2,088 cm^2), 940 nm	15 min 2.6 J/cm^2, daily for 7 days	improved pulmonary function, SpO_2 increased 88 to 96, leukocytes –32%, shorter hosp days

[1] Physician performing therapy and collecting data declares no affiliation with manufacturer. Manufacturer co-authored paper.

[2] Physician performing therapy and collecting data declares no affiliation with manufacturer. Physician curating data is a principal author of the paper.

[3] Relationship between manufcaturer and physician performing therapy and collecting data is undisclsoed. Physician curating data is a principal author of the paper.

[4] Experimental device was developed by physician performing therapy, collecting data, and co-authoring paper.

Human Acute COVID-19 Studies. Although numerous papers discuss the treatment of acute COVID-19 using PBM, most papers provide a survey or meta-analysis of data gleaned from only ten published case studies. Summarized in chronological order in **Table 2**, photonic optical delivery in case reports include conformal LED pads [259,260,261,262]; laser scanners [263,264,265]; handheld probes [266]; and rigid LED panels [267]. In addition to laser scanning, one study [257] also employed handheld probes to treat organs not accessible by beam scanning.

Chronologically, the first case PBM of human COVID studies commenced in March of 2020 in Texas using conformal 3D-bendable LED pads (manufacturer Applied BioPhotonics aka ABP) [259], and in Massachusetts using a laser scanning solution (ASA laser) [263]. Specifically, in February, ABP issued a warning to all its clients [268] (including the Texas clinic) concerning the spread of a highly transmissible dangerous contagion. In hindsight, the newsletter was prescient. Soon thereafter the Texas clinic starting receiving patients infected with SARS-CoV-2.

The ABP issued email included a prescriptive anti-inflammatory anti-infective PBM protocol as a recommendation – a regimen previously developed from extensive clinical experience with MERS, SARS, and H1N1 epidemics and from treatment of pneumonia, COPD, and ARDS. While COVID positive patients in the Texas clinic study presented primarily respiratory symptoms ranging from stage 0 (asymptomatic) to stage 5 (severe), the clinic did not have access to stage 6 (very severe) hospitalized/ICU patients, or those on mechanical ventilation.

Facing pandemic outbreaks in New York City, Boston, and neighboring cities, Massachusetts doctors turned to scanned laser PBM to contend with stage-6 COVID-19 patients on mechanical ventilation. By July the laser team published a paper proposing PBM as a modality to reduce demand for mechanical ventilation in patient rescue [269]. For both the Texas and Massachusetts studies, physicians in charge of patient care, performing PBM treatments, and collecting data were unaffiliated with device manufacturers.

It should also be noted for completeness that the earliest reported use of PBM on novel pneumonias occurred in France and the UK [267] using rigid LED panels held at a distance above the patients. Despite pneumonia-like symptoms, these patients tested negative for COVID. Moreover, compared to the widely observed benefits of conformal LED pad and laser scanner trials, the observed improvements using rigid panels were unremarkable. As discussed extensively in Part I of this paper, rigid LED panels suffer poor optical coupling severely limiting depth penetration.

Thereafter PBM trials mostly coincided with outbreaks able to supply large patient populations for study. Based on epidemiological data for COVID-19 distributions chronologically and geographically [270,271], the column entitled "genomics" in **Table 2** describes the best estimates as to viral variants treated in each study. Performed globally over a three-year period, the consistency of beneficial therapeutic outcomes confirms the antiviral mechanisms of photobiomodulation are insensitive to viral mutation and genetic variants therefrom.

Long COVID. Numerous publications support the efficacious application of PBM in the treatment of long COVID. PBM therapeutic regimens include convalescence of muscle atrophy and articular inflammation [272,273]; functional restoration of organs [273,274] and vascular endothelia [275]; and rehabilitation of neurological [276] and brain fog [277]. Because long COVID may appear six-months to one-year following acute viral infection and since long COVID is challenging to identify and diagnose, many papers remain unpublished at this juncture.

Study Limitations. As documented in this literature survey, numerous publications report favorable and even remarkable results in treating acute COVID-19 with photobiomodulation. Pragmatically however, when interpreting the spectrum of PBM COVID publications, the challenges of real-life use must be considered. In particular, just because a controlled study is successful doesn't mean it can be scaled for clinical use.

Firstly, the application of high-power lasers in the treatment of COVID-19 represents a burn and eye-safety risk to both patient and therapist. Because of concentrated optical energy density of its optical beam, special care must be taken when administering laser treatments to the face and sinuses as even reflected light can permanently damage the eyes. As such, laser PBM is strictly contraindicated in the treatment COVID-19 induced conjunctivitis. Moreover, since higher power levels are capable of inflicting severe burns, class III and IV lasers should not be performed on patients unaccompanied by doctors or laser trained medical staff.

Secondly, another deficiency in the content of published studies is that many scientists and research institutes studying COVID-19 do not have access to active infectious-disease patients, especially those remanded to hospital care. This

means the distribution in published paper topics is skewed by patient access. Given the epidemiology of SARS-CoV-2 as a single-strand RNA virus, PBM clinical trials of COVID-19 are especially problematic. Specifically, as the coronavirus genome mutates, the prevalence of each new variant surges then unpredictably subsides, making it impossible to recruit a population of homogenously infected patients in time to complete a trial (before the disease evolves into a new and unrecognizable form). As such, numerous clinical trial attempts have been suspended or cancelled altogether [278], reinforcing the unfortunate reality that deadly pandemics are not good opportunities for conducting randomized clinical trials [279].

Thirdly, PBM studies employing small area (spot) probes [280,275] are particularly problematic, requiring a nurse or therapist delivering the treatment to remain in close proximity to an highly-infectious patient for extended durations in order to thoroughly treat whole organs (such as the lungs). In hospital settings, it means an unfortunate therapist or front-line worker must remain in close proximity to infected patients for the entire work shift (possibly ten hours). According to WHO and CDC guidelines, indoor infectious transmission in close proximity to symptomatic patients shedding the virus has a high probability of infection and should be altogether avoided. Ideally, contact PBM therapy should be delivered "hands-free" where after pads are positioned and the program commences, the entirety of the session occurs without the need for therapist involvement. Although laser scanners avoid even this step, a patient once positioned onto a table must remain perfectly still to avoid uneven radiation distributions.

Another factor to consider in reviewing published PBM papers is optical coupling efficiency. For example, the use of rigid LED panels, light walls, and LED beds for deep tissue PBM is problematic, not for reasons of safety but for matters of efficacy and reproducibility. As (discussed extensively in Part I of this paper), optical delivery from a distance involving diffuse or off-angle light beams do not penetrate into deep tissue. Without uniform deep-tissue application of energy, portions of organs remaining untreated can reinfect treated tissue causing an infection relapse. Another important consideration specific to LED pads is sanitation. Specifically, professional medical therapy requires pads be constructed of non-porous aseptic materials, not using low-temperature low-density rubbers (like Neoprene) able to trap and harbor pathogens.

Lastly, papers discussing the medical application of light activated pharmacological agents [281] in the treatment of COVID-19, referred to as photodynamic therapy (PDT) are excluded from this summary, not because they are not efficacious but because they represent an entirely different technology invoking pharmacological mechanisms-of-action.

Whole- & Multi-Organ PBM of COVID-19

Whole-Organ PBM System

To administer whole-organ and multi-organ photobiomodulation of acute and long COVID-19 patients, physicians in this study report employed the Mark II dynamic-drive LED PBM system ABPT1003-2 shown in **Figure 3** (or its predecessor the ABPT1003 Classic) manufactured by Applied BioPhotonics Ltd. (available regionally by brands LightDr™, LightMD™, and AraLight™). Both the Mark II and Classic models provide identical independently-controlled dual-channel pulse modulation outputs for driving multi-wavelength LED arrays.

To maximize tissue specificity, treatments comprise algorithmically-sequenced light wavelengths using programmable pulse frequencies with adjustable duty factor (for frequency-independent brightness and temperature control). While the Classic unit requires each individual treatment to be manually selected, in the Mark II treatment sequences are fully automated, selected using predefined OneTouch™ menu sessions. Both models comprise independent dual-output photonic controllers, each capable of driving 1-to-3 LED pads.

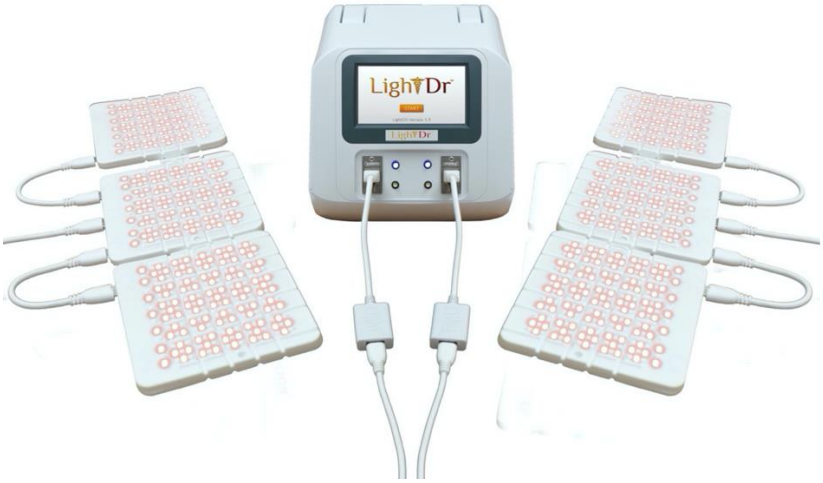

Figure 3. The The ABPT1003-2 Mark II PBM system used in the COVID-19 studies comprises a dual output algorithmic controller able to drive up to six reconfigurable 3D-bendable ABLP203 LED pads covering 1,200 cm^2 for deep-tissue whole organ treatment. Photo courtesy of Applied BioPhotonics (as LightDr commercial brand).

Assembled in non-porous aseptic polymeric enclosures, ABLP203 pads used in these studies comprise equal-quantity arrays of red (650 nm) and NIR (850 nm) LEDs with integrated circuitry to maintain consistent uniform brightness over time from LED-to-LED, pad-to-pad, and manufacturing batch-to-batch. A separate LED pad, the ABLP205 (not shown), is used for the neck and also as a headband in transcranial therapy. Sanitized ultrathin silicone sanitary barriers are included for added hygienic protection and to better facilitate disinfection.

Exemplary LED pad placements for whole organ PBM are shown in **Figure 4**. The left and center images illustrate anterior pad placements for prophylactic and acute COVID-19 treatments focused on the upper and lower respiratory tracts for early infection and viral incubation phases. To reduce session times, both therapies can be delivered concurrently using the system's two output channels. The rightmost image illustrates the posterior application of six LED pads positioned transversely across the upper-to-mid back for concurrent treatment of lungs, spinal cord, and marrow of the spine (immune function) – a configuration useful when treating severe cases of COVID pneumonia, especially for stage 6 infections presenting bronchial inflammation and edema.

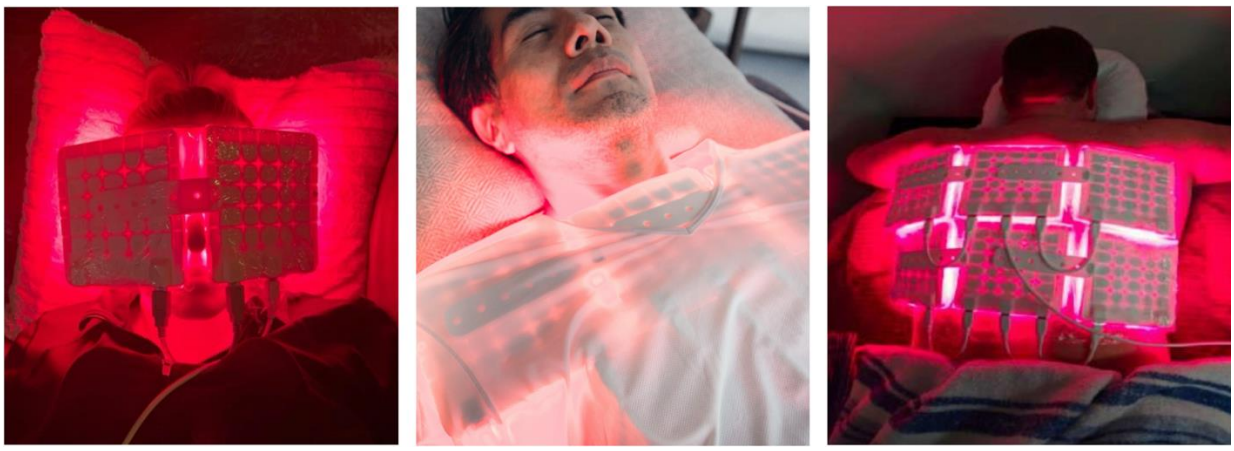

Figure 4. Examples of LED LightPad™ placements used in case studies. Left image illustrates two-pad treatment of sinuses for early phase COVID-19 infections. Center image illustrates 3-pad anterior transverse placement for treating acute COVID-19 bronchial inflammation of the lungs, heart and thymus. Right image illustrates whole organ posterior treatment of the lungs. Images courtesy of UltraRed Light Therapy.

COVID-19 Protocol Design

To optimize PBM protocols for treating a multi-organ multi-system inflammatory disease like COVID-19, it is in insightful to consider organ involvement metabolically and mechanistically as represented schematically in **Figure 5**. During infection and incubation the disease begins with a mild viral sinus infection which soon spreads through airways into the lungs. Once there, it elicits an immune response involving proinflammatory cytokines which together with viremia employs the circulatory system to spread throughout the body into multiple organs, in essence amplifying the infection by inflammation of visceral epithelia and vascular endothelia.

Over time, the disease progresses into both systemic hyperinflammation and neurological inflammation, in turn causing dysfunction of visceral organs and the central nervous system exacerbated by deregulation of neuroendocrine organs adversely impacting healthy hormone levels. Left untreated, organ dysfunction leads to *metabolic* long COVID while nervous system dysfunction results has adverse neurological consequences, i.e. *neurologic* long COVID. The graphic also illustrates why in the earliest stages of viral incubation and inflammation, it is important to administer an anti-inflammatory PBM protocol preventing progression into the hyperinflammatory phase to avoid organ, tissue, and nerve damage.

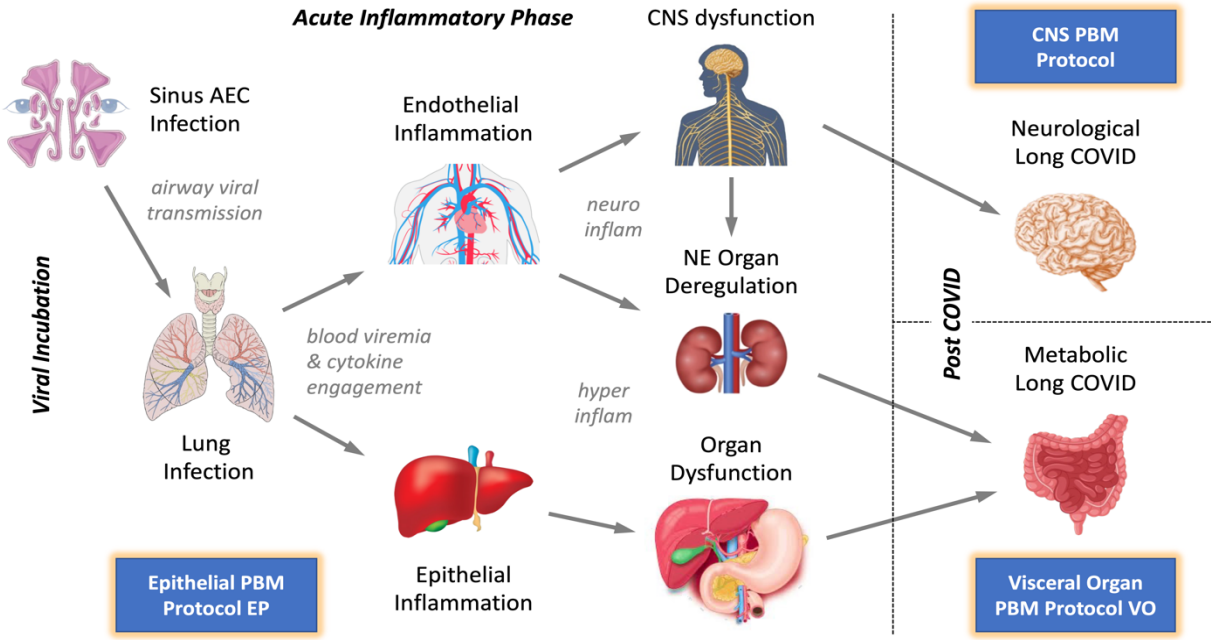

Figure 5. COVID-19 infection mechanisms and disease trajectory including viral infection and incubation, systemic inflammatory response evolving into hyperinflammation and neurological dysfunction, left untreated progressing into neurological and metabolic long COVID. PBM treatments for COVID-19 are arranged into three modalities – an epithelial protocol (EP) for inflammatory conditions, and two long COVID protocols – one for visceral organs (VO) and another for neurological damage (CNS). Attributions: sinuses by Servier Medical Art, CC 3.0; lungs by Patrick J. Lynch, CC 2.5; circulatory system by LadyofHats, CC 1.0; liver – none required; nervous system by Encyclopædia Britannica; kidney emoji by Kidney News Feb 2022]; stomach, pancreas, duodenum and liver at AnatomyTOOL.org by Ron Slagter under CC; human brain by rawpixel.com and intestines by brgfx on Freepik

The PBM protocol for the acute infection and inflammatory phase targets epithelium within visceral organs (and also vascular endothelium) without regard to the organ type. Accordingly, the PBM session is referred to as an epithelial protocol (EP). In long COVID therapy, tissue damage and repair is subdivided into treatment of visceral organs and of the central nervous system, designated by the session nomenclature VO and CNS.

Depicting a sequenced algorithmic PBM used in the treatment of acute phase COVID-19 infections, **Figure 6** illustrates two exemplary session protocols of 84- and 64-minute duration. The suggested regimen concurrently treats both sinuses and lungs with identical session protocols.

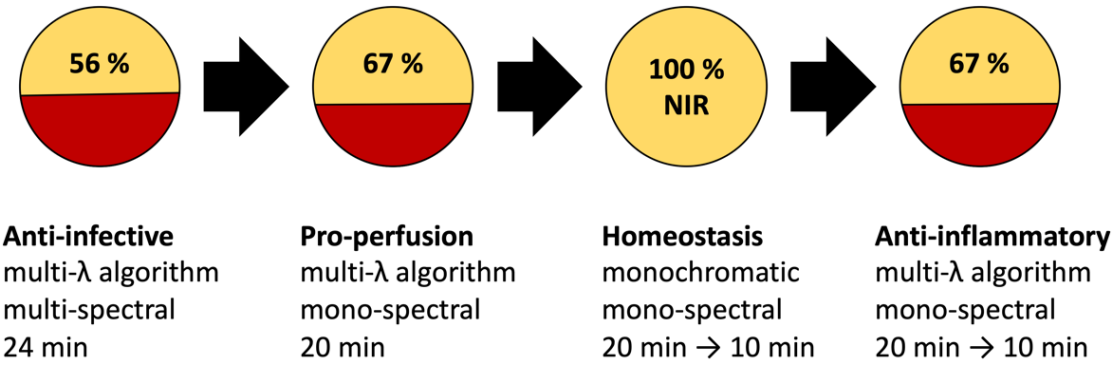

Figure 6. Epithelial protocol (EP) for the PBM of acute phase COVID-19 delivers multi-spectral pulse modulated algorithms comprising multi-λ and monochromatic light in the red and NIR bands. The session sequentially delivers anti-infective, pro circulation, homeostatic, and anti-inflammatory treatments. Original protocol EP0 of 84 min duration was subsequently shortened to 64 min EP3 with no observable impact on therapeutic efficacy.

Both protocols begin with a 24-minute multi-spectral multi-wavelength treatment designed to stimulate anti-infective immune response through anti-inflammatory cytokine stimulation. With over 20 years of clinical use, the immune protocol includes algorithmically programmed pulse modulation covering 2 decades of audio range frequencies. The second step in the protocol employs a blend of NIR and red light modulated at a fixed frequency, where two-thirds of the session fluence is delivered in the NIR spectrum. The third step promoting metabolic homeostasis comprises pure monochromatic NIR light photochemically establishing steady-state metabolic processes. Originally developed using a 20-minute treatment duration, the step was reduced to 10 minutes in order to shorten the session time (to accommodate more patients).

The final treatment in the epithelial protocol, an anti-inflammatory procedure is bi-chromatic and mono-spectral. In order to encourage tissue healing and wound-repair, the step employs the lowest modulating frequency in the entire EP protocol, more than an order-of-magnitude below the session's highest frequency. The step time was also halved to 10 minutes to shorten the overall session. The changes allowed the original epithelial session EP0 to be reduced from 84 minutes (55 J/cm^2) down to 64 minutes (42 J/cm^2) referred to as EP3. Monitoring of patient improvements and blood analysis of inflammatory markers show no adverse impact of shortening the session time. Importantly, by shortening session times to approximately one hour, clinics can comfortably schedule and treat patients for acute COVID-19 PBM therapy at a rate of one patient per 1.5 hours (per system), including check-in, set-up. and post-session disinfection.

Acute COVID-19 PBM Case Study 1 (Ambulatory Care)

The first case study in the whole-organ PBM of acute COVID-19 patients occurred in the summer of 2020 during the initial severely dangerous ancestral SARS-CoV-2 outbreak. Given limited and uncertain pharmacological options at the time complicated by a lack of hospital beds, a shortage of skilled medical staff, and constant reports of unfavorable clinical outcomes, many exposed or infected patients sought outpatient care during the early pre-lockdown phase of the pandemic. As a result (and upon their own initiative) 67 patients all exposed to other symptomatic COVID-19 patients, requested ambulatory administration of photo-biomodulation therapy. In accordance with medical standards for compassionate care and given the uncertainty of any therapeutic modality in treating this newest novel coronavirus, all patients were treated free-of-charge using the longer higher-dose EP0 PBM protocol (described previously).

Study Cohorts. Among the treated patients, 50 persons were confirmed positive by laboratory rapid antigen tests (RATs) as testing positive for COVID-19 infection (Mar 2020). With direct contact to symptomatic COVID positive family members, the other untested persons requesting therapy comprised 9 symptomatic and 8 asymptomatic patients. Either because they thought it unnecessary or because did not have timely access to testing, these 17 patients elected to receive PBM therapy without a confirming test. Medical data was collected on all 67 patients.

Data from the fifty COVID positive patients was recorded and aggregated into a case study of PBM therapy as reported in the Journal of

Biophotonics [259]. Although the device manufacturer participated in curating the data for publication, the application of all therapeutic PBM sessions and the corresponding patient data collection were exclusively performed by the patients' attending physicians without manufacturing involvement or third-party intervention.

The remaining 17 patients' data was recorded for subsequent evidence-based analysis of PBM as a potential prophylactic modality. **Table 3** reports patient data and disease severity for the entire treated population including untested patients (symptomatic and asymptomatic) directly exposed to symptomatic COVID-19 patients.

Symptomatic severity is ranked into six levels or disease stages comprising stage 1 (mild sinus conditions, ranked low); stage 2 (lower respiratory involvement, ranked medium-low); stage 3 (respiratory distress, ranked medium); stage 4 (early-stage pneumonia with systemic involvement, ranked medium-high); and stage 5 (hyperinflammation and onset of multi-organ inflammatory disease, ranked severe). Publications with less descriptive granularity categorizing severity may combine stages 1 and 2 into a grouping called mild infection; stages 3 and 4 together as medium grade COVID-19 disease; and stages 5 and 6 merged into a severe COVID-19 class. These broad categories while symptomatically descriptive, ignore the infection's spread and progressive organ involvement, factors important in properly administering an efficacious PBM regimen.

As a reference, stage 0 is used to describe asymptomatic infected COVID-19 patients, which potentially may include silent spreaders (i.e. undiagnosed carriers). Stage 6 (severe pneumonia with multi-organ inflammatory disease, ranked very high or very severe) generally requires ICU care and possibly mechanical ventilation.

Table 3. Summary of patient data from PBM COVID-19 (case study 1). The variable n represents the cohort population. TTAR is the time-to-acute recovery measured from the time of the first PBM treatment.

Cohort	RAT	Stage	n	Presentation	# of Sess	TTAR (days)
Symptomatic COVID positive (50 patient case study)	+	1	6	itchy throat, rhinorrhea, fatigue	1	1
		2	16	mild cough, sore throat, low grade fever, rhinitis, malaise	1–2	1
		3	11	cough, febrile, body aches, sore throat, dyspnea, malaise	1–3	≤ 2
		4	10	urgent cough, febrile, body aches, sore throat, dyspnea, reduced SpO_2	1–3	≤ 2
		5	7	paroxysmal cough, febrile, aches, dyspnea, chest pain, low SpO_2	1–5	≤ 3
Symptomatic COVID exposed	NT	1-2	9	itchy throat, mild cough, low grade fever, fatigue	1	1
Asymptomatic COVID exposed	NT	0	8	no symptoms	1	0

Since stage 6 necessitates hospitalization, patients in this category were not available for ambulatory care and therefore not included in this study's data set. Mechanically ventilated patients were also neither available nor included in his study. It should be noted that photobiomodulation of intubated and ventilated patients comprises adjunctive medicine introducing experimental variables unrelated to PBM of COVID-19, and is therefore not a true measure of PBM efficacy. In particular, positive pulmonary pressure increases intrathoracic pressure and can induce profoundly decreased venous return [282]. Extreme pressures may also damage heart valves already compromised by COVID-19 [283] leading to mitral valve regurgitation.

Among the patient population treated, 59/67 were symptomatic of which 17 were severely affected. Nearly all symptomatic patients suffered malaise. Fever and associated body aches occurred in 80% of the population (40/50 for COVID positive patients, 47/59 of all symptomatic patients). Febrile temperature did not exceed 38.3°C (101°F). Dyspnea (shortness of breath and/or wheezing) while notably pervasive in severe stages, represented roughly one-fifth of the overall infected population. COVID cough was much more prevalent, manifested in over 70% of cases (37/50 of COVID positive population, 42/59 of symptomatic population), a third of which involved severe (paroxysmal) fits of uncontrolled coughing with persistent throat pain.

Slightly more than half of all patients (28/50 COVID positive, 31/59 symptomatic) exhibited rhinitis, sinus congestion, and upper

respiratory tract infection (URTI). Since the URTI fraction is less than COVID coughing, it supports the premise that the novel coronavirus replicates more efficiently in the bronchia of the lungs, preferring it over AEC of the sinuses or the GI in advanced stages. Other symptoms observed include cramping and abdominal distress at 6%, non-febrile nausea at 4%, and COVID eye infections of the conjunctiva at 2% of the infected population.

Time-To-Acute-Recovery (TTAR). The rightmost columns of **Table 3** describe the total number of PBM sessions performed on a patient in this study and recovery from acute symptoms. Specifically, the term *Time-To-Acute-Recovery* and its acronym TTAR specify the number of days following the first PBM treatment before acute symptoms were ameliorated. Acute medical presentations of early COVID-19 cases included fever, chills, body and back aches, dyspnea, and severe coughing. As recorded, patients in stages 1-to-4 exhibit a TTAR or 2 days or less, requiring only one session. Severe patient conditions of stage 5 took slightly longer, requiring as many as two PBM sessions and 3 days to resolve the acute disease phase.

No sham group was available for comparison. Absent a sham as a control, historical empirical evidence must be considered in order to gauge observed benefits of the experimental PBM regimen against standard medical care available at the time. In this context, during the pandemic's initial outbreak in early 2020, physicians reported most COVID-19 patients as unresponsive to nearly all available pharmacological interventions. Patients contracting COVID-19 experienced a progressively worsening state of health requiring weeks-to-months to resolve (if ever). Predictably, those requiring hospitalization experienced more severe presentations and less favorable outcomes. The prognosis for patients requiring mechanical ventilation was considerably worse. In any event, patients contracting the ancestral viral genotype required weeks-to-month to recover, with no cases reportedly resolving within a few days.

In this context, it is noteworthy to consider as a primary therapeutic modality unaccompanied by pharmaceutical intervention, the described whole-organ PBM regimen resulted in clinical outcomes where 50/50 of COVID-19 positive patients (and 59/59 symptomatic patients) resolved all acute presentations of illness within three days of commencing PBM treatment, i.e. TTAR $\leq$ 3 days.

Time-To-Full-Recovery (TTFR). As stated, acute relief of COVID-19 using whole-organ PBM requires 1-to-3 days irrespective of pre-treatment severity of the infection. In contrast, ameliorating all effects of the infection to make a full recovery takes longer, generally requiring a number of PBM sessions scaling in proportion with the infection's severity. This principle is illustrated in **Figure 7** categorizing the number of PBM sessions needed to fully recover from a COVID-19 infection. The definition of full recovery is complete elimination of all symptoms of the infection with no long COVID symptoms persisting.

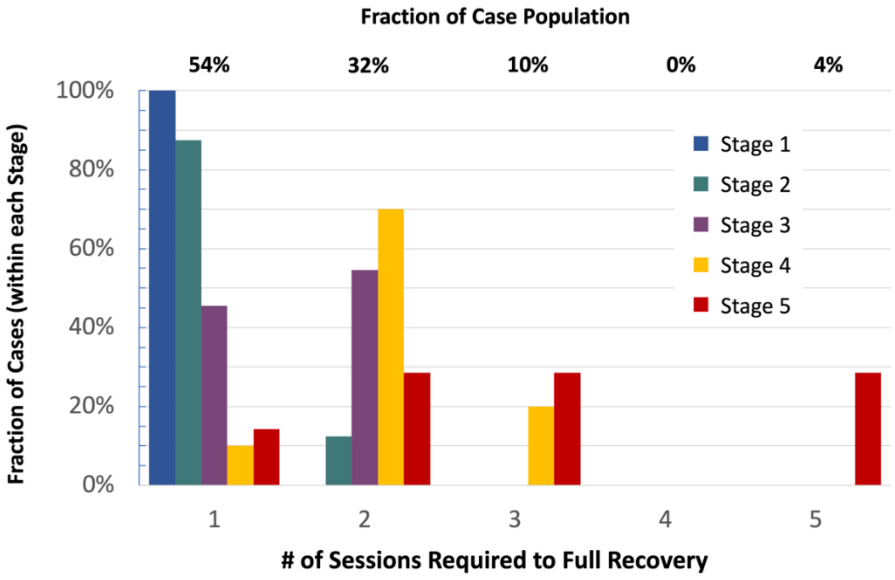

Figure 7. Graphical representation of the fraction of symptomatic PBM cases fully resolved as a function of the number of PBM sessions administered, made in accordance with the initially reported stage of the disease. Data adapted from ref 259.

Graph data is grouped by the disease stage (patient condition) at the time of the first PBM treatment. Note that each group (color) sums to 100% where the percent shown represents the fraction of cases in each stage, not normalized to the entire study population. Stage 4 (moderately-severe) cases, for example shows 10% of patients recover in one session, 70% more fully recover after two sessions, and the remaining 20% required three treatments to fully recover.

In total, 54% of all COVID-19 infected patients treated fully recover with one PBM session, 86% (i.e. 54+32 %) were resolved within two treatments, a 96% recovery occurs by three PBM sessions, and 100% of all study patients fully recovered by their fifth session. Only patients starting with stage 4 or stage 5 COVID, required three or more sessions. As an ambulatory care study, no stage 6 or intubated patients were available for inclusion in the trial.

The observation that only the most severe cases require three or more PBM sessions for full recovery, although expected, begs the question as to what factors contribute to this association. An investigation into disease chronicity reveals a noteworthy correlation between the required *time-to-full-recovery* (acronym TTFR) and the time-to-treatment TTTx as illustrated in **Figure 8**. In this context, the time-to-treatment is defined as the number of days from the first reported onset of symptoms, to the date of the first PBM therapy sessions.

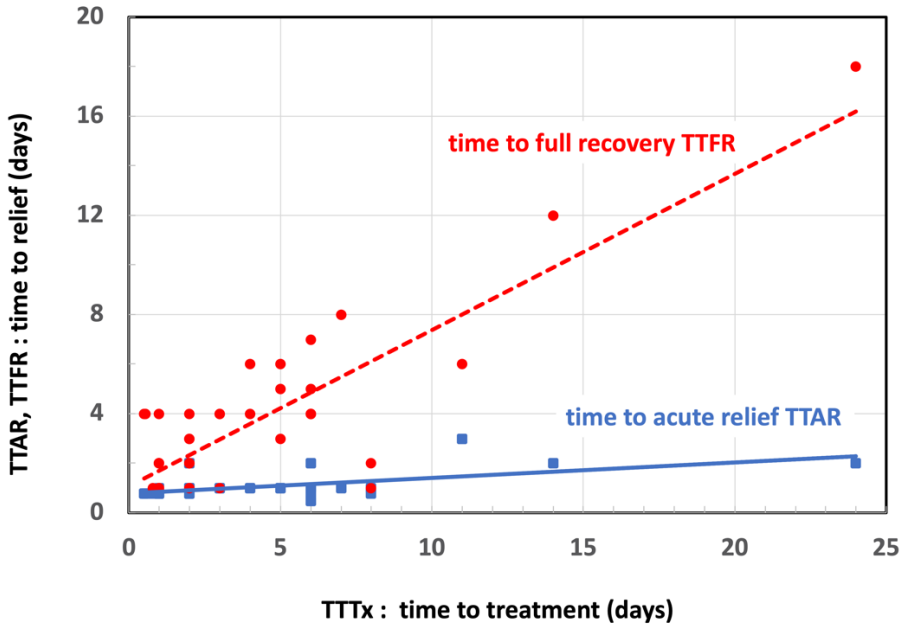

Figure 8. Scatter chart of TTAR (time to full recovery) and TTAR (time to acute recovery) plotted against time to treatment TTTx from ref 259. Correlation analysis suggests a linear dependence of TTAR on time to treatment while acute recovery time is uncorrelated.

Recorded TTTx values in the 50-patient COVID-positive cohort ranged from 1-to-24 days with the majority of cases resolved within one week. As shown, a 14-day delay in therapy required 12 days to recover fully while a 24-day delay required 19 days, roughly requiring an extra 0.7 days in recovery for every day of delay before commencing PBM therapy.

Curiously, while TTFR was correlated to TTTx (especially beyond 2 days), the time-to-acute-relief TTAR was nearly constant between 1-to-3 days irrespective of delays in commencing PBM treatment. The authors hypothesized that because acute relief involves mitigating anti-inflammatory mechanisms, PBM is able to immediately provide symptomatic relief via a rapid decline in proinflammatory cytokines (mechanisms described previously in this paper). In contrast, TTFR is correlated to tissue and organ damage which accumulates over time. Removing scar tissue and other sequelae requires scheduling cell replacement (apoptosis), breaking apart dead tissue and removing cellular debris (phagocytosis), then remodeling new tissue with healthy cells and fresh collagen. In this sense COVID full recovery represents a process of wound healing.

Managed by macrophages, cellular debris removal and tissue remodeling requires roughly an equivalent amount of time to effect repairs as it took to cause damage in the first place. In other

words, the longer a patient waits to commence PBM therapy, the more scar tissue is formed and the longer the time needed for macrophage mediated wound healing. Also considering the time-consuming processes of apoptosis, phagocytosis, cell proliferation, and tissue remodeling, COVID-19 wound healing involves energy-intensive biochemical processes. The ATP generated during PBM fuels these processes, shortening the time needed for tissue inflammation and accelerating the entire process of proliferation and wound maturation.

PBM Prophylaxis. Referring again to **Table 3**, reported data includes 17 untested patients known to be in direct contact with symptomatic COVID-19 positive patients. Among these two cohorts, 9 patients were symptomatic of stage 1 or stage 2 infections. After receiving one PBM therapy session, all 17 were asymptomatic with 24-to-36 hours of therapy. Although the sample data is anecdotal, given the high infectivity and severity of the original ancestral COVID-19 viral strain, the lack of infection in these groups strongly suggests the anti-infective anti-inflammatory feature of photobiomodulation may offer prophylactic benefits. More studies are recommended.

Long COVID. Of the 67 patients treated in Case Study 1, no patient (i.e. 0/67) developed long COVID symptoms (including all 50 patients confirmed as COVID-19 positive at the time). This observation suggests by limiting the peak severity of an inflammatory infection through the expeditious application of PBM therapy, organ injury and long COVID can be avoided.

Acute COVID-19 PBM Case Study 2 (Hospital Care)

In the summer of 2021, approximately one year after Case Study 1, an independent study assessing the effect of PBM on COVID-19 was conducted in a Taiwan hospital [260]. Unlike the outpatient study in the United States which lacked the opportunity to perform radiometric and blood tests, Case Study 2 had full access to all hospital diagnostic capability.

The study involved five COVID-19 infected patients, two in a control group receiving only standard care, and three in the test cohort receiving PBM therapy. As described in **Table 4**, all study subjects tested positive for SARS-CoV-2 by polymer chain reaction (PCR) evaluation and presented severe COVID-19 disease symptoms (stage 5) including respiratory distress (low SpO_2 levels, coughing, dyspnea, chest tightness); GI distress (diarrhea, abdominal cramping); and general discomfort (headaches, body aches).

Table 4: Case study 2 – PBM of hospitalized COVID patients (Taiwan), from ref 260.

Cohort	Case	Desc	PCR	Presentations at admission	Days no PBM	PBM days	PBM sess
COVID positive control group	0	Male 40 yo	+	Low SpO_2 (86 RA), lung opacity, resp distress, GI distress, discomfort, O_2 suppl, inflam markers	16	–	0
	00	Male 62 yo	+	Low SpO_2 (91 RA), int fever (36-38.6°C), hypertension, lung opacity, resp distress, GI distress, discomfort, O_2 suppl, inflam markers	23	–	0
COVID positive PBM test group	1	Male 34 yo	+	Low SpO_2 (90 RA), int hypertension, lung opacity, resp distress, GI distress, discomfort, O_2 suppl, inflam markers	15	4	4
	2	Male 60 yo	+	Low SpO_2 (90 RA), COPD, lung opacity, resp distress, GI distress, discomfort, O_2 suppl, inflam markers	19	3	2
	3	Male 60 yo	+	Low SpO_2 (88 RA), COPD, lung opacity, hypertension, resp distress, GI distress, discomfort, O_2 suppl, inflam markers	9	4	5

SpO_2 saturated blood oxygen (%)
RA room air; sess: session; resp: respiratory
GI gastrointestinal; int: intermittent; suppl: supplemental inflammatory markers (CRP, transferrin, LDH, D-dimer…)

Fever was unremarkable throughout the study population. In addition to respiratory distress and hypoxia, all patients exhibited increased ground-glass lung opacity in chest X-rays. Minimal upper respiratory distress was observed, symptomatically consistent with alpha variant [270] predominant in Taiwan's May-June 2021 outbreak [271] transmitted into the island via international travel [284] before the emergence of delta variants [285]. All study patients received conventional medical care prescribed under physician direction irrespective of inclusion in the COVID-PBM study. Prescriptions included:

- Antibiotics: clavrate or ceftriaxone, clarithromycin.
- Anti-inflammatories: dexamethasone, remdesivir, talizumab.
- Mucolytics and antioxidants: ectoprotein, acetylcysteine.
- Oxygen supplementation (without mechanical ventilation).
- Maintaining patient standard prescription drug regimens, including medicines for diabetes, hypertension, and chronic obstructive pulmonary disease (COPD).

All patients were unvaccinated. No patients in the study received mechanical ventilation or were concurrently treated with non-standard therapeutics or experimental coronaviral regimens (such as convalescent plasma, stem cell therapy, or monoclonal antibodies). Regular monitoring of patient conditions and vitals followed standard hospital procedures including automated recording of heart rate (HR), blood pressure (BP), and saturated blood oxygen (SpO_2). Radiographic evaluations and blood tests were performed as ordered by attending physicians. Standardized blood tests for COVID pneumonias include WBC (white blood cell) counts; C-reactive protein (CRP); D-dimer; ferritin (EIA); monocytes; lactic dehydrogenase (LDH); platelet assays; lactic acid; and alanine aminotransferase ALT (GPT) serum tests for liver function.

With a limited available population of five COVID patients available at the time, a randomized clinical trial was not feasible. Instead, a limited scope case study was performed comprising experimental group (cases 1, 2, and 3) receiving identical PBM regimens, and control group (cases "0" and "00") used as reference without PBM intervention performed in the course of their medical care. To ensure a common epidemiology, the control and test groups were evaluated concurrently.

Control Group. The graph of **Figure 9** illustrates (case 00) patient SpO_2 measurements and corresponding supplemental oxygen flow rates for the final 11 days of a 24-day hospital stay. As shown, the patient had difficulty maintaining SpO_2 levels above the hospital's minimum of 95 without ongoing supplemental oxygen at a flow rate of 2 L/min through day 16. Each time patient oxygen stabilized above the limit (e.g. on day 14) removal of supplemental oxygen resulted in an rapid drop in SpO_2 down to 90-91 forcing immediate resumption of oxygen therapy. Although data was missing for days 17-thru-20, by day 20 the patient's condition had worsened, with a greater degree of chest tightness, deep coughs, and dyspnea. As a result, the physician increased oxygen flow rates to 3 L/min. As previously observed, any attempt to interrupt supplemental oxygen produced the same precipitous drop in SpO_2 levels. Still consuming oxygen at a flow rate of 3 L/min, the patient was discharged from the hospital on the 23rd day with no resolution of pulmonary dysfunction or oxygen demand. In contrast, case 0 in the control cohort (a younger patient and with fewer comorbidities) required hospitalization for only 16 days before being discharged but with no need for oxygen support.

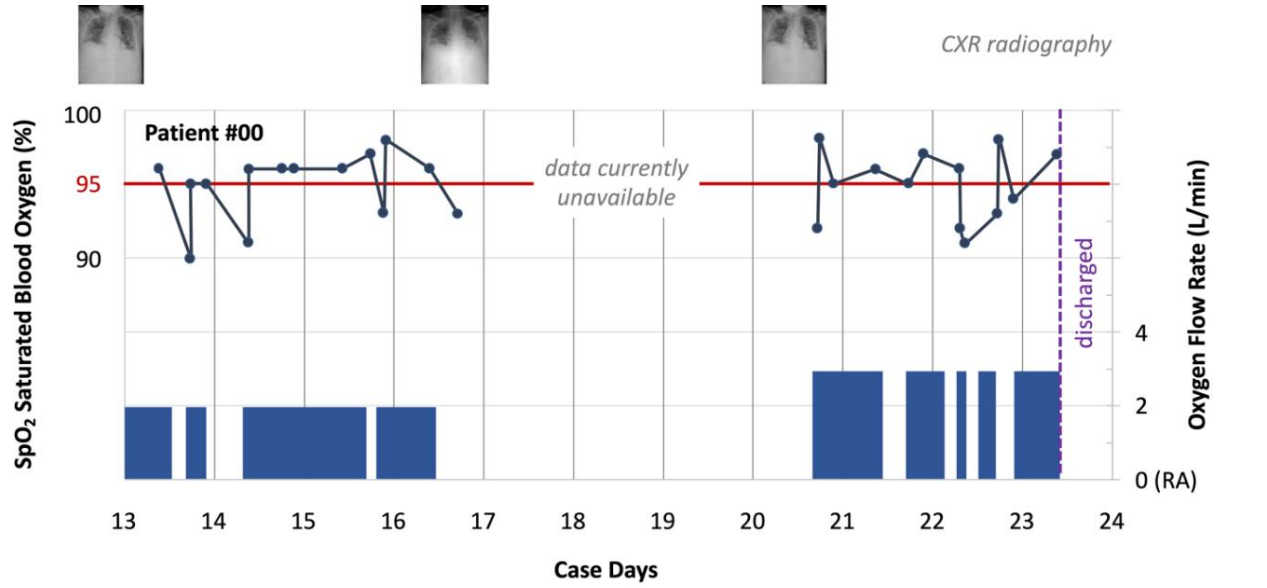

Figure 9. Measured SpO_2 levels for control group patient (case 00) for a 23-day hospitalized COVID patient. Data confirms patient required oxygen supplementation of 2 L/min increasing to 3 L/min before discharge.

In accordance with mandatory governmental criteria for discharging hospitalized contagious COVID-19 patients (circa June of 2021) in Taiwan regulatory parlance, "any patient hospitalized over ten days whose symptoms have been relieved for at least three days either with two negative PCR tests; or one negative PCR test plus one Ct value of 34 or more; or two tests with Ct values of 34 or more, the patient will be released from isolation." Translated into the common tongue, this criteria means (absent any extenuating circumstances) a patient once no longer infectious or requiring intensive care should (must) be discharged from the hospital even if suffering chronic pulmonary dysfunction. In other words, restored breathing is not a criteria for hospital discharge, necessarily pushing a portion of COVID population into convalescent care.

Put into context, starting in May-June of 2021, a mostly unvaccinated Taiwan population experienced its first significant surge in COVID-19 hospitalizations and necessarily had to manage the availability of hospital beds in accordance with consideration of public health. The chest X-rays of **Figure 10** illustrate the widespread cardiopulmonary damage caused by COVID-19 resulting in a high degree of ground-glass occlusion and pulmonary infiltrates – the quintessential radiographic signature of COVID-19 disease. Despite twenty days of receiving the "best available" COVID therapies circa 2021, the pulmonary function of the patient of case 00 only worsened. At discharge, the patient required ongoing oxygen supplementation. In this regard, the post COVID requirement for breathing assistance represents a fundamental adverse change in a patient's quality-of-life (QoL).

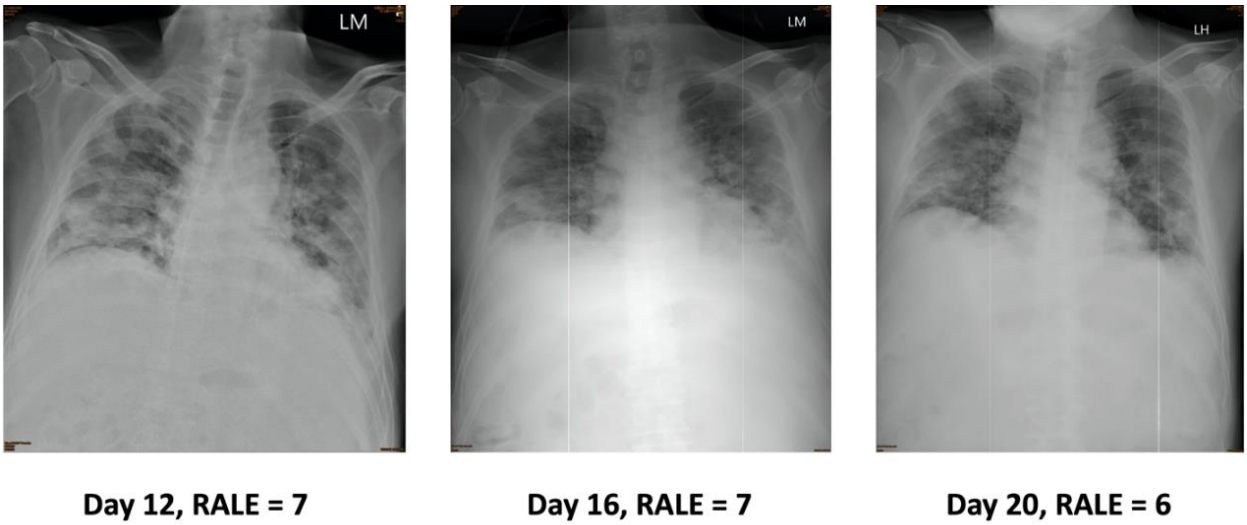

Figure 10. Chest X-rays of COVID-19 COVID patient 00 receiving standard medical care circa summer 2021. Radiographs show no improvement in pulmonary clearance in 20 days of hospitalization. A common term of art in chest X-rays, RALE is the acronym for "radiographic assessment of lung edema".

PBM Test Group. Three patients in the Taiwan case study of 2021, namely cases 1, 2, and 3, received PBM therapy comprising posterior application of six LED pads transversely arranged in two rows (as shown in the rightmost image of **Figure 4**). Using the 64-minute protocol EP3 test group patients received a blended wavelength of red and NIR light with an area-normalized surface fluence over 42 J/cm^2. Covering the entire lungs, the total delivered dose exceeded 50 kJ.

In exemplary PBM case 1, the patient exhibited severe COVID-19 symptoms alternating between severity stages 5 and 6. For the first 15 days of hospitalization, the patient remained severely symptomatic and PCR positive for COVID-19 with no demonstrable symptomatic improvement of pulmonary dysfunction or of inflammatory markers assessed by repeated blood tests. **Figure 11** illustrates, for example on day 13, an interruption in supplemental oxygen caused a rapid and dangerously precipitous drop from 97% to 90%. Oxygen supplementation was restored to 4 L/min then dropped to half that after the patient stabilized. Chest X-rays (CXRs) showed significant pulmonary ground-glass opacity indicating severe inflammation, edema, and lung infiltrates. Physician prognosis remained neutral to unfavorable.

On day 15, the otherwise unresponsive patient received the first (of four) PBM posterior lung treatments performed daily using the aforementioned EP3 protocol while receiving oxygen supplementation at a flow rate of 2 L/min. Immediately SpO_2 level jumped to 100% as illustrated in the SpO_2 timeline as shown.

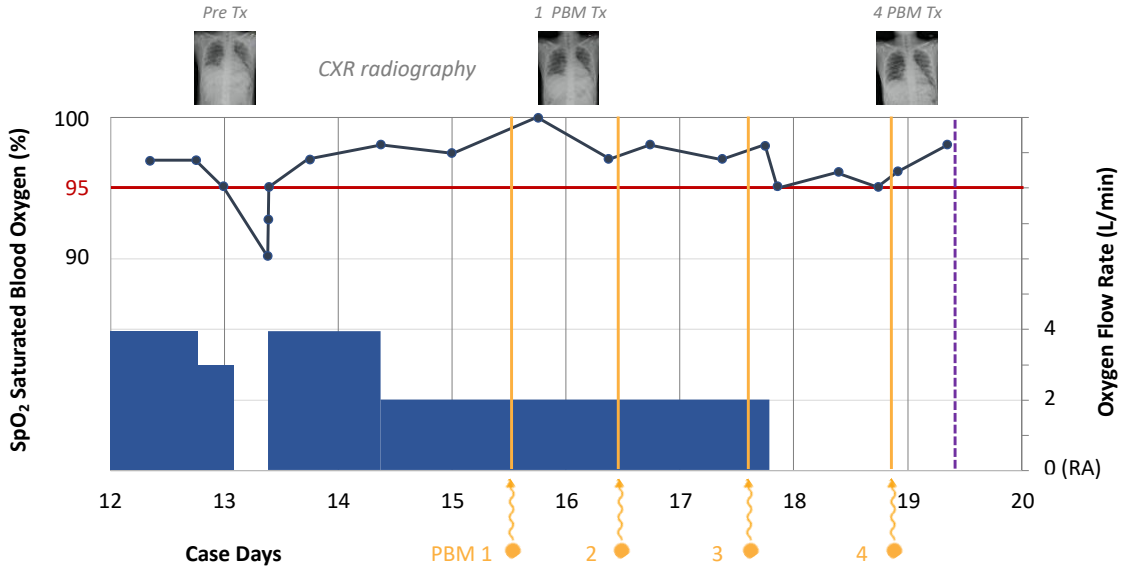

Figure 11. Timeline of SpO_2 oxygen levels before and after commencing PBM therapy. After 4 PBM sessions patient was able to sustain 98% oxygen levels even after discontinuing oxygen supplementation.

Discontinuing oxygen supplementation on day 17 after the third PBM session reduced SpO_2 levels to 90, but a fourth PBM session restored levels to 98 with only room air, after which the patient of case 1 was discharged with no subsequent need for oxygen supplementation.

The improvement in pulmonary function is easily observable in the chest radiographs (CXR) of **Figure 12** confirming significant pulmonary clearance by day 19. The CXR images show left-to-right, the progression of pre-PBM opacity (RALE = 6-7) to RALE = 2 after 4 PBM sessions.

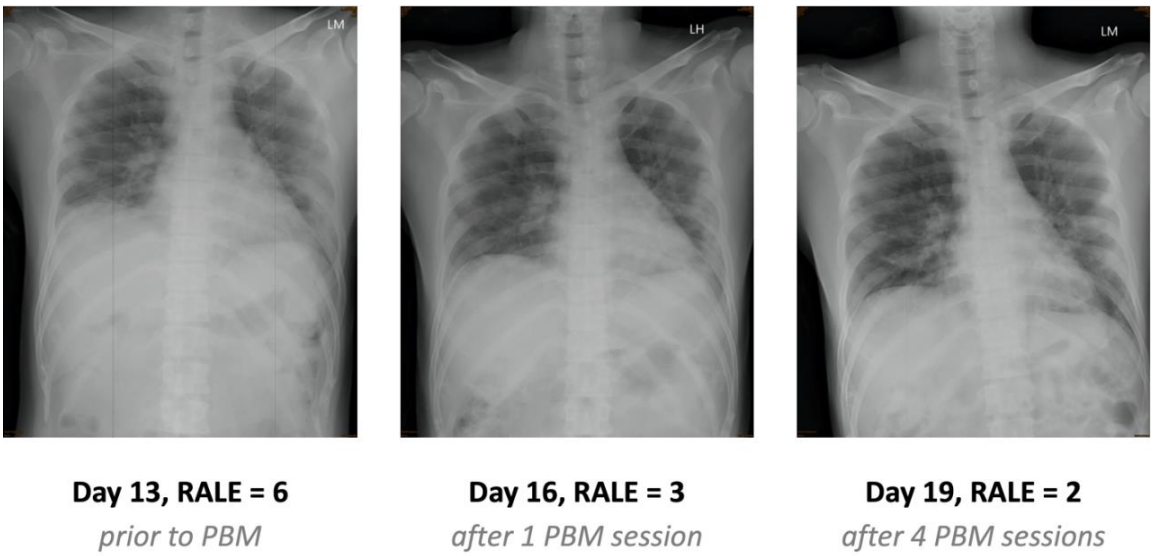

Figure 12. Improvement of X-ray pulmonary optical transmissibility as a result of photobiomodulation sessions. Immediate improvement is discernable after 1 PBM session with significant change after four.

The rapid improvement in pulmonary opacity, lung function, and SpO_2 can be better understood by analysis of blood tests for inflammatory factors. Comprising a protein produced by the liver, C-reactive protein or CRP is a particularly insightful measure of systemic and organ inflammation. Measured volumetrically in mg/L, high levels of CRP comprise any concentration over 1 mg/L. The higher the number, the more severe the inflammation.

Shown in **Figure 13**, despite the best attempts of doctors to contain inflammation on day 13 measured CRP levels jumped to 9.04 indicative of severe infection and inflammation. Following a

single PBM session CRP dropped to 3.54. After two sessions CRP levels fell to 0.65 (normal range), confirming PBM's strong anti-inflammatory benefits.

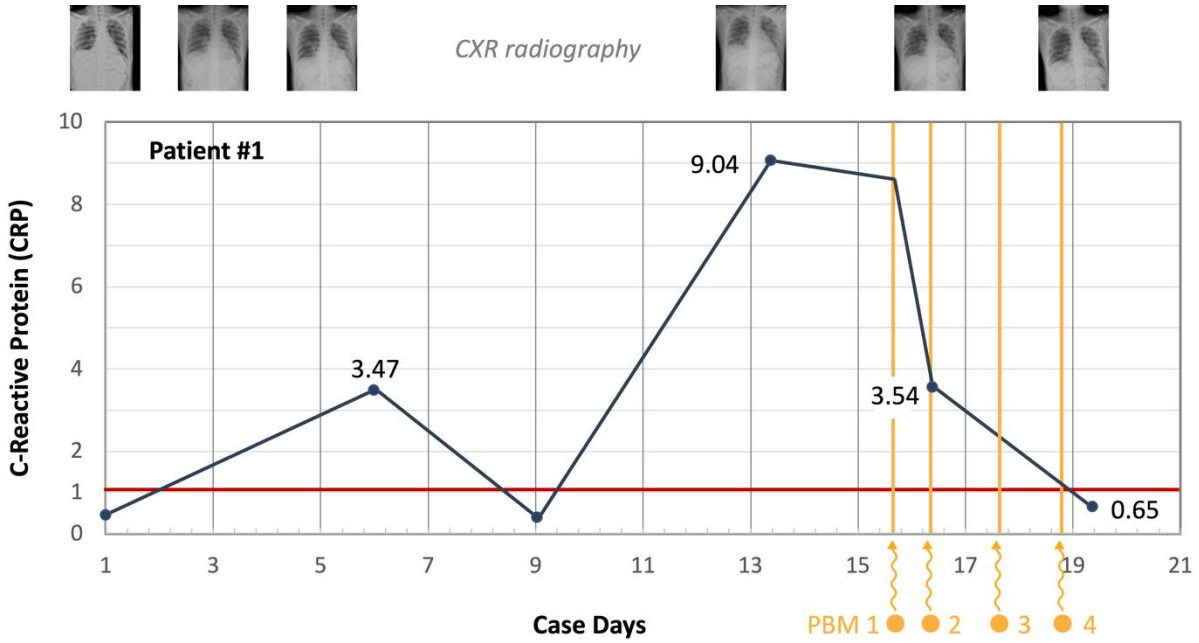

Figure 13. Measured CRP levels for 19-day hospital stay for COVID patient case #1 illustrates dramatic rise in inflammation and CRP levels on day 13, an increase undeterred by pharmacological attempts on day 7 to limit hyperinflammation. Commencing PBM on day 15 caused a precipitous decline in CRP to 3.54 in one day and to 0.65 within the normal range after 4 days.

PBM Recovery Times. As detailed previously in **Table 4**, in case #1 PBM promoted rapid patient recovery, eliminating inflammation, restoring breathing, and increasing blood oxygen levels over 95 in 4 days despite experiencing 15 days of degrading health prior to receiving PBM. Patient case #2 recovered in 3 days after suffering severely impaired cardiopulmonary function and COPD for 19 days prior to PBM. Patient case #3 had only been admitted as a patient for 9 days before first receiving PBM.

Once treatment commenced, the patient rapidly recovered and was discharged from the hospital within only 4 days. Comparing the 3-to-4 day recovery (average of 3.7 days) for the PBM experimental cohort to the average hospital duration of 16-to-23 days (19.5 days average) for the COVID control group represents a 80% reduction in hospital days, reducing recovery times to 20% of the that required without the PBM modality (i.e. a 5X improvement).

Case Study 2 Discussion. According to the Case 2 study results, PBM represents a safe and effective potential therapeutic modality for the treatment of COVID-19 pneumonia offering shorter recovery times and improved outcomes. Adjuvant photobiomodulation has a significant effect on severe COVID-19 pneumonia, especially when $SpO_2 \leq 94\%$. Observed benefits include:

- PBM produces rapid (1 hour) rescue of oxygen desaturation, SpO_2 improving by 2-4%.
- Lung infiltration is significantly improved with 2-3 days after PBM as confirmed by chest X-ray radiographic analysis.
- Lung damage is significantly reduced by PBM, restoring normal organ function and blood oxygen levels in room air eliminating the need for oxygenation supplementation.
- PBM dramatically reduces inflammatory cytokines as evidenced by changes in CRP and other inflammatory markers in the blood.
- PBM reduces hospital days by 80%, i.e. requiring hospitalization only one-fifth of the time needed without photobiomodulation.

Researchers of Case Study 2 thereby concluded that whole-organ PBM therapy has a remarkable effect in the treatment of severe and very severe (stage 5 and stage 6) COVID-19 pneumonia. This study independently corroborates the beneficial results of deep tissue PBM on severely ill hospitalized patients first demonstrated in ambulatory Case Study 1.

As the two case studies treating COVID-19 disease involved different genotypes and phenotypes of SARS-CoV-2 – one comprising the original ancestral virus the other its alpha variant, the observed results supports the hypothesis that the anti-inflammatory anti-infective therapeutic mechanism of PBM is insensitive to viral mutation. It also demonstrates the LED based PBM system used in the study is equally applicable for hospital use as it is for outpatient and ambulatory care.

The device manufacturer (although curating recorded data in the preparation of this manuscript) had no role in performing therapeutic treatments on patients in this study, in managing patient care, or in data collection. All patient data was independently recorded by hospital nursing staff and through automated monitoring of patient vital signs.

Radiographic chest X-ray (CXR) and blood test data were prepared by independent departments within the hospital, uninvolved and unaware of the case study being performed. A more detailed case study manuscript including a complete discussion of blood test results is under preparation for future publication.

Long COVID PBM Case Reports

Long COVID, also referred to as post COVID, refers to the diverse collection of medical and health conditions and presentations resulting from exposure to SARS-CoV-2 virus and COVID-19 disease, from adverse reactions to viral components present within vaccines, or from a combination of both. Cases include inflammatory, metabolic, and neurological presentations.

Case Statistics. Since March 2020, doctors using the ABP whole-organ PBM system and protocols have successfully treated approximately three-hundred fifty COVID-19 cases in aggregate comprising both 60% acute and 40% post-acute patients. Among the PBM cases, less than half-a-dozen patients (under 0.2%) failed to recover fully, including two patients with severe comorbidities unrelated to coronavirus, and two mental health cases involving intermittent bouts of severe anxiety. Only one acute COVID-19 case treated with PBM returned as a long COVID patient. Aside from a few gastrointestinal presentations, the long COVID cases are roughly split evenly at 20% among metabolic organ dysfunction (mostly respiratory and chronic fatigue) and 20% neurological dysfunction (mostly brain fog). Mental health issues such as anxiety, sleep disorders, and depression represented a small and intermittent component in long COVID patients.

Exemplary Case Reports. A sampling of long COVID cases is summarized in **Table 5**. The sample includes 6 cases of tissue and organ dysfunction (5 respiratory, 1 digestive, 1 cutaneous) and 5 neurological (3 brain fog, 2 mental health) two of which also included organ involvement.

Table 5: PBM of various long COVID cases

Patient	Presentation	Protocol	Sessions	Outcome	Clinic
45F	Wheezing, unventilated dyspnea at 2 LPM SpO_2 = 87, high flow O_2 (30 LPM) for SpO_2 > 95%	EP protocol (anti-inflam): lungs	*10 total sessions* once every 3 days	Terminated suppl O_2 after 5 days, full recovery in 30 days	Raimondo et al
42F	Post exercise dyspnea for athlete	EP protocol (anti-inflam): lungs	*9 total sess* once every 3 days	Full recovery in 28 days now able to run 4 miles without being winded	Raimondo et al
44M	Oxygen toxicity from 1 mo of 6 LPM O_2, limited mobility, disuse atrophy	EP protocol (anti-inflam): lungs	*24 sessions* 4/wk then 3/wk after 1.5 wks	Terminated suppl O_2 after 14 days, full recovery in 35 days	Raimondo et al
M35	Dyspnea, atrophy from 2 mo ventilation, chest tightness	EP protocol (anti-inflam): lungs	*4 total sess* over 2 wks	Improved breathing after 1 sess, full recovery after 4 sess	LightMD
F57	COVID recurrence (post Remdesivir therapy), kidney, liver, lungs dys	EP protocol (anti-inflam) + VO protocol (repair): lung, liver, kidney	*1 total sess* 1 long sess (tri-organ)	Full recovery, no pain, increased energy after a single (long) session	LightMD
73F	Skin rash & hives (COVID/Paxlovid) on body, arms, thighs, steroid unresponsive	VO protocols (repair): skin; CNS protocols (repair): spine	*5 total sess* alternate days	Rash worsened after 1 session, skin relief after 2, full relief (bumps gone) after 5 sess	UltraRed Light

27M	Brain fog, headaches, weak immune, low energy, fatigue, skin pallor	tPBM protocol (calm→cog CNS); CNS protocol (repair): spine; VO protocols (repair): skin	*5 total sess* alternate days	Headache diminished after 1 sess, ended at 3; brain fog ended at 2 sess, skin revived after 4 sess	UltraRed Light
38F	Brain fog (8 wks) following 1 mo hosp, chest tightness, discomfort	tPBM protocol (cog CNS); EP protocol (anti-inflam): lungs;	*2 total sess* in 4 days	brain fog reduced by 80% in 24 hr, fully recover in 2 sess	Raimondo et al
36F	Brain fog	tPBM protocol (cog CNS)	*1 session*	Full recovery in 1 session	Raimondo et al
24M	Severe anxiety, sys pain, tachycardia, insomnia, dyspnea, paresthesia, nausea, dizzy, weight loss	tPBM + CNS protocols (repair, calm): brainstem brain, spine; EP protocol (anti-inflam): lungs	*7 total sess* alternate days	Sleep improved after 1 sess, heart slowed at 3, appetite after 5, not dizzy after 5, some anxiety recurrence	UltraRed Light
46F	Extreme anxiety attacks (up to 5 hrs), small fiber neuralgia, nosophobia	tPBM protocol (calm CNS) only no neuralgia	*16 total sessions* 3/wk	Relief after 5-min PBM, recurring relapse, Rx MD redirected therapy	Raimondo et al

As described previously, PBM therapy involves the anti-inflammatory epithelium protocol EP for respiratory long COVID, the VO visceral organ protocol for metabolic long COVID, and two versions of CNS (central nervous system) PBM protocols for neurological long COVID – one for the spine and peripheral nerves, the other for transcranial photobiomodulation (tPBM) of the brain. These whole-organ PBM regimens have been broadly applied with a high degree of positive outcomes treating a plethora of medical conditions.

For example, of the clinical cases reported involving long COVID respiratory distress, most patients experienced full recovery within six weeks with no need for supplemental oxygen after completing the PBM regimen. One of the more severe long COVID cases complicated by oxygen toxicity from high flow O_2 therapy (30 LPM) further confirmed that even lung damage can be reversed using deep-tissue PBM. The case of severe skin rash with pustules (wholly unresponsive to steroidal treatment) fully resolved within two weeks of PBM.

The skin rash example typifies the challenge of treating long COVID cases. Because there exists no standard for long COVID therapy, it becomes difficult to distinguish the condition's etiology as a disease symptom or as an adverse reaction from a therapeutic, in this case from a Paxlovid allergy (reportedly occurring in about 10% of all users). Likewise in the successful PBM treatment of liver and kidney dysfunction, the etiology is difficult to separate injury arising from the viral infection from side effects of the patient's prescribed pharmacological cocktails.

Transcranial PBM treatment of brain fog and headache was found to be highly successful with most patients requiring only two sessions to fully recover. The transcranial photobiomodulation (tPBM) protocol, principally in the NIR spectrum comprises a multifrequency sequence of pulsed waveforms including those coinciding with the gamma band of EEG brain waves. Reported mechanisms of tPBM include (i) enhanced circulation throughout the brain, (ii) increased neural connectivity, (iii) decreased neurotoxicity, (iv) reduction in scar tissue impeding neural transduction, and (v) neurogenesis. In one tPBM related study [286], transcranial blood flow shown in **Figure 14** reveals a dramatic improvement in perfusion after a single PBM session.

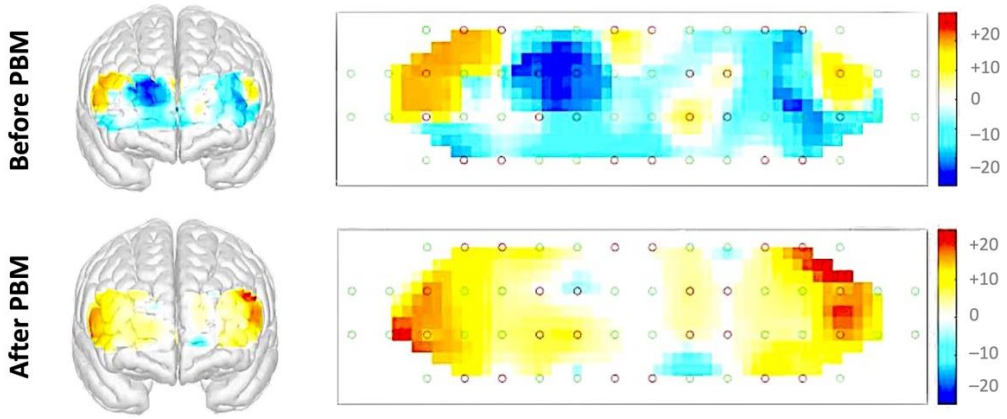

Figure 14: Normalized blood flow distributions in brain before-and-after tPBM, from ref 286.

The same study also shows significant improvement in transhemispheric communication as depicted in a Brodmann map of the neocortex shown in **Figure 15**. Improved edge connectivity correlates with greater executive function, enhanced memory, and overcoming cognitive deficits.

While long COVID brain fog and headache resolved completely without relapse, two patients suffering post COVID anxiety attacks had a different prognosis. Although experiencing temporary symptomatic relief and improved relaxation immediately following PBM therapy, the patients continued to present unpredictable panic attacks with no identifiable triggers. More study of post COVID anxiety syndromes are necessary.

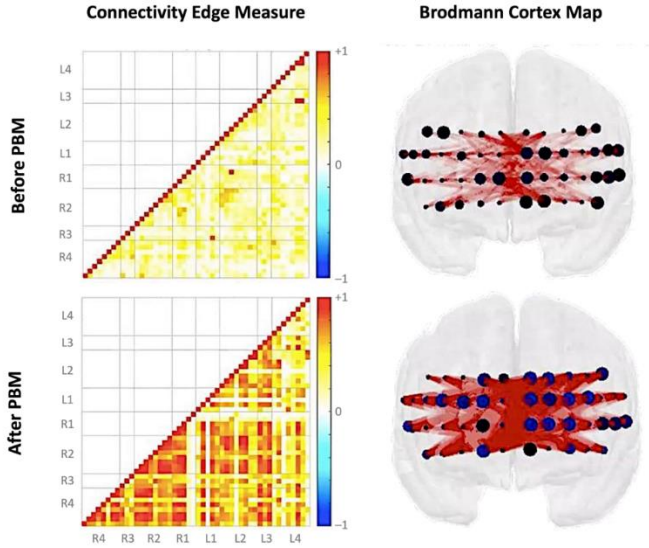

Figure 15: Brain edge connectivity and Brodmann cortex map before and after tPBM, from ref 286.

Discussion & Insights

COVID-19 Infection. The trajectory of SARS-CoV-2 infection though the body in acute COVID-19 disease directly correlates to those tissues expressing a preponderance of ACE-2 receptors which the novel coronavirus targets to infect cells and to replicate, starting with the mucosal membranes of the sinus and AEC and ultimately migrating into the bronchia. By disturbing the homeostatic balance of angiotensins (causing vasoconstriction and localized hypoxia) and by provoking pro-inflammatory cytokine production, the virus promotes bronchial hyperinflammation causing pulmonary distress, edema, and systemic hypoxemia.

The inflammatory cytokines combined with viremic diffusion (blood borne pathogen transmission) enables COVID-19 to inflame and infect other organs susceptible to ACE-2 targets including the liver, kidneys, intestines, endocrine organs, and reproductive glands. Systemic inflammation also impairs the central, peripheral (and autonomous) nervous systems and the brain, impacting organ function and disturbing hormone

release from the hypothalamus-pituitary-pineal axis, deregulating the entire neuro-endocrine system.

The ubiquitous distribution of ACE-2 receptors thereby enables COVID-19 to function as a multi-organ disease and multi-system inflammatory syndrome (MIS) presenting severe acute symptoms manifesting chronic "long COVID" after effects.

PBM - the Quintessential COVID Antagonist. The unique property of PBM is its redox state-dependent mechanisms-of-action. In healthy cells, red and NIR light stimulates normal inflammatory immune response designed to kill invading pathogens. Cells in an oxidative state however react differently to light, where photobiomodulation upregulates the activity of M2 macrophages and Th2 T-cell helper cells creating anti-inflammatory cytokines and downregulating pro-inflammatory mediators. So while ACE-2 receptors represent the targets for SARS-CoV-2 tissue infection, they also identify tissue targets for whole-organ PBM able to limit inflammation, starve the pathogen, and confound its replication.

Accordingly, Case Study 2 confirmed a single PBM session for a stage 6 severe COVID patient reduced CRPs (a key inflammatory marker) from 9 by more than 50%, then in a second treatment drove CRP below 1 into the normal range. Concurrently the ground glass opacity and lung infiltrates diminished significantly from RALE = 6-7 reduced to 2, allowing a patient wholly unresponsive after two weeks of standard care to be discharged from the hospital after only four PBM sessions performed successively in 4 days. At discharge, the patient was able to maintain SpO_2 above 97% with no oxygen supplementation.

In aggregate, hospitalization days with PBM were reduced by 80%. Case Study 1 further indicated that PBM provides immediate relief of acute conditions within 4 days from only 2 PBM sessions irrespective of the severity of the patient's infection. In contrast, full recovery required longer treatments. Tissue damage of visceral epithelium and vascular endothelia is a time-consuming process, needing up to 2 weeks to heal. In general, the longer a COVID infected patient waits to commence PBM, the longer full recovery takes.

Using the same whole organ PBM technology (but adapting the protocols for the targeted tissue), required recovery times ranged up to 5 weeks for lung damage, 1 week for organ dysfunction, but less than a week for brain fog and neurological damage (excluding mental health effects). The PBM success rate for treating all forms of long COVID is extremely high.

PBM Delivery and Dosage. Comparing the energy dosage (fluence) of LED whole-organ PBM to published reports of laser scanned PBM reveals a discrepancy. While the whole organ LED therapy discussed herein employs a 42 J/cm^2 fluence on the skin surface administered in 64 min, reported values for laser scanning suggest a surface fluence of 7.2 J/cm^2 delivered in 14 min is sufficient to treat the infection.

Since, in accordance with quantum dynamics (as detailed the section on biophysics in Part I of this paper), pulse power does not determine depth, then further study is needed to understand the difference. Specifically, the energy E_{trgt} (x) reaching a targeted organ at depth x is equal to the optical surface fluence E_λ /A multiplied by the transmissivity coefficient Ψ_{trgt} (x) of intervening tissue, or

$$E_{trgt}(x)\ /A = \Psi_{trgt}(x)\ E_\lambda/A$$

then only a fraction Ψ_{trgt} (x) of the optical energy E_λ/A impinging the surface reaches an organ. If we assume in accordance with published works, the minimum fluence for photobiomodulation is 0.5 J/cm^2 then at a surface fluence of E_λ /A = 42 J/cm^2 the minimum required optical transmissivity is Ψ_{trgt} (x) = (0.5/42) = 1.2% meaning only one-hundredth of the surface energy needs to penetrate to efficaciously stimulate PBM.

By contrast, if the surface fluence is only 7.2 J/cm^2 (as reported by for a laser scanner [263] then the minimum required transmissivity is Ψ_{trgt} (x) = (0.5/7.2) = 7%, a ratio well above Monte Carlo simulations considered in part I of the paper. To explain this incongruence either (i) published models of tissue transmission overestimate optical absorption, or (ii) the requisite fluence to stimulate efficacious PBM is lower than the accepted minimum energy of 0.5 J/cm^2, or (iii) the average surface fluence is higher than calculated.

Conclusion

From the independently published sources and case studies described herein, red and near infrared whole-organ PBM represents a pragmatic and efficacious means to non-invasively treat acute and long COVID-19 disease. Using protocols targeting tissue with a preponderance of ACE-2 receptors, whole-organ deep tissue PBM in the treatment of acute and long COVID-19 has been demonstrated to provide symptomatic relief of

disease symptoms while shortening patient recovery times. Acute COVID-19 patients receiving PBM therapy shown significant reduction in tissue inflammation as evidenced by marked improvements in chest X-ray ground-glass opacity, patient discomfort, reduced inflammatory markers (such as CRP), and elimination of the need for oxygen supplementation. Both scanning lasers and conformal LED pads demonstrate favorable outcomes. LED pads deliver higher fluences than scanned lasers in the same session times. Further studies of the prophylactic benefits of PBM are indicated.

About the Studies

No funding was involved in the case studies discussed in this paper. No researchers or physicians received financial support or special compensation from the device manufacturer Applied BioPhotonics (ABP) or from its representative agents (LightMD Inc in USA, LightDr in Asia, AraLight in IMEA) for using its photobiomodulation or participating in any case study. All case studies were conducted by patients' attending physicians performed in accordance with medical standards-of-care of participating hospitals, international domiciles, and jurisdictions. No patient was denied therapy in treating COVID-19 disease.

Patients receiving or refusing to take certain medications and pharmacological agents did so upon their own volition, decisions made in conjunction with their attending physician without influence of PBM device manufacturers. Furthermore, the device manufacturer was not involved in designing, conducting treatments, collecting data, or reporting patient conditions in any case study including the long COVID case reports. No COVID-19 study patient receiving PBM treatments suffered chronic disease, injury, or death during or as a result of these investigations.

Patient PBM therapies performed by doctors Hung TC et al, Raimondo et al, Chang HA; or by Wei-Gong Mem Hosp, Tri-Service Gen Hosp, LightMD, and UltraRed Light therapy center were conducted without the participation or involvement of device manufacturer. In accordance with international privacy standards (GDPR, HIPAA, PDPA), no personal patient information was shared by any care provider with the device manufacturer or with any third parties.

Although LightMD and UltraRed Light operate as agents of the device manufacturer Applied BioPhotonics, therapy services were performed independently without the supplier's participation.

Disclaimers

Richard K. Williams is founder, CEO, president, CTO (chief technology officer), and a shareholder of Applied BioPhotonics, Ltd. (ABP). He is also co-founder, CEO, and CSO (chief science officer) of LightMD, Inc., a member of the ABP group of global affiliates. ABP is a good manufacturing practice (GMP) certified device manufacturer, system specifier, and IP holder of medical devices and PBM therapy products. LightDr is a wholly owned business division of ABP.

As a matter of full disclosure as an entrepreneur Richard is also founder, CEO, and CTO of technology-innovator Adventive Technology Ltd., a founding member of HyperSphere.ai, and of several blockchain decentralized autonomous organizations (DAOs) unrelated to medical technology. The author received no financial sponsorship or compensation in the preparation of this article nor had any role in delivering PBM treatments to patients or in recording patient data in any study discussed herein.

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