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EXCELLENCE

Harnessing the Energy of Light For Therapeutic Modalities with Third Generation Photosensitizers

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Financial Disclosures

Hired Medical Research Consultant for several International Med-Tech Companies in Medical, Dental and Pharmaceuticals.

OBJECTIVES

- 1. A review of the current status in Cancer, Antibiotic Resistance Bacteria's and the Multifactorial Pathogenesis of the new Stealth Viruses. A look at plausible cost effective solution with the enhanced effects of Photodynamic Therapy (PDT) PhotoBiomodulation (PBM) and its influence on natural and synthetic Nano Photosensitizers (NPS) and their role as a supportive therapeutic.
- 2. Introduction to PDT / PBM and NPS, their therapeutic value in health maintenance / prevention and improving intracellular metabolism as well as treatment of acute and chronic diseases.
- 3. Incorporating PDT / PBM and NPS to potentiate existing protocols for health care practitioners.

Antibiotic Resistance

- O'Neill report published 2015, forecasts that by 2050 the acceleration of antibiotic resistance could cause 300 million additional deaths and cost an extra US$100 trillion.
- Antibiotic era as we all know is on the verge of ending. A novel classes of antibiotics rather slow and unlikely.
- The need for discovery of alternative antimicrobial technologies to which bacteria will not be able to develop resistance, and which will work equally well regardless of present resistance status.

O'Neill J: Tackling a global health crisis:initial steps. The □ □ Review on Antimicrobial Resistance Chaired by Jim O'Neill. 2015. Fowler T, Walker D, Davies SC: The risk/benefit of predicting a post-antibiotic era: is the alarm working? Ann NY Acad Sci 2014, 1323:1-10.
Cole ST: Who will develop new antibacterial agents? Philos Trans R Soc Lond B Biol Sci 2014, 369:20130430.

Cancer, Antibiotic Resistance Bacteria's and the Multifactorial Pathogenesis of the new Stealth Virus

War on Cancer

- Cancer costs US more than $156 billion annually, with drugs a leading expense.
- *Date:*October 6, 2021
- *Source:* Penn State University
- *Summary:* Care for the 15 most prevalent types of cancer in the U.S. cost approximately $156.2 billion in 2018, according to a team researchers. The team also found that medication was the biggest expense and that medication expense for breast, lung, lymphoma and colorectal cancers incurred the most costs.

Antibiotic Resistance

- In a review of Lancet Infectious Diseases, alternatives for antibiotics were reviewed and discussed from a medical and economical point of view (Czaplewski et al. 2016).
- Alternatives mentioned included antibodies, probiotics, phage lysins, different classes of bacteriophages, immune stimulation (e.g. phenyl butyrate and vitamin D), vaccines, antimicrobial, anti-biofilm, and innate host defense peptides, etc. to name a few.
- In conclusion without sufficient funding, most of these new therapeutic modalities which could replace or supplement antibiotics will not become available to practitioners, as funding is the limiting factor that is stalling a global response to antibiotic resistance.

Czaplewski L, Bax R, Clokie M, Dawson M, Fairhead H, Fischetti VA, Foster S, Gilmore BF, Hancock REW, Harper D, et al. 2016. Alternatives to antibiotics-a pipeline portfolio review. Lancet Infect Dis. 16:239–251.

Viruses and Their Complex Multifactorial Pathogenies

PDT/PBM and MB
And its effects on SARS-CoV-2

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Methylene Blue Inhibits the SARS-CoV-2 Spike–ACE2 Protein-Protein Interaction–a Mechanism that can Contribute to its Antiviral Activity Against COVID-19:

1Diabetes Research Institute, University of Miami, Miami, FL, United States, 2Department of Molecular and Cellular Pharmacology, Miller School of Medicine, University of Miami, Miami, FL, United States. Frontiers in Pharmacology; published: 13 January 2021 doi: 10.3389/fphar.2020.600372

Ali RezaieID1*, Gabriela G. S. Leite1, Gil Y. Melmed2, Ruchi Mathur1, Maria Jesus Villanueva-Millan1, Gonzalo Parodi1, Jon Sin3, Juliana F. Germano3,Ultraviolet A light effectively reduces bacteria and viruses including coronavirus **1** Medically Associated Science and Technology (MAST) Program, Cedars-Sinai Medical Center, Los Angeles, California, United States of America, **2** Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai, Los Angeles, California, United States of America, **3** Cedars-Sinai Heart Institute, Cedars- Sinai, Los Angeles, California, United States of America,
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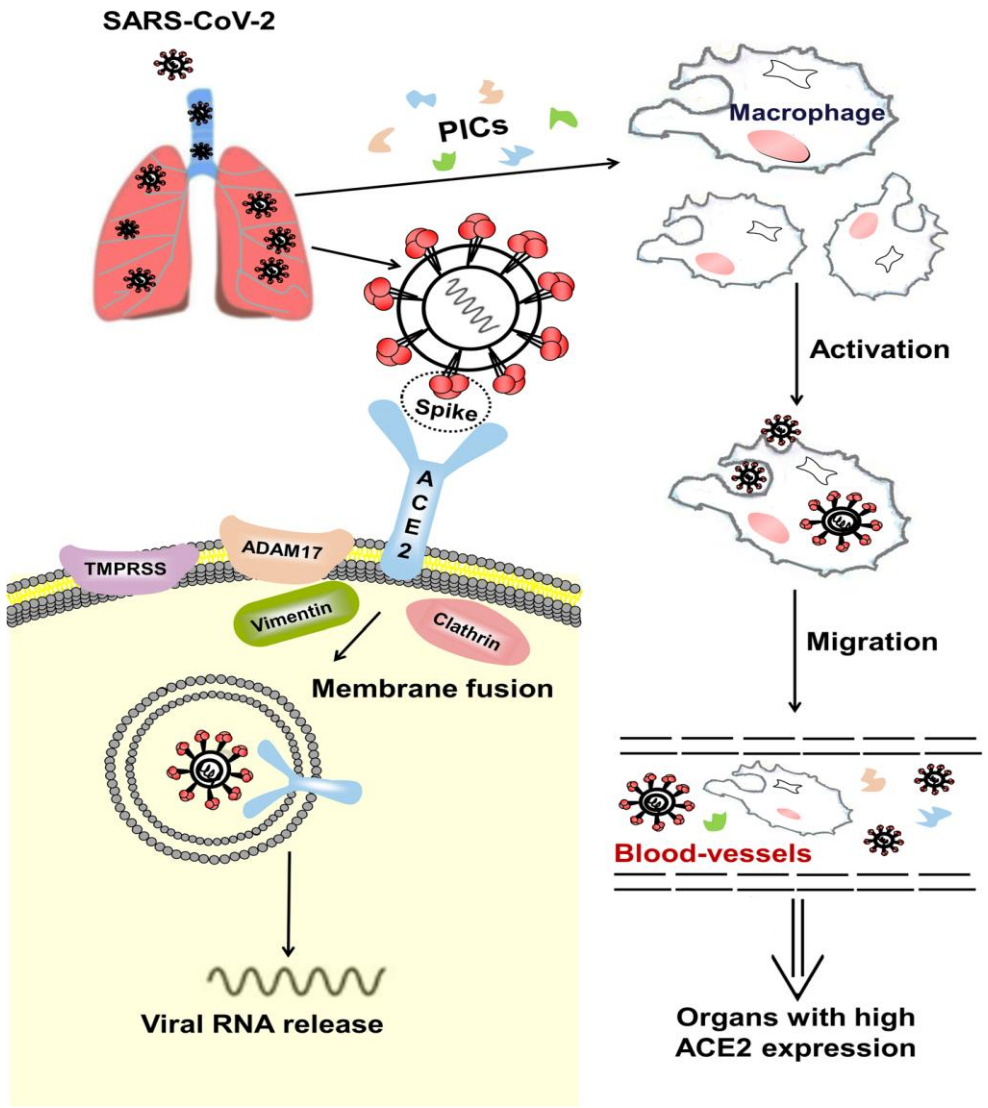


SARS-CoV-2/COVID-19
Patient treated in
Mexico City.

Introduction

Photodynamic (PDT)

Photo Biomodulation (PBM)

Third Generation Nano Photosensitizers (NPS)

History of Light Therapy

- Dr. Niels Ryberg Finsen, a Danish physician/researcher, found that ultraviolet light could effectively treat skin disorders. He was awarded the 1903 Nobel Prize for Physiology in Medicine for his use of UV light against lupus vulgaris, tuberculosis of the skin.

History of Light Therapy

- 1913 - A courage's physician by the name Myer Betz did an experiment which was one of the initial discoveries in modern photo-biology treatment. He injected himself with 200 mg of a material called hematoporphyrin and then observed his reactions to the exposure to sunlight. This was one of the first modern demonstrations that porphyrins have “photo-dynamic effect” in humans.
- 1961 – Lipson and Baldes of the Mayo Clinic demonstrated that tumors are very sensitive to porphyrins and will absorb them more selectively than normal cells. They used hematoporphyrin derivative (HpD), by adding sulfuric and acetic acids to hematoporphyrin.
- 1972 – Dr. Ivan Diamond demonstrated in California that irradiation of tumor tissue with Ultraviolate light does kill the tissue.
- 1976 – By this time there was enough knowledge accumulated to start treatments in humans. Research groups from around the world started doing work on tumor photo-therapy, Australia, Canada, China, Britain, Italy, Japan, Norway, and U.S.

History of Light Therapy

- Emmett K. Knott one of the pioneers of Photodynamic Therapy irradiated the blood of his first humane subject in 1928.
- Early published literature on Photodynamic Therapy by Hankock and Knott revealed positive results in advanced hemolytic streptococcal septicemia of patients.
- Researcher Emmett K. Knott from Seattle Washington during 1948 was credited for developing the first ultraviolet blood irradiation machine for patient therapeutic use.

Emmett K Knott

The Knott Hemo-Irradiator

History of Light Therapy

- Photo Therapy has shown to be effective and safe as a viable therapy for Viral, Bacterial and Fungal infections as well as for malignancies. Ultraviolet blood irradiation therapy was successfully used to cure 15 of 15 cases of viral pneumonia in hospitalized patients in the 1940s by doctors Miley and Christensen.

History of Light Therapy

- Dr. William Campbell Douglas II was one of the principal physicians responsible for the rebirth of UVBI after so many years of being in obscurity. He spent a year at the Pasteur Institute, St. Petersburg, Russia in 1991, researching UVBI and bringing back the latest re-search which most, if not all physicians in the Americas had abandoned. We were so very fortunate to have collaborated on many occasions with Dr. Douglas.

How it works

- Historically Photodynamic Therapy was started with the use of ultraviolet light UVA/ UVC alone in producing Reactive Oxygen Spices (ROS) with direct treatment of the Blood, Ultraviolet Blood Irradiation (UVBI).
- Photo-dynamic effects occur in sensitizing substances, most of which are fluorescent, but the fluorescence is not the cause of the reaction. The photodynamic effects occur in the presence of Oxygen.
- There are many Photosensitizers as in methylene blue, curcumin, rose bengal, rhodamine, acridine dyes, some amino-acids, quinine, Adriamycin,tetracycline,chloropropyl, hypericin,porphyrins, and 8-MOP.

How it works

- We must emphasize that ultraviolet irradiation of the blood works very well in the treatment of many infections without the use of photosensitive drugs. The photosensitive agents greatly enhance the effectiveness of the therapy.

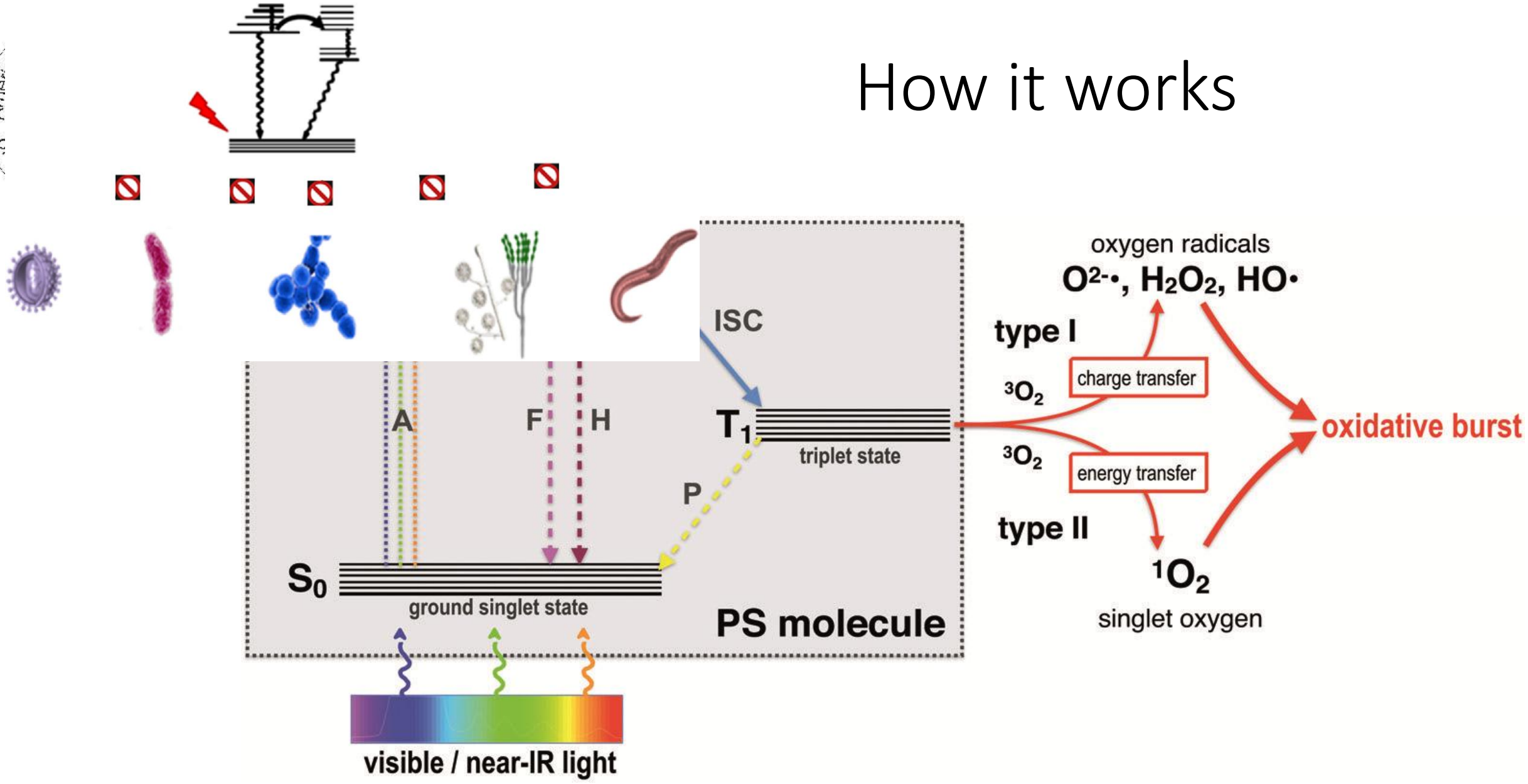
How it works

- Photodynamic therapy (PDT) uses photosensitizers (non-toxic dyes) that are activated by absorption of visible light to form reactive oxygen species (including singlet oxygen) that can oxidize biomolecules and destroy cells. Antimicrobial photodynamic inactivation (aPDI) can treat localized infections. aPDI neither causes any resistance to develop in microbes, nor is affected by existing drug resistance status.

How it works

- One of the key aspects of photodynamic therapy is the light source that is used to irradiate the lesion to be treated. The devices used must ensure that their emission spectrum matches the absorption spectrum of the photosensitizer, so that treatment radiation is delivered only on the injured area, without irradiating healthy tissue at superficial or deep levels. Irradiance values must be adequate in order to avoid thermal damage, exceed the oxygen replenishment rate and avoid long treatment times.

How it works



Jablonski diagram showing photochemical pathways in aPDI. The ground state 1PS absorbs a photon to form excited singlet state 1PS* that can undergo intersystem crossing (IC) to form the triplet state 3PS*. This long-lived species can undergo energy transfer (Type II) to form singlet oxygen ‘O2* or elkectron transfer (Type I) to form hydroxyl radicals HO. Both these ROS are capable of killing a broad spectrum of pathogens

Photobiomodulation (PBM Therapy)

History of PBM

Dr. Endre Mester form the Semmelweis University Budapest, Hungary is considered the father of PBM due to his research in 1967 which revealed that low powered ruby laser did not cause cancer but stimulated hair growth on the mice which he had shaved to better expose them to the laser trying to cause cancer.

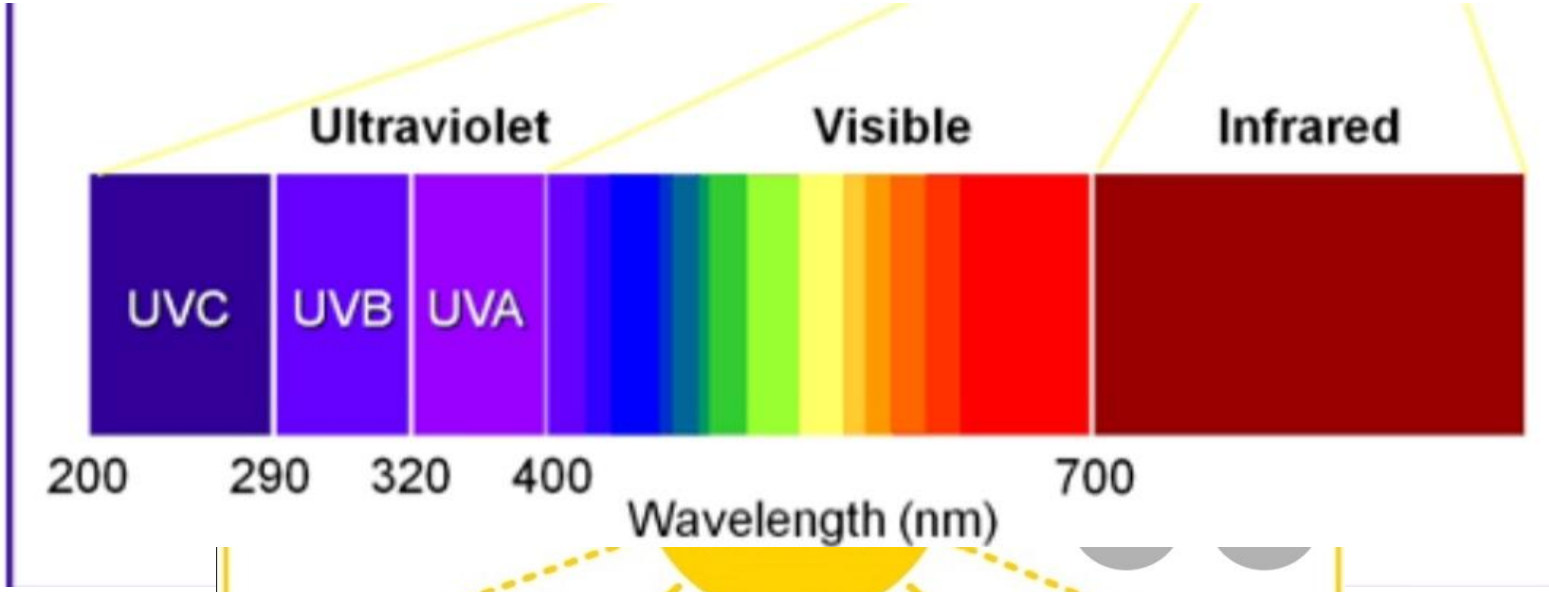
Photobiomodulation

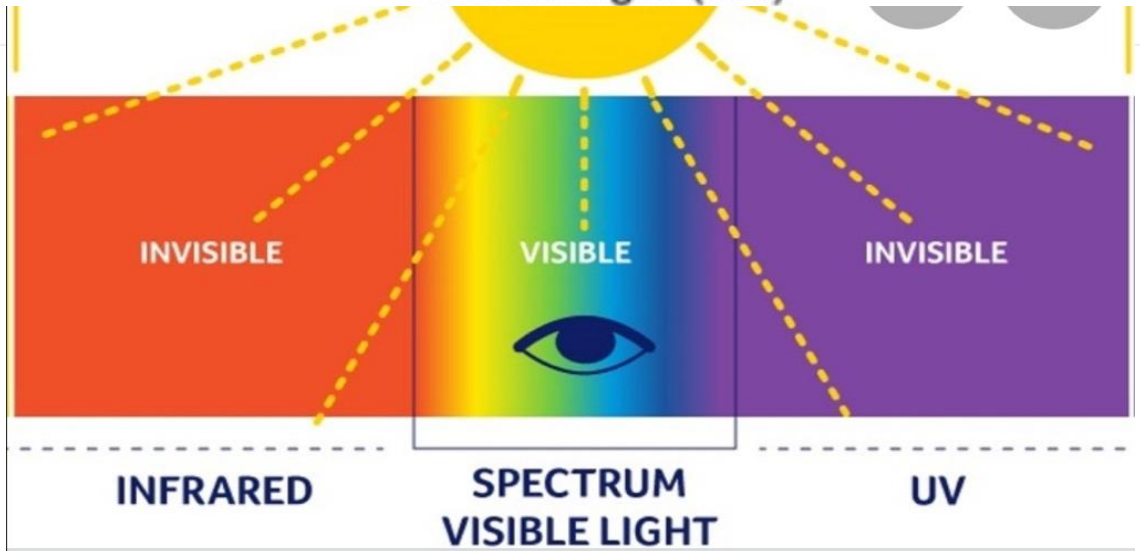
Photobiomodulation (PBM Therapy)

Previously known as Low Level Laser Therapy (LLLT).

It is a laser or LED light therapy that improves tissue repair (skin wounds, muscle, tendon, bone, nerves), reduces inflammation and reduces pain wherever the beam is applied. Usually applied by a doctor, therapist or technician, treatments typically take 1 - 10 minutes two or more times a week.

Light Range Spectrum for Therapeutic Effect.





How it works

How much is enough, how much is too much?

There is a dose response: not enough power density and there is no effect, too much and there can be inhibitory effects which can slow down healing and lose the anti-inflammatory effects.

The analgesic mechanism

This depends on an PBM overdose; Higher power density PBM >300mW/cm² reduces ATP production in C fibers and A delta fibers resulting in an immediate neural blockade lasting up to approx 24 hr.

Three kinds of PBM

High power density is necessary for analgesia and deep tissue targets, low power density (< 100mW/cm²) is necessary to promote healing and reduce inflammation in superficial wounds, tendons and joints (the target is the synovia not the joint). Both high and low power density for best healing, deep penetration, analgesia effects as well as third generation photosensitizer.

PDT/PBM Combination Therapy

- PDT/PBM requires the combined action of three elements.
- The mechanism depends on concentrations of molecular oxygen, photosensitizer and light properties used.
- A light source, a special dye or combination photosensitizer (PS) of type 1 and type 2 which work down two different path ways to achieve the desired effects of ROS.

How it works

- The two different photochemical pathways, called Type 1 and Type 2 are Type 1 which involves an electron transfer to produce superoxide radical and then hydroxyl radicals (HO), while Type 2 involves energy transfer to produce excited state singlet oxygen (‘O2). Both HO and ‘O2 are highly reactive oxygen species (ROS) that can damage nearly all types of biomolecules (proteins, lipids and nucleic acids) and kill cells.

How it works

- Depending on the specific targets cell damage from PDT can occur directly by apoptosis, autophagy and necrosis pathways, or indirectly by vascular destruction and immune response.
- Currently the primary aim is to destroy or damage the malignant cells with the PDT induced immunologic response against metastasis and recurrence.

How It Works

- In Photodynamic Therapy there are three principle Fundamentals.

1) The primary Chromophores have been identified as Cytochrome-C-Oxidase (CCO) and the Calcium ion channels mediated by light absorption by opsins.

2) Secondary effects of photon absorption include increase in ATP, a brief burst of Reactive Oxygen Species, an increase of Nitric Oxide and modulation of calcium levels.

3)Tertiary effects include activation of a wide range of Transcription Factors leading to improved cell survival, increased proliferation and migration, and new protein synthesis.

How It Works

When cells are stressed and mitochondria is inefficiently producing ATP, nitric oxide (NO) inhibits oxygen consumption by mitochondrial Cytochrome - C - Oxidase (CCO), levels of carboxy hemoglobin increase indicating high levels of carbon monoxide, which reduces production of ATP and causes oxidative stress leading to increased inflammation.

Photodynamic Therapy displaces NO as well as Carbon Monoxide from cytochrome c oxidase thereby reducing inflammation and restoring ATP production, which increases the efficiency of Mitochondria.

How It Works

Cytochrome - C- Oxidase in the mitochondria is a unit IV in the the mitochondrial electron transport chain. It transfers one electron from each of the four cytochrome-C molecules to a single oxygen molecule producing two molecules of water. Photon absorption by the CCO leads to increased of the enzyme activity, increases oxygen consumption and increases ATP production based on the photodissociation of inhibitory Nitric Oxide (NO). Since NO is a non-covalently bound to the heme and CU centers and competitively blocks oxygen at a ratio of 1:10, a relatively low energy photon can kick out the NO and allow a lot of respiration to take place.

How It Works

- The other primary Chromophore is the Opsins which are Light gated ion channels. More recently it has become apparent that another class of photoreceptors must be involved in transducing cellular signals, particularly responding to Blue and Green Light which range in the 400 to 500 nm of light.
- The receptors are members of the family of light- Sensitive G protein coupled receptors known as opsins (OPN).
- OPN's function by photoisomerization of a Cis-retinal cofactor leading to a conformational change in the protein.

How It Works

- There are other members of the OPN family from OPN1 which is responsible for mediating vision in the rod and con photoreceptor cells in the mammalian retina as well as OPN2-5 which are expressed in many other tissues of the body including the brain.
- One of the best defined signaling events that occurs after light activation of OPN's is the opening of light – gated ion channels such as members of the Transient Receptor Potential (TRP) family of calcium channels.
- Activation of TRP causes non-selective permeabilization (mainly of the plasma membrane) to calcium, sodium and magnesium.

How It Works

Wound Healing:

904 nm on burns wounds increase healing decrease inflammation decrease expression of TNF-∞ and NF-KB the proinflammatory factor and upregulates expression of VEGF, FGFR-1, HSP-60, HSP-90,HIF-1∞ and matrix metalloproteinases -2 &9.

All wave lengths have a reduction effect on IL-8 expression.

In addition 405nm also have an effect on reduction of IL-6.

635nm reduce IL-6, IL-8, P38 phosphorylation, and increase JNK phosphorylation(C-Jun N-terminal Kinases).

Phototherapy in the range of 830nm up to 6.3J /cm2 reduce levels of COX 2 (cyclooxygenase-2), Prostaglandins E2 (PGE2) as well as reduction in IL1B.

Photoactivated Substances

Photoactivated substances to potentiate therapeutic effect.

Organic and Inorganic photoactivated materials, as in Liposomal Methylene Blue, Micellized Curcumin, Micellized Hematoxylin, Carbon nano particles as in C-60 and Quantum Dots.

Nano formulations of liposomal, polymeric nanoparticles, polymeric micelles, conjugates, cyclodextrins, solid dispersions.

These substances within capsulation have their light absorption and excitation wave lengths which serve as **diagnostic and therapeutic protocols**.

Photoactivated Substances

Bioavailability, Stability and Solubility are very important for therapeutic effect. Targeting membrane efficiency of different strains of fungus, bacteria and viruses are important as well.

Of particular interest is active targeting of various types of cancers by way of molecular markers, i.e. Solid tumors and Blood cancers.

Several of the substances utilized are mediated through its regulation of various Transcription Factors, Modulation of Mitochondrial Function, Growth Factors, Inflammatory Cytokines, Protein Kinases and other important Enzymes, one small example is Calcium ATPase.

PDT/PBM in Detoxing

Aiding in accessing deep tissue and muscle compartments via TRP for detoxification of pesticides, mercury and lead as in heavy metals and bisphenol as in petrochemical toxicity, fluoride, fire retardants, food additives and dyes as well as other pathogens found deep in our cellular structure for example Borrelia burgdorferi as in Lyme disease, viral and other pathogen are irradicated via photo-oxidation. (Manipulating cellular membrane light gated ion pathways).

Light Therapy in Cellular and Exosome Therapies

Light has shown to have a profound effect on Stem Cells, blood rich in Exosomes have recently been exposed to light as well and appear to be affected in a very positive manor by upregulating their potential.

Blue and green light 400-500nm (but not red or 810nm NIR), increases intracellular calcium in adipose mesenchymal stem cells, that could be blocked by ion channel inhibitors.

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