PhotoBioModulation: Overview of the Pubmed Literature on Low Level Light Therapy

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Opinion Article

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OVERVIEW

"Low-level light therapy (LLLT), also known as photo biomodulation (PBM), is a type of optical therapy that uses red or near-infrared lasers or light-emitting diodes (LEDs) for medical treatment. The laser wavelengths involved in PBM typically range between 600-700 nm and 780-1100 nm, with power densities ranging between 5 mW/cm2 and 5 W/cm2. PBM is a series of biochemical cascades exhibited by biological tissues after absorbing a certain amount of energy from light." It has been used (in the clinic and the laboratory) for treating myriad diseases and conditions, and offers a non-painful and "non-invasive" primary or supplementary approach to ameliorating these medical conditions. Some of the application areas addressed include dermatology, pain, neurodegeneration, dentistry, bone repair, musculoskeletal disorders, depression, diabetes, coronary, thyroid disorders, among many others.

The present Op-ed uses a comprehensive query to search Pubmed and identify a wide range of existing and potential applications of PBM. This study presents 1) a

taxonomy of the Pubmed-retrieved literature, 2) an overview of the diseases/symptoms/conditions and parts of the anatomy treated by PBM, and 3) an analysis of PBM application to four of the major side-effects from Covid-19 vaccines.

INTRODUCTION AND BACKGROUND

PBM with advanced light sources has been around since the 1960s, shortly after the demonstration of lasers by Theodore Maiman. While lasers have been the main light source used in Low Light Level Therapy (LLLT) (aka PBM), recent years have seen the advent of light-emitting diodes (LEDs) as an alternative source. The main frequencies used are in the red/near-infrared in the ranges shown in the Overview, although other frequencies, such as blue, are used in targeted applications.

Part of the benefits from PBM may have a hormetic basis. "at very low levels of irradiation, photons are absorbed by subcellular chromophores present inside intracellular organelles, most notably, mitochondria. Absorption of energy by cytochrome C oxidase (CCO) in the mitochondrial respiratory chain is the primary initiating interaction triggering PBM effects.…..Both adenosine triphosphate (ATP) production and oxygen consumption by the cells increase. This may lead to changes in nitric oxide (NO) levels, activation of secondary messenger pathways, activation of transcription factors, and growth factor production.…..At this very low level, energy is absorbed by the cell but at such low amounts of energy that there are no observable gross changes (temperature or photochemical damage).

As the number of absorbed photons increases, stimulation of cellular metabolism, as noted above, begins to affect cellular activity, producing positive PBM effects. Both the number of photons and rate at which they are delivered has a significant influence on the response…..As the number of photons increases beyond a particular level, the cellular stimulation disappears, and if the number of photons is even further increased, inhibition and cellular damage occurs."

The remainder of this Op-ed consists of the Methodology developed to 1) retrieve the Pubmed PBM literature, 2) generate a taxonomy of the Pubmed PBM literature, 3) retrieve and analyze the literature of the four major side-effect diseases of the Covid-19 vaccine, and 4) identify the diseases, symptoms, and parts of the anatomy treated by PBM in the laboratory and clinic. The Methodology is followed by Results and Discussion, which in turn is followed by Summary and Conclusions.

METHODOLOGY

The Methodology has four components. Component 1 is the query used to retrieve relevant PBM records from Pubmed. Component 2 is the taxonomy that assigns relevant records to specific clusters/categories using a text clustering algorithm. Component 3 is the query developed to identify records in four thematic categories. Component 4 is the methodology used to identify phrases relevant to symptoms, diseases, anatomy parts treated, etc. See Appendix 1 for the detailed Methodology.

RESULTS AND DISCUSSION

Taxonomy of the PBM Literature

Appendix 2 (Table 2A-1) contains the taxonomy of the PBM literature. It consists of 124 of the 128 leaf (lowest-level) clusters generated by the CLUTO text clustering software clusters. Four clusters were not deemed relevant or useful for the analysis, and were removed. The 124 clusters are divided among fourteen thematic categories. In Table 2A-1, each of the fourteen thematic categories is boxed, capitalized, bolded, and followed by the title of, and titles of selected papers within, the leaf clusters within the thematic category. The title of each leaf cluster is bolded and italicized, followed by the number of records within the cluster in parenthesis.

For example, the first of the fourteen thematic categories shown is Cancer. The first of its leaf sub-categories ***BREAST CANCER TREATMENT SIDE-EFFECTS, ESPECIALLY LYMPHEDEMA***, contains 57 Pubmed articles, of which six were selected for inclusion in the table. Treatment of side-effects from cancer therapy (such as lymphedema, neuropathy, mucositis, etc.) was a strong component of this thematic category. Other thrust areas include treatment of Tumors, Cancer Cells, and use of Nanoparticles for Converting Light to Heat.

The side-effects thrust of the Cancer category tends to use low-level light therapy. The photodynamic and especially photothermal approaches have been increasingly focused on low-light levels mainly in the near-infrared range, where light absorption by the photothermal agents and conversion to heat is efficient. Some approaches employ higher power levels for direct ablation, but the focus here

is on the low-power level photodynamic and photothermal approaches. Most of the component record titles are self-explanatory.

The second thematic category is Neurologic Non-Pain. It focuses on topics such as Bell's Palsy, EEG Networks, Spinal Cord Injury, Depression, Nerve Regeneration, Parkinsonism, Traumatic Brain Injury, Alzheimer's Disease, and other Brain Disorders. While it is listed as Non-Pain, some of the categories, especially injury, will certainly include pain as well. The Non-Pain category focuses on the treatments for paralysis/nerve destruction; obviously, both aspects could be addressed by light therapies. Most of the papers use the low-light levels for therapy.

The third thematic category is Neurologic Pain. Thrust areas include Neck Pain, Carpal Tunnel Syndrome, Low Back Pain, Fibromyalgia, and Pain. Two of the many benefits of low-level light therapy are reduction of inflammation and increase of circulation, both of which can contribute to pain reduction. Low-level light is used for most of the records.

The fourth thematic category is Heart. Only one thrust area is included in this thematic area, namely, Myocardial Infarction. One reason is that it is targeted toward a particular organ, whereas the three previous much larger thematic categories are targeted toward system-wide phenomena. However, as the next section will show, the Cardiovascular category (identified by a query) is quite large. Because of the multi-thematic nature of many records in this database, the text clustering algorithm

assigned many of these heart-related papers to other thematic areas. While the Myocardial Infarction theme from the text clustering had 79 records, the Cardiovascular category had 1537 records.

The fifth thematic category is Musculoskeletal. Thrust areas include Plantar Fasciitis, Achilles Tendon Injury, Mandibular Distraction Osteogenesis, Knee Osteoarthritis, Bone Regeneration, Osteoblast Proliferation to Enhance Bone Formation (A Companion to the Previous Sub-Category), Medication-Related Osteonecrosis of the Jaw, Muscle Injury, Musculoskeletal Disorders, Orthopedic Rehabilitation, and Bone Repair. There are many thrust areas because of system-wide targets including bone, joints, connecting tissue, muscles, ligaments, etc. Most of the human applications tend to be on the near-surface musculoskeletal components (because of the previously-discussed radiation penetration limitations), while the animal studies can include deeper musculoskeletal components because of their smaller size.

The sixth thematic category is Dental. Thrust areas include Dentine Hypersensitivity, Chronic Periodontitis, Pain and Swelling Following Third Molar Extraction, Human Dental Pulp Stem Cells, Dental Implant Stability, Accelerating Orthodontic Tooth Movement, Er:Yag Laser for Tooth Structural Problems, Temporomandibular Disorders, Neurosensory Disturbances Following Jaw Surgery, Bleaching-Induced Tooth Sensitivity, Postoperative Endodontic Pain, Adjunct to Non-Surgical Periodontal Treatment, Dental Post Bonding, Orthodontic Pain, Dental Anesthesia, Post-Free Gingival Graft Surgery, and Tooth Structure Improvement. While dental is a

specific area, much of the PBM application is surface or near-surface, allowing more effective results. A substantial portion of the effort in this thematic area is reduction of pain from dental procedures, which could just as easily have been placed in the neurological pain category. The jaw disorders could have been placed in the musculoskeletal category. Other thrusts focus on enhancing tooth structure and controlling tooth movement.

The seventh thematic category is Skin. Thrust areas include Skin Flap Viability, Oral Lichen Planus, Tattoo Removal, Apthous Stomatitis, Burning Mouth Syndrome, Androgenic Alopecia, Vitiligo, Acne Scars, Port-Wine Stains, Oral Mucositis in Chemotherapy/Radiotherapy/Transplantation Patients, Acne Vulgaris, Hair Loss, Melasma, Burn, Oral Mucositis, Excimer Laser for Psoriasis, Melasma: Combination Therapies including Lllt, Skin Resurfacing, Pulsed Dye Lasers for Skin Problems, Melasma Treatment with Picosecond Lasers, Intense Pulsed Light for Skin Problems, Oral Complications from Head-And-Neck Cancer Radiotherapy, Laser Treatment of Scars, Pulsed Dye Lasers for Treating Scars, Laser Hair Removal, Fractional Photothermolysis, Vascular Lesions, Wound Healing, KTP Laser for Skin Problems, Skin Rejuvenation, and Laser Therapy for Dermatology. This is a very large area, as would be expected for a surface issue. Areas covered include cosmetic issues (e.g., skin rejuvenation, hair removal, etc.), disfiguration issues (e.g., scars, wounds, etc.), discolorations (e.g., melasma, skin discoloration, etc.), and surface expressions of disease (e.g., psoriasis, acne, etc.).

The eighth thematic category is Metabolism. Thrust areas Include Melbomian Gland Dysfunction, Hyposalivation/Xerostomia, Diabetic Wound Healing, Venous Leg Ulcers, Combination of Photobiomodulation with Static Magnetic Field to Enhance Athletic Performance, Muscle Fatigue, Exercise Performance Improvement, and Autoimmune Thyroiditis. Diabetes, thyroid abnormalities, and exercise performance play a central role in this category. Results seem to improve as the manifestations of the metabolic disorders treated approach the surface.

The ninth thematic category is Eye Problems. The only two thrusts are Macular Degeneration and Retinal Diseases, but given the importance of vision in daily functioning, these are important targets for PBM.

The tenth thematic category is Ear Problems. This category contains only one thrust, Tinnitus, but given the number of people who suffer from Tinnitus, it should not be downplayed, if indeed PBM has the capability to alleviate the problem.

The eleventh category is Inflammation. The algorithm produced three thrust areas in this category, two of which are Inflammation in general, and the third is Prostatitis. This biological mechanism is system-wide, and occurs in many processes and diseases. Some variant of Inflammation appeared in 1879 records of the present database. A fuzzy clustering algorithm would have included many/most of these records in the Inflammation category, consequently increasing its size substantially.

PBM tends to reduce Inflammation, which in the case of chronic Inflammation can be beneficial.

The twelfth category is Infection. Thrust areas include Covid-19 Infection, Herpes Labialis, Antibacterial Therapy, and Oral Infection. PBM has an antibacterial effect, and can be used to combat infectious processes. It can also be used to help erase some of the disfiguration associated with infections, such as oral lesions, and reduce other manifestations of infection.

The thirteenth category is Cells. This pervasive category relates to every part of the body, and the multi-themed records that contain references to cells could have been assigned to a number of the previously-identified categories. The thrust areas include Enhancement of Human Adipose-Derived Stem Cells, Enhancing Osteogenic Differentiation in Myriad Stem Cells, Apoptosis, Proliferation of Human Gingival Fibroblasts, Proliferation of Mesenchymal Stem Cells, Fibroblasts, and Cell Proliferation. In general, the overall effort is aimed toward enhancing or reducing cell growth and proliferation, or cell modification.

The fourteenth and final category is general, focusing on Light Sources (mainly lasers) for Multiple Medical Applications. Specific thrusts include Q-Switched Nd:Yag Lasers for Multiple Biomedical Applications, Carbon Dioxide Lasers for Multiple Biomedical Applications, Fractional Co2 Lasers for Myriad Biomedical Applications, Laser Acupuncture for Myriad Biomedical Applications, Comparison of Different Types of Lasers for Photobiomodulation Treatment of Myriad

Symptoms/Diseases, Low Intensity Lasers for Myriad Symptoms/Diseases, Low-Energy Laser Irradiation for Myriad Symptoms/Diseases, Neodymium:Yttrium-Aluminum-Garnet Laser for Myriad Symptoms/Diseases, Low Intensity Laser Radiation for Myriad Symptoms/Diseases, Red-Near-Infrared Light, Light Emitting Diodes for Myriad Symptoms/Diseases, Photobiomodulation for Myriad Symptoms/Diseases, Low-Level Laser Therapy, Photobiomodulation, and Light Penetration.

The main categories in terms of numbers of thrusts are Skin, Dental, and Neurological. Skin and Dental reflect surface/near-surface problems, which could be impacted directly by light sources. Neurological, and to a lesser extent Musculoskeletal, would be more amenable to the near-infrared, and good results could be expected for near-surface applications. The amount of radiation actually reaching the target (especially deeper into the body) in individual patients would be quite variable, given all the differences possible in radiation sources and individual structures. The next section addresses the concept of windows-of-effectiveness, as follows: "Absence of positive results in some cases occurs for almost all therapies, and there are usually windows of effectiveness for myriad therapies. Given the large number of variables/parameters in the experiments/applications, and the diversity of the recipients of the PBM, large numbers of experiments would be required to define these windows more precisely than at present." Also, the next section addresses the possibility that the healing effects from PBM on the deeper organs and tissues (in some cases) may not require the direct impact of the radiation

on the affected tissues and organs, but rather the positive impact on the blood and subsequent positive impact of the blood on the affected tissues and organs.

Overall, pain reduction appears to be one major benefit and subject of study, and other benefits include inflammation reduction, circulation improvement, cellular modifications, anti-microbial effects, and many others. Side-effects from more intensive therapies (e.g., chemotherapy, radiotherapy, etc.) have also been ameliorated. The next section provides a comprehensive overview of symptoms, diseases, and parts of the anatomy that have been treated with PBM in the laboratory or clinic.

PBM for Four Diseases that are among the Most Frequent Following Covid-19 Vaccination

I have published a number of Op-eds addressing diseases following Covid-19 vaccination, and have summarized them in a recent Op-ed. Among the most frequent diseases are cardiovascular, neurological, autoimmune/(link1), and cancer (more recently, because of its long latency period). Some scientists also show excessive blood clotting as a separate after-effect of the Covid-19 vaccines, but I have included blood clotting terms (e.g., embolism, thrombosis, coagulopathy, etc.) in the cardiovascular and neurological diseases categories, because of the prominent role clots play in these diseases.

The query used to identify these disease-related records is shown in Appendix 1, Tables 1A1-1A4, and the records retrieved by the main query's four sub-queries are shown in Appendix 3, Tables 3A1-3A4. The numbers of records

in each of these four categories are shown in parentheses following the title of each table. The very large numbers in the neurological category reflect the wide range of important neurological symptoms that comprise this category (pain, paralysis, Motor and Executive Function disorders, etc.). Based on the numerous studies with positive outcomes in each of these four categories, it appears that PBM could be part of the armamentarium of treatments that could address (to some extent) the myriad side-effects following the Covid-19 vaccines.

Some of the positive outcomes from PBM in each of these four diseases (in the clinic or laboratory) include (but are not limited to):

Cardiovascular

"Evaluation of Photobiomodulation on myocardial function of Patients with Advanced Ischemic Cardiomyopathy, A Case Series….. it can be concluded that interventions in cardiomyopathic patients have shown promising improvements in certain cardiac function parameters. Specifically, the significant enhancement in the six-minute walk test post-intervention…..suggests a positive impact on functional capacity"

"Level of LDH and CPK was significantly lower in the PBM group…..in the 4th day postoperatively. The PBM group also showed significantly lower post-surgery complications, including pericardial effusion, ejection fraction, pathologic ST changes, pathologic Q, rehospitalization, heart failure, and mediastinitis…..Likewise, the VAS pain score after surgery was significantly lower in patients in the laser

group…..PBM seems a promising, safe, cost-benefit therapeutic modality to reduce postoperative complications of CABG"

"Implantation of low-level laser irradiated mesenchymal stem cells into the infarcted rat heart is associated with reduction in infarct size and enhanced angiogenesis."

"Laser therapy can be considered an effective method of increase of endothelial functional activity in patients with stable angina pectoris"

"An improvement of functional capacity and less frequent angina symptoms during exercise tests without a significant change in the left ventricular function were observed. Laser biostimulation in short-term observation was a very safe method."

"Our study shows a noticeable positive effect of low-intensity laser radiation on blood lipid spectrum and hemostasis. This makes laser therapy promising in combined rehabilitation of postmyocardial infarction patients"

"We conclude that percutaneous myocardial laser therapy in selected patients with severe, medically refractory angina not treatable with conventional revascularization induces significant and sustained symptomatic benefit"

"This gave arguments for feasibility of laser beam usage as a neurohormonal modulator in IHD patients to reduce cardiac remodulation and prevent cardiac failure."

Neurological

“The pilot clinical trial to evaluate brain-gut PBM therapy demonstrated the tolerability and feasibility of the novel PBM-based treatment for mild-to-moderate AD patients. Compared to the sham patients, the PBM-treated patients had lower Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) comprehension sub-scores, higher forward verbal spans, and lower Trail Making Test (TMT) Part B (TMT-B) execution times, which suggest an improvement in cognitive functions.”

“We compared the effects of different doses of photobiomodulation (PBM) on cognition and resting state brain functional connectivity in 25 cognitively normal adults aged 55-70 years. They were randomized to a single session of the sham group, "low-dose" and "high-dose" groups receiving NIR light with transcranial fluence of 26 and 52 J/cm2 respectively, and intranasal fluence of 9 and 18 J/cm2 respectively. There was a significant increase in resting state functional connectivity of the left superior frontal gyrus (SFG) with the left planum temporale (PT)…..and with the left inferior frontal gyrus, pars triangularis…..in the "high-dose" group only compared to the "sham" group. There was also a significant improvement in visual search and processing speed…..in the "high-dose" group.”

“Concomitant use of cell therapy and photobiomodulation therapy can improve the symptoms of PD”

“A number of clinical signs of PD were shown to be improved by remote PBM treatment, including mobility, cognition, dynamic balance, spiral test, and sense of smell. Improvements were individual to the participant. Some

improvements were lost for certain participants during at-home treatment, which coincided with a number of enforced coronavirus disease 2019 (COVID-19) pandemic lockdown periods"

"pulsed 1064 nm PBM delivered with a flat-top handpiece protocol is a valid and its treatment protocol modified, depending on the origin and severity of the condition, which is fundamental in optimizing facial paralysis recovery and alleviating neurological symptoms"

"Photobiomodulation (PBM) demonstrated significant improvements in muscle performance, reducing fatigue and pain levels, and enhancing range of motion in post-stroke patients with spastic hemiparesis. These findings support the potential integration of PBM into rehabilitation protocols"

"These findings highlight the potential of PBMT, combined with CeONPs-loaded scaffolds, in promoting functional motor recovery and alleviating pain-related responses following SCI. The study underscores the intricate interplay between various interventions and their cumulative effects, informing future research directions for enhancing neural repair and pain management strategies in SCI contexts"

"Improvements in sensitivity and an increase in the perception of muscle contraction were found in the active PBM group 30 days after treatment compared with the sham group. The results of the WHOQOL-BREF questionnaire revealed a significant difference in general quality of life favoring the active PBM group over the sham group after treatment. Physiotherapy combined with

PBM leads to better sensory-motor recovery in patients with SCI as well as a better perception of health and quality of life"

Autoimmune

"This study aimed to examine the effects of low-level laser therapy (LLLT) combined with levothyroxine replacement therapy on thyroid function, oxidative stress (OS), and quality of life in patients with Hashimoto's thyroiditis (HT)….. Improvements in glutathione levels and quality of life were significantly higher in the active treatment group than in the sham-controlled group. LLLT was found to be more effective on OS and quality of life in patients with HT than in patients in the sham-controlled group. It was concluded that LLLT is a safe and effective method that can be used in the treatment of patients with HT."

"PBM has positive effects on MS by regulating the inflammatory process, controlling immune cell activity and mitochondrial functions, as well as inhibiting free radicals production which finally leads to a reduction in neurological defects and an improvement in the functional status of patients."

"A group of 59 patients presenting with acute viral hepatitis B was available for examination. A single course of pulsed infrared laser irradiation with autoresonant amplification resulted in the improvement of clinical conditions of the patients and normalization of ALAT activity, total and direct bilirubin levels"

"Our study showed that exposure to the 308-nm excimer lamp effectively induced hair regrowth in solitary alopecia

areata lesions. Apart from erythema, there were no significant adverse effects. Therefore, we suggest that it may be considered as a treatment modality for recalcitrant alopecia areata"

"Combination 830-nm and 633-nm light-emitting diode phototherapy shows promise in the treatment of recalcitrant psoriasis: preliminary findings.…..All patients completed their LED regimens (4 requiring 1 regimen, 5 requiring a second). Follow-up periods were from 3 to 8 months, except in two patients who were lost to follow-up. Clearance rates at the end of the follow-up period ranged from 60% to 100%. Satisfaction was universally very high"

"Autoimmune thyroiditis (AIT) is an autoimmune disorder that is characterized by thyroid gland dysfunction.…..LLLT reduced thyroid gland inflammation and inhibited immune cell trafficking. LLLT modulated inflammatory responses and improved thyroid gland regeneration.…..Investigations indicated that besides current treatment strategies, LLLT could be a promising therapeutic approach for the treatment of AIT."

Cancer

"To evaluate the efficacy of dihematoporphyrin ether (PHOTOFRIN)-mediated photodynamic therapy (PDT) for the treatment of diffuse field cancerization and Tis-T2N0M0 squamous cell carcinoma (SqCCA) of the oral cavity and oropharynx in patients not amenable to or that have failed conventional head and neck cancer treatment.…..PDT provides a surgical oncologic modality for potentially curative treatment of early stage oral cavity

and oropharyngeal malignancies either as a primary modality or for treatment in patients that have previously failed surgery and/or radiation therapy"

"To determine the response of dysplasia, carcinoma in situ (CIS), and T1 carcinoma of the oral cavity and larynx to photodynamic therapy with porfimer sodium….. Photodynamic therapy with porfimer sodium is an effective treatment alternative, with no permanent sequelae, for oral and laryngeal dysplasia and early carcinoma"

"Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis…..The LLLT group showed lower mean OTS and VAS scores during the course of RT. A significant difference was observed in pain evaluation in the 13th RT session (p=0.036). In both groups, no interruption of RT was needed. The prophylactic use of both treatments proposed in this study seems to reduce the incidence of severe OM lesions. However, the LLLT was more effective in delaying the appearance of severe OM."

"The present study examines the feasibility of a low power argon laser-induced thermal therapy to Ehrlich carcinoma, employing a direct administration of spherical gold nanoparticles (GNPs)…..All laser-GNPs treated tumors exhibited a significant suppression in tumor growth throughout 15 days…..it can be concluded from this study that the intense surface plasmon resonance exhibited by spherical GNPs in the visible range could be very useful as a noninvasive technique for photothermal

therapy of skin or near-surface type tumors that need much less laser energy and lower concentrations of GNPs"

"Oral verrucous hyperplasia (OVH) and oral erythroleukoplakia (OEL) are two oral precancerous lesions with relatively high malignant transformation potential. One of the best cancer prevention strategies is to use a conservative and effective treatment modality to eliminate oral precancers to stop their further malignant transformation.…..This study indicates that the laser light-mediated topical ALA-PDT is also very effective for OVH and OEL lesions. Therefore, we suggest that topical ALA-PDT using either the LED or laser light may serve as the first-line treatment of choice for OVH and OEL lesions"

"Treatment of post-mastectomy lymphedema with laser therapy: double blind placebo control randomized study.…..Laser treatment was found to be effective in reducing the limb volume, increase shoulder mobility, and hand grip strength in approximately 93% of patients with postmastectomy lymphedema"

"Topical 5-aminolevulinic acid-mediated photodynamic therapy (topical ALA-PDT) using a 635-nm light-emitting diode (LED) light is an effective treatment modality for oral verrucous hyperplasia. This study tested whether topical ALA-PDT using either the LED or laser light was also an effective treatment modality for oral erythroleukoplakia (OEL) lesions.…. Topical ALA-PDT using either the LED or laser light is an effective treatment modality for OEL lesions. There is no

significant difference in clinical outcomes of OEL lesions treated with PDT using either the LED or laser light"

"Preclinical studies have shown that photodynamic therapy (PDT) enhances immune responses. To examine the role of the direct effects of PDT in liver cancer with regard to enhancement of the antitumor response, we injected PDT-generated H22 liver cancer cell lysate (as a tumor vaccine) intradermally into Kunming mice.....Our findings suggest that PDT-generated vaccines can significantly enhance the antitumor immune response and may have the potential to be used as an adjuvant therapy clinically"

Windows of PBM Effectiveness

For most papers in the Pubmed retrieval, application of PBM in the research laboratory and in the clinic gave positive results. However, there were cases where positive results were not shown, and where negative results (after-effects) resulted. Absence of positive results in some cases occurs for almost all therapies, and there are usually windows-of-effectiveness for myriad therapies. Given the large number of variables/parameters in the PBM experiments/applications, and the diversity of the recipients of the PBM, large numbers of experiments would be required to define these windows more precisely than at present.

Following are a few illustrative examples of each of these two cases:

1. Positive results not shown

"To explore the effect of photobiomodulation on quadriceps strength and endurance torques in asymptomatic adults….. Photobiomodulation does not improve quadriceps strength and endurance outcomes in asymptomatic adults."

"The objective of this study is to evaluate the efficacy of low-level laser therapy in adults with RA….. infrared laser may not be superior to sham in RA patients. There is insufficient information to support or refute the effectiveness of red laser, laser acupuncture and reflexology for treating patients with RA."

"The objective of this randomized clinical trial was to evaluate Low-Level Laser Therapy (LLLT) effectiveness in spontaneous and chewing pain reduction following initial orthodontic archwire placement….. LLLT, with the suggested parameters, is not effective in pain reduction following initial orthodontic archwire placement"

2. Negative results shown

"Our results show that LLLT increases cell proliferation in a dose-dependent manner in HNSCC cells but not in normal epithelial tonsil cells. These results suggest that LLLT has to be used with caution when treating oropharyngeal mucositis in HNSCC patients since tumor cells present in the LLLT irradiation field could be triggered by LLLT."

"The effects of low-level laser therapy (LLLT) on tumor growth are inconsistent. In this study, we investigated the

effects of LLLT on melanoma tumor growth and angiogenesis.…..Our findings indicate that LLLT induces melanoma tumor growth by promoting angiogenesis. Therefore, it should be avoided in patients with melanoma"

"LLLT is a nonthermal phototherapy used in several medical applications, including wound healing, reduction of pain, and amelioration of oral mucositis. We discovered by accident that LLLT increased tumor size while testing a photodynamic therapy (PDT) model for the treatment of thyroid cancer. Although therapeutic effects of LLLT on cancer or dysplastic cells have been studied, LLLT has been recently reported to stimulate the aggressiveness of the tumor.…..In conclusion, LLLT led to a decrease in TGF-β1 and increase of p-Akt/HIF-1α which resulted to overproliferation and angiogenesis of anaplastic thyroid carcinoma (ATC). Therefore, we suggest that LLLT can influence cancer aggressiveness associated with TGF-β1 and Akt/HIF-1α cascades in some poorly differentiated head and neck cancers."

Diseases, Symptoms, Anatomy Parts Treated by PBM based on N-Gram Phrases

Appendix 4, Table 4A-1, contains a list of diseases, symptoms, mechanisms/phenomena, and parts of the anatomy treated by PBM in the laboratory or clinic. The incidence frequencies (number of times the phrase appears in the total literature) of each phrase on the list are shown as well.

The highest frequency anatomy parts treated include skin, bone, tissue, oral, muscle, blood, nerve, collagen, tooth,

face, brain, vessels, knee, neck, joints, hand, etc. Because of the difficulty of electromagnetic radiation in the red/near-infrared range penetrating the skin and underlying structures to any large extent, much of the effort has been concentrated at/near the surface. As the reference shows, achieving deeper penetration into the body to access the shielded organs and deep bone and tissue structures requires careful selection of electromagnetic radiation source, frequency of radiation, pulsing of radiation delivery, and other parameters. Obviously, in some cases, these requirements can be circumvented by inserting electromagnetic radiation conducting cables to reach the desired internal targets, but that eliminates the non-invasive benefits of the therapy.

Also, as the reference shows, for some applications well beyond the skin, LLLT may deliver insufficient doses of power, and higher-power light therapy may be required. This could (in theory) create a situation where higher power fluxes (with damage potential) would be present at the initial body penetration on the path to delivering beneficial radiation to the deeper targets. Interestingly, this would conceptually overlap the cell tower problem, where 1) harmful levels of non-visible non-ionizing radiation occur near the transmitter as a consequence of 2) providing the much smaller levels required for connectivity to users relatively far away from the transmitter. In the cell tower case, the radiation intensity is decreased with distance because it spreads out, whereas in the PBM case, the radiation intensity is decreased with distance because of absorption, scattering, etc.

The highest frequency diseases and symptoms treated include pain, wounds, injuries, lesions, cancer, diabetes, mucositis, acne, periodontal, scars, tumors, melasma, ulcers, osteoarthritis, fatigue, alopecia, hyperpigmentation, vitiligo, stroke, tinnitus, back pain, carcinoma, breast cancer, hair loss, psoriasis, lymphedema, osteonecrosis, neuropathy, anxiety, memory, lichen planus, melanoma, alzheimer's disease, dermatitis, temporomandibular disorders, etc. Most of these diseases/symptoms occur near the skin surface. Also, for the specific case of the cancers/cancer treatments, many of the records address the use of PBM for treating the therapy side-effects, as discussed previously, although some records do address use of PBM for treating the cancers directly.

The highest frequency mechanisms/phenomena/biomarkers associated with PBM treatment include inflammation, ischemia, stimulation, regeneration, fibroblasts, mitochondrial, cytokines, osteogenic, ATP, necrosis, VEGF, rejuvenation, metabolism, degeneration, impairment, phosphorylation, atrophy, cell death, adhesion, microcirculation, reperfusion, hyperalgesia, etc.

The above reference, which focuses on Traumatic Brain Injury (TBI), contains the following interesting statement: "Lastly, some authors have suggested that NO created at the site of irradiation and carried throughout the body in the blood is responsible for the beneficial effects of NIR phototherapy. This effect could account for the clinical benefits seen in TBI if NIR does not penetrate to the depths of 3 cm or greater in living tissue". The reference cited is from a Russian group. Further research shows

that this group, and related Russian groups, have published other studies on alterations to the blood from NIR phototherapy. These complementary papers include enhancement of fibroblast growth promoting activity of human blood, enhancement of growth promoting activity of human blood on keratinocytes, changes in blood cytokine content, modulation of blood lymphocytes proliferation, changes in the expression of membrane markers and blood monocytes, and many others. If this concept that blood modulation can have impact on organ/tissue/bone damage is valid to any extent, then many alternate approaches to healing (involving blood modulation by different phenomena, including, but not limited to, NIR) become available.

SUMMARY AND CONCLUSIONS

The purpose of the present Op-ed was to identify a wide range of existing and potential applications of PBM, based on open-literature publications in Pubmed. The study presented a taxonomy of the Pubmed-retrieved literature, an overview of the diseases/symptoms/conditions and parts of the anatomy that have been treated by PBM in the laboratory and clinic, and an analysis of PBM application to four of the major side-effects from Covid-19 vaccines (cardiovascular, neurological, autoimmune, cancer).

The taxonomy analysis showed that the main categories in terms of numbers of thrusts (subcategories) are Skin, Dental, and Neurological. Skin and Dental reflect surface/near-surface problems, which could be impacted directly by light sources. Neurological, and to a lesser

extent Musculoskeletal, would be more amenable to the near-infrared, and good results could be expected for near-surface applications.

The amount of radiation reaching the target (especially deeper into the body) in individual patients would be quite variable, given all the differences possible in radiation sources and individual structures. For most therapies, there are windows-of-effectiveness in which positive results can occur, and outside of which positive results may not exist for specific patients. This appears to be true for PBM as well. Given the large number of variables/parameters in the PBM experiments/applications, and the diversity of the recipients of the PBM, large numbers of experiments would be required to define these windows more precisely than at present.

The possibility that the healing effects from PBM on the deeper organs and tissues (in some cases) may not require the direct impact of the radiation on the affected tissues and organs was also discussed. Some references hypothesized that the healing demonstrated was a consequence of the positive impact of PBM on the blood and subsequent positive impact of the blood on the affected tissues and organs. If valid, that could expand healing by myriad promoters of blood modulation substantially.

Overall, pain reduction appears to be one major benefit and subject of study, and other benefits include inflammation reduction, circulation improvement, cellular modifications, anti-microbial effects, and many others.

Side-effects from more intensive therapies (e.g., chemotherapy, radiotherapy, etc.) have also been ameliorated.

The highest incidence frequency (number of times a phrase occurs in the total database) anatomy parts treated include skin, bone, tissue, oral, muscle, blood, nerve, collagen, tooth, face, brain, vessels, knee, neck, joints, hand, etc. Because of the difficulty of electromagnetic radiation in the red/near-infrared range penetrating the skin and underlying structures to any large extent, much of the effort has been concentrated at/near the surface. As this reference shows, achieving deeper penetration into the body to access the shielded organs and deep bone and tissue structures requires careful selection of electromagnetic radiation source, frequency of radiation, pulsing of radiation delivery, and other parameters. Obviously, in some cases, these requirements can be circumvented by inserting electromagnetic radiation conducting cables to reach the desired internal targets, but that eliminates the non-invasive benefits of the PBM therapy.

Also, as the reference shows, for some applications well beyond the skin, LLLT may deliver insufficient doses of power, and higher-power light therapy may be required. This could (in theory) create a situation where higher power fluxes (with damage potential) would be present at the initial body penetration on the path to delivering beneficial radiation to the deeper targets. Interestingly, this would conceptually overlap the cell tower problem, where 1) harmful levels of non-visible non-ionizing radiation occur near the transmitter in order to 2) provide

the much smaller levels required for connectivity to users relatively far away from the transmitter. In the cell tower case, the radiation is decreased with distance because it spreads out, whereas in the PBM case, the radiation is decreased with distance because of absorption, scattering, etc. Obviously, because of scattering, there will also be some spreading.

The highest frequency diseases and symptoms treated include pain, wounds, injuries, lesions, cancer, diabetes, mucositis, acne, periodontal, scars, tumors, melasma, ulcers, osteoarthritis, fatigue, alopecia, hyperpigmentation, vitiligo, stroke, tinnitus, back pain, carcinoma, breast cancer, hair loss, psoriasis, lymphedema, osteonecrosis, neuropathy, anxiety, memory, lichen planus, melanoma, alzheimer's disease, dermatitis, temporomandibular disorders, etc. Most of these diseases/symptoms occur near the skin surface, for the reasons discussed previously. Also, for the specific case of the cancers/cancer treatments, many of the records address use of PBM for treating the therapy side-effects, although some records do address use of PBM for treating the cancers directly.

The highest frequency mechanisms/phenomena/biomarkers associated with PBM treatment include inflammation, ischemia, stimulation, regeneration, fibroblasts, mitochondrial, cytokines, osteogenic, ATP, necrosis, VEGF, rejuvenation, metabolism, degeneration, impairment, phosphorylation, atrophy, cell death, adhesion, microcirculation, reperfusion, hyperalgesia, etc.

An interesting reference, which focuses on Traumatic Brain Injury (TBI), contains the following statement: "Lastly, some authors have suggested that NO created at the site of irradiation and carried throughout the body in the blood is responsible for the beneficial effects of NIR phototherapy. This effect could account for the clinical benefits seen in TBI if NIR does not penetrate to the depths of 3 cm or greater in living tissue". The reference cited is from a Russian group. Further research shows that this group, and related Russian groups, have published other studies on alterations to the blood from NIR phototherapy. If this concept that blood modulation can have impact on organ/tissue/bone damage is valid to any extent, then many alternate approaches to healing (involving blood modulation by different phenomena, including, but not limited to, NIR) become available.

Finally, as our studies on preventing and reversing chronic diseases have shown, true healing is not possible until (at least) the major causes of the disease have been eliminated. I would expect this to be true for PBM as well. It may ameliorate unpleasant symptoms of these chronic diseases in the short-term, but true reversal should not be expected until the causes of/contributing factors to these chronic diseases are eliminated.

Consider the example of Terri Wahls, an MD, who was able to reverse her own case of Multiple Sclerosis (MS). She used two main types of treatments: lifestyle changes (mainly dietary) to reverse the MS and neuromuscular electrical stimulation (NMES) to reverse the damage resulting from MS. It was only when her diet achieved

substantial improvement that the NMES produced positive effects.

Comments (0)

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