PhotoBioModulation Therapy

PhotoBioModulation (PBM), is a general term that refers to therapeutic approaches based-on the PhotoBioModulation (PBM) principle that causes biological alterations in organisms, secondary to interactions of photons in the visible or infrared spectral regions with molecules in the cells or tissues.

Therapeutic PBM, originally known as Low Level Laser Therapy (LLLT) has received many names over the years. Low-level laser therapy led to the adoption of the acronym "LLLT," which is an official Medical Subject Heading (MeSH) as defined by the U.S. National Library of Medicine. LLLT now retrieves 4,161 citations on PubMed (Jan 2016). In 2015, the term "photobiomodulation" also became an official MeSH term and now retrieves 215 citations. It has been agreed that "photobiomodulation" or "photobiomodulation therapy" should be adopted as the preferred term going forward. However, there exists a plethora of alternative terminology that have been used in one form or another: low-level laser therapy, low-level light therapy, low-intensity laser irradiation, low-reactive laser therapy, cold laser, nonthermal laser, soft laser, biostimulation laser, photobiomodulation laser, or even light-emitting diode (LED) therapy and organic LED therapy. The adjectives in these phrases emphasize a comparison with surgical lasers, which can cut, ablate, and coagulate biological tissues due to a photothermal effect. PBM does not generally increase the macroscopic tissue temperature because the power density used is much smaller than the threshold needed for photothermal effects.

The most common PBM procedures are performed by the irradiation of tissue with relatively low-powered lasers or LED arrays. The light is generally applied to sites of injury in order to hasten cellular processes, leading to better healing, decreased inflammation, and reduced pain. Almost all PBM treatments are conducted with red or near-infrared (NIR) light (600-1100 nm), with a total output power of 1-10,000 mW, using a power density that does not heat the tissue (<1 W/cm^2, depending on the wavelength and tissue type). These PBM procedures are generally noninvasive because light can penetrate through skin and overlying tissues to reach the underlying target tissue. The light is nonthermal; just like photosynthesis, it causes photochemical reactions, and it has a wide scope of different clinical applications.

The range of PBM applications has increased exponentially in recent years. The vast and ever-increasing body of literature in PBM provides many creative ways of using different light sources and some innovative ways to deliver light to target cells or tissues. In contrast with the past well-established terminology that was inextricably linked to the use of lasers (low-level laser therapy), LLLT or PBM is now performed with a wide variety of different light sources, such as LEDs, organic LEDs (OLEDs), and lamps that are filtered by bandpass filters or by monochromators. A question that is often asked is, "if light is so beneficial for all these different diseases, why can a person not just absorb sunlight?" For some superficial indications requiring PBM, sunlight is in fact beneficial, but because the peak emission is in the green wavelengths (500 nm), the light does not penetrate well. Moreover, sunlight contains a fair amount of harmful UVB radiation, so if one exposed oneself for a long enough time to get sufficient photons of the correct wavelength to the target tissue, the result would include a nasty sunburn.

Some biological processes can be modulated by photochemical reactions triggered by photons with a wavelength that is either shorter or longer than the optical window of 600-1100 nm, e.g., blue light (400-520 nm), green light (520-560 nm), or yellow light (560-600 nm); mid-infrared radiation (11003000 nm); and far-infrared radiation (>3000 nm). These intriguing observations are one of the driving forces behind the search for the chromophores (light-absorbing molecules) responsible for the biological effects of PBM. It has been suggested that because a relatively broad range of wavelengths have been shown to have beneficial biological effects (at the correct doses), it is therefore unlikely that there can only be a single chromophore (for instance, cytochrome c oxidase) responsible for absorbing the photons.

The optimal dosimetric parameters for PBM are usually 1-1000 mW/cm^2 for power density and 0.1-100 J/cm^2 for energy density. The time exposure is primarily measured in minutes rather than seconds or hours. However, good results can occasionally be found with parameters that fall outside these ranges. Interestingly, there are many ways to deliver light to a specific tissue: a focused laser spot on the skin; a large-area LED array, contact or not; a light source introduced inside a body cavity (mouth, ear, nose, vagina, etc.); or even intravenous or interstitial irradiation (where an optical fiber inside a needle (or a catheter) is inserted into the tissues). Taking all of these possibilities into account, PBM could have even more clinical applications than are obvious at first glance, given this is a developing field of knowledge

real effect could be evoked by that "little light," as they might say. It can be difficult to make them understand, or even accept, the photochemical and photobiological events that occur inside them during the therapy. Moreover, PBM still remains to some extent controversial, even among researchers and clinicians; sometimes this skepticism is related to lack of knowledge or previous distrust of unconventional (alternative and complementary) medicine. In these cases, personal experience of the effectiveness of PBM will remove the uncertainty. There are three fundamental points of controversy:

- even though the biochemical mechanisms behind PBM have been investigated, our understanding remains incomplete;
- a large number of parameters related to PBM, about which there is no consensus; and
- the effectiveness of PBM varies among individuals depending on genetic, epigenetic, and phenotypic differences that are poorly understood, and thus treatments may need to be personally tailored.

Today it is generally accepted that PBM is triggered by photon absorption by the complex enzyme called cytochrome c oxidase, located inside mitochondria; however, the chain of reactions that follows this initial photon-absorption event remains incompletely understood. To fully define a specific PBM procedure, it is necessary to specify many parameters, such as the wavelength, fluence, power density, pulse structure, and timing. The choice of such parameters must be adapted to each patient, because the skin color, age, gender, amount of hair, and state of the tissue can all influence the light absorption and scattering throughout the tissues. A mistake in the selection of parameters for each patient can lead to a less-effective (or even negative) outcome of the therapy.

The first PBM procedures were performed using lasers, and in the early days of this field researchers were not sure if the biomodulation processes triggered by PBM depend on the special properties of laser light, e.g. monochromaticity (narrow bandwidth), coherence, or polarization, or whether similar therapeutic benefits can be achieved by other light sources. Considerable evidence has accumulated over the last decades that suggest other light sources can produce PBM effects and that the major determining parameters for the effectiveness of PBM are the wavelength and the dose. The wavelength must be capable of being absorbed by a photoacceptor molecule in the cell or organism. Noncoherent light sources, such as LEDs, or 'halogen or other incandescent lamps connected to filters can be equally effective. Even more recent are organic LEDs (OLEDs),

which extend the possibilities of PBM because an OLED can emit light uniformly from a flexible surface.

The term "laser" originates from an acronym that stands for "light amplification by stimulated emission of radiation." The physical concept of stimulated emission was proposed by Einstein in 1916,[1] but it was only in 1960 that the first working laser was built by Maiman (see Chapter 2).[2] The key concept in the mechanism of laser action is "population inversion." The laser medium must be able to be excited into a state in which the majority of the atoms or molecules exist in higher excited states compared to those in lower unexcited energy states. Only then can the excited states be stimulated by spontaneously emitted photons to release even more photons and lasing can take place (see Fig. 1.1). Only a few materials can meet this criterion, including certain crystals, glasses, gases, semiconductors, and dye solutions. The laser has interesting properties, such as a high degree of spatial and temporal coherence, that make this light source unique. A laser acts as a point source that can be focused into a small spot, kept as a collimated narrow beam that can travel over long distances, or expanded by lenses to form a large spot, if necessary. Although light from gas and crystal lasers is naturally collimated, light from diode lasers is divergent and requires a lens to focus and to couple it into an optical fiber. In addition, the coherence property allows lasers to have a very narrow spectral-emission bandwidth (that can reach as narrow as approximately 10^{-3} nm) and can also allow the production of pulses of light that last only a few attoseConds (10^{-18} s). In fact, the shortest controlled laser pulse achieved by researchers was a pulse of 12 attoseconds.[3] The temporal coherence can be important to PBM because it allows the creation of lasers capable of matching the exact absorption peak of a predetermined photoreceptor or photoacceptor. The first lasers were based on crystals (ruby) or gases (helium-neon or argon) as the lasing medium. Since the early days, the vast majority of PBM lasers have been based on semiconductors such as gallium arsenide (GaAS) and gallium-aluminum-arsenide (GaA1As).

A LED consists of a semiconducting material doped with some impurities to create a gap of energy between the valence and conduction bands of the electrons (called a bandgap). When the LED is switched on, a voltage is applied to bring the electrons in the conduction band close to the holes from the valence band, making them recombine and release energy in the form of photons. This phenomenon is known as electroluminescence. The color of the emitted photon (wavelength of the LED) is determined by the energy bandgap,

and the intensity (brightness) of the LED depends exponentially on the applied voltage, assuming it is kept below a limit that would damage the device. Although the phenomenon of electroluminescence has been known since 1907, it was only in 1962 that the first practical LEDs were developed that emitted either infrared or red light. Today, LEDs can be made with a variety of inorganic semiconductor materials, and thus they can emit many different colors, from the ultraviolet (X < 400 nm) to infrared (X. > 750 nm), or else different semiconductors can be combined to emit white light. A common value for the spectral bandwidth (full width at half maximum, FWHM) is approximately 30 nm, and the area of each LED emitting surface is usually smaller than 1 mm^2. A recent advancement is the OLED, which uses small organic molecules as the electroluminescent material. Among other advantages, OLEDs can emit from a large (>1 cm^2) and flexible surface; they are also more efficient and have a narrower bandwidth than standard LEDs.

The electromagnetic spectrum of radiation ranges from gamma rays (X < 10^{-12} m) to radio waves (X between 10^{-1} and 10^8 m). The light visible to humans is a small portion of the spectrum (Fig. 1.2) between 400-750 nm that, along with ultraviolet (100-400 nm) and infrared (750 nm to 1 mm) light, composes the optical region of the entire spectrum. Electromagnetic waves are created by the perpendicular oscillation of electric and magnetic fields, which are described by Maxwell's equations. Light, interpreted as a waveform, can be characterized by amplitude, wavelength and polarization, which determine the intensity (or brightness), color, and orientation of these oscillations, respectively. With the advent of quantum theory, the physics of light was better understood and can be interpreted as a particle complementary to the wave interpretation, i.e., light can behave as either waves or particles, depending on the physical situation being studied. These particles of light (photons) are massless packets ("quanta") of energy moving at approximately 3 x 10^8 m/s. The wavelength of light is determined by the energy of the single photons, and the number of photons in a single direction determines the intensity in that direction.

Light interacts with biological tissue in two ways, absorption and scattering.[4] Light absorption occurs when a photon interacts with an atom, a bond, or a molecule, and the entire energy of the photon is transferred to the atom or molecule. Light-scattering interactions can change both the direction and energy of photons (inelastic), or only the direction (elastic scattering). Visible and near-IR light interactions with biological tissue mainly produce elastic scattering. The

scattering depends on the size, shape, and refractive index of the scattering center and on the wavelength of the incident light. Complete knowledge of the penetration and distribution of light inside biological tissues is difficult to acquire because absorption and scattering depend on wavelength, tissue biochemistry, and anatomy.[5]

The effectiveness of PBM is determined by the amount of light reaching the target tissue depth (penetration).. However, in many cases, precise and not possible. For this reason, the best description of the • PBM procedures requires extrapolation from the surface irradiation and dose parameters determined by the output of the device, to the light penetrating to various depths of the tissue (or other biological medium). Overall; PBM dosimetry can be described and divided into two parts: (1) the irradiation parameters, i.e., "the medicine," and (2) how light is delivered, i.e.; "the dose." The irradiation parameters, such as wavelength (nm), power (W), beam area (cm^2), and pulse structure, are related to the specific light source. On the other hand, the dose parameters, such as energy (J), energy density. (J/cm^2), treatment repetition, and irradiation time (s) and area (cm^2), are operator-controlled. In addition, light dosimetry to some extent depends. on the specific characteristics of each patient (e.g., skin color) and of the physiological tissue (e.g., the amount of subcutaneous fat). All of these interrelated considerations and patient-specific factors make PBM dosimetry rather complex, and it may be difficult to optimize in many research and clinical situations.

For PBM to be effective, the various irradiation parameters (wavelength, power, irradiance, and pulse parameters) need to lie within certain ranges and be applied for a suitable amount of time (usually minutes). These therapeutic sessions are typically applied several times (1-10 treatment sessions) at intervals ranging from twice a week to twice a day.

In many cases (both experimentally and clinically), it has been found in PBM that more light is not necessarily therapeutically better than less light. This somewhat unexpected relationship has been termed, response, practitioners must determine at what point the amount of light becomes too much.

PBM can inhibit as well as stimulate, and the techniques and settings for consistently achieving these effects have not always been clearly stated. Many options exist: laser or LED, red or infrared wavelengths, a high- or low-total-power laser (with a small spot size, the latter can produce a high power density), pulses or a continuous wave, treatment twice a day or twice a month.

A systematic review of tendinopathies by Tumilty[6] found that 11 out of 20 studies failed to produce a positive result. The reason identified for the ineffective studies was that either the laser power density was too high or the treatment time was too long. If clinicians want to reduce the risks of using ineffective protocols for their patients and increase their chances of getting the best results, they need to understand the fundamentals about dosimetry. This section reviews the calculation of treatment parameters and dose, followed by the published evidence to see what works.

A biphasic dose response has been frequently observed where low levels of light have an improved ability to stimulate and repair tissues than higher levels of light. Many reports refer to stimulation of biological processes at relatively low levels of energy density or power density; the positive effect diminishes as the dose is increased, and inhibitory effects predominate eventually, which worsens clinical conditions. The so-called Arndt—Schulz curve is frequently used to describe this biphasic dose response.[7]

If the wrong irradiation parameters are used or applied for the wrong irradiation time (dose), then treatment will be ineffective. If the irradiance is too low or the time is too short, then there is likely to be no significant effect; alternatively, if the irradiance is too high or the treatment time is too long, then the benefit is lost and inhibitory effects may occur.[7,8] Many authors of research papers fail to accurately measure or even report some of these parameters. This shortcoming is due in part to a poor appreciation of the relevance of these parameters by authors and reviewers and also because some of these measurements require expensive instruments that need trained operators.[9]

As mentioned earlier, light is composed of packets of energy called photons. These photons sometimes behave like a particle and sometimes like a wave. The color of light is usually expressed by its wavelength (rather than its frequency or photon energy). LEDs and lasers are useful for PBM therapy because they produce just one wavelength or a narrow spectrum of wavelengths (+1 mu for diode lasers and up to +20 nm for LEDs).

Most PBM research is conducted in the red and near-infrared spectrum (630-980 nm) because these wavelengths penetrate tissue relatively easily, although some penetrate better than others. Coincidentally, these wavelengths exert some action on cytochrome c oxidase, which is usually credited as the

other chromophores that absorb light in this range exist (e.g. water at the upper end of this spectrum) that may also contribute to the effects of PBM.

Kendric Smith's 1991 paper[10] on photobiology fundamentals describes an experiment by Karl Norris. Broad-spectrum light was projected through a hand and was measured with a spectrophotometer that showed that red and near-infrared light (630-1100 nm) penetrated particularly well. Many other papers[11-13] have been published comparing the penetration of specific wavelengths, and all are fairly consistent with the original Karl Norris experiment.

Penetration depth is a contentious subject because *many PBM product manufacturers like to claim that their system penetrates deeper than others by virtue of extra-high power or "super pulses." This metric does depend on light parameters, such as power, but the term "penetration depth" should be defined as the depth at which there is a sufficient power density to be above the threshold necessary for a therapeutic benefit. For example, the application of a 100-mW laser will deliver higher irradiance at a given depth than a 1-mW laser (assuming all other parameters are equal). The former might generate enough light (threshold) to produce a meaningful therapeutic effect at the required depth in the target tissue, whereas the latter will not, regardless of. the length of the illumination time. Therefore, technically speaking, a claim such as "this system penetrates deeper than others by virtue of extra-high power" may be true.

Other factors contribute, such as increased blood perfusion in .case of heating at higher average output powers, and at very high temperatures the optical properties of the tissue may change (ablation, .carbonization, etc.). This means that the temperature (heating of the tissue) will ultimately be a limiting factor when increasing the power (as a means of increasing pehetration depth in the tissue), as will the dose (very high power means very short treatment times to reach the same dose). However, there is some evidence that the treatment time must be longer than a certain minimum value to produce any benefit.

Fairly significant peak powers using short pulses (super pulses) can be applied without heating the tissue while at the same time keeping the average output powers similar to what lower-power continuous wave (cw) instruments would deliver. However, claims of 10-cm effective penetration with pulsed lasers are exaggerated. Different tissue types have slightly different scattering and absorption characteristics, but all of the studies produce broadly similar patterns of results.

One of the best studies on penetration was provided by Tedford et al.[13] in 2015. They performed a light-penetration study on human unfixed cadaver with the world's leading authority on light propagation in tissue, Prof. Steve Jacques. They compared 660-nm, 808-nm, and 940-nm laser penetration. 808 nm achieved the best penetration, and they concluded that 808-nm-wavelength light penetrates the scalp, skull, meninges, and brain to a depth of approximately 40 mm. Pulsed light and continuous wave were also compared, and no differences were observed in the effective penetration depth.

The following list defines key terms:

Wavelength (nm): Light consists of packets of electromagnetic energy that also have a wave-like property. Wavelength is expressed in nanometers (nm) and is visible from approximately 400-750 nm; beyond 750 nm, the light is invisible. From 750-1500 nm, light is defined as near-infrared. The structure of chromophores and their redox state determine which wavelengths will be absorbed. LLLT devices are typically within the range of 600-1000 nm because there are many absorption peaks for cytochrome c oxidase in that range, they penetrate tissues better than other wavelengths, and many clinical trials have been successful with them (though not in the 700-750-nm range). Wavelengths longer than 900 nm are also absorbed by water and not just by cytochrome c oxidase (CCO). It is speculated that these longer wavelengths are also absorbed in phospholipid bilayers and cause molecular vibration sufficient to perturb ion channels and alter cellular function. If deep penetration is required (>1 cm, up to 5 cm), then wavelengths in the 690-850-nm range penetrate best.[10,14]

Power (W): Energy (J) per second (s), peak and average when pulsed (see pulsed beam).

Beam area (cm^2): The beam area must be known to calculate irradiance, but it is difficult to measure and frequently misreported.[9] Diode laser beams are typically not round—more often they are elliptical (unless they are derived from fiber optics), and the beams are usually brighter in the middle and gradually weaker toward the edge (Gaussian distribution). This behavior has been poorly understood by many researchers, and errors are frequently made when reporting the beam area. For example, many assume that the aperture of a device defines the beam size, but it rarely does. The correct way to measure the beam area uses a beam profiler and reports the $1/e^2$ area. This task is more appropriate for a laser engineer or physicist rather than a doctor or therapist.

Irradiance (power density, W/cm^2): Irradiance is the power (W) divided by the beam area (cm^2). This parameter is frequently misreported because of the

difficulty of measuring the beam area. Assuming that the reported parameters can be trusted, studies of beam irradiance report successful tissue repair and anti-inflammatory effects from 5-50 mW/cm^2 at the target tissue depth.[15-17] Analgesia is a different matter; a systematic review of laboratory studies found that higher irradiances of 300-1730 mW/cm^2 are necessary to inhibit nerve conduction in C fibers and A-delta fibers.[18]

Pulsed beam: If the beam is pulsed, then the reported power should be the average power, calculated as follows: peak power (W) x pulse width (s) x pulse frequency (Hz) = average power (W). A review" concluded that there is some evidence that pulsed light has effects that are different from those of cw light. However, further work is needed to define these effects for different disease conditions and pulse structures. Many laser systems produce a continuous beam only, but some produce a fixed pulse width and fixed pulse frequency. More common is a variable pulse frequency with a fixed duty cycle, e.g., a 10-Hz pulse with a 50% duty cycle has a pulse width of 1/10 x 0.5 = 0.05 s (50 ms) on and a 50-ms off period. If the pulse frequency is increased, then the average power remains constant, so a 100-mW-peak-power laser will deliver a 50-mW average power. Other duty cycles are sometimes used, e.g., 90:10, with 90% on and 10% off, so a 100-mW-peak-power laser will deliver 90 mW on average. Another common format is a fixed pulse width and variable pulse frequency, as in "super-pulsed" lasers. In this format, reducing the pulse frequency reduces the average power. For example, if the pulse is 200 ns and the frequency is 1,000 Hz, then there are 1000 pulses 200 ns long. If the peak power were 10 W, then the average power would be 10 W x 200 ns x 1000 Hz = 2-mW average power. If the pulse frequency were increased to 10,000 Hz, the average power would increase to 20 mW, and so on. Super-pulsed lasers are usually 904- or 905-nm devices. Claims of better penetration from super-pulsed lasers have been discredited.

Coherence: Coherent light produces laser speckle, which has been postulated to play a role in the PBM interaction with cells and subcellular organelles. The dimensions of speckle patterns coincide with the dimensions of organelles such as mitochondria, and it is speculated that the intensity gradients produced by these speckles may help improve clinical effects particularly in deep tissues where irradiance is low. No definitive trials have been published to date to confirm or refute this claim.[19,20]

Polarization: Polarized light may have different effects than otherwise identical nonpolarized light (or even 90-deg-rotated polarized light). Polarized light is rapidly scrambled in tissue (probably in the first few hundred micrometers). However, for birefringent protein structures such as collagen, the transmission of plane polarized light will depend on the orientation. Several

authors have demonstrated the effects of polarized light on wound healing and burns.[21-23]

Energy: Calculated as power (W) x time (s) = energy (J). The use of joules as an expression of dosage is potentially unreliable because it assumes an inverse relationship between power and time, and it ignores irradiance. If a 100-mW laser is applied over two points on an Achilles tendon injury for 80 s, then 8 J has been delivered per point. What this does not indicate is the irradiance of the beam, which could cause the treatment to fail if it is too high. Systematic reviews have established that superficial tendon injuries should. have a beam irradiance <100 mW/cm^2.[6,25] Unfortunately,• many authors have failed to report irradiance, so the treatment effect is difficult to replicate. A second problem is that • of reciprocity. If the power is doubled and the time is halved, the correct energy may be applied with different results.[16,24] To ensure the replication of a successful treatment, the same power, beam area, and time should be used. The use of more powerful lasers as a way of reducing the treatment time is not a reliable strategy.

Calculated as power (W) x time (s) / beam area = fluence (J/cm^2). The use of fluence as an expression of dosage is also potentially unreliable because it assumes an inverse relationship between power, time, and irradiance. Again, there is no reciprocity. If the power is doubled and the time is halved, the correct energy may be applied with different results.[16,24] If the beam area is halved, the irradiance may remain correct but the total energy applied will be halved and may not cover the whole pathology. To ensure the replication of a successful treatment, the same power, beam area, and time should be used. The use of more powerful lasers as a way of reducing the treatment time is not a reliable strategy.

Irradiation time (s, min): Given the lack of reciprocity described earlier, the safest way to record and prescribe LLLT defines the irradiation parameters and then defines the irradiation time so as not to rely on energy or fluence parameters. Treatment times vary significantly from a few seconds to many minutes, but they are more often in the range of 30-150 S.[25,26]

Treatment interval (h, days, weeks): The effects of different treatment intervals is underexplored at this time, although there is sufficient evidence to suggest that this is an important parameter.[17] With the exception of some early treatments of acute injuries, LLLT typically requires two or more treatments a week for several weeks to achieve clinical significance.[17]

A multidisciplinary approach to a scientific field crosses many disciplinary boundaries to create a holistic and deeper understanding of a specific subject. Photomedicine, and in particular PBM, is an absolutely multidisciplinary and

collaborative field of research. In order to achieve new findings in PBM mechanisms, a team of researchers should have some expertise and knowledge about biophysics and biochemistry; new biomedical applications are developed not only by physicians but also scientists and engineers in collaboration. Conversely, the improvement and development of new devices usually has insights from scientists and clinicians. Therefore, in general, laboratory teams researching PBM comprise clinicians, scientists, and engineers from diverse backgrounds. Figure 1.4 shows a graph of the numbers of publications cited in PubMed in the field of PBM/LLLT. The first sizeable increase occurred in 2002, and there was a second notable jump in 2009.

Translational research refers to the "bench-to-bedside" enterprise, of moving knowledge from basic scientific discoveries to produce new drugs, better devices, and improved treatment options for patients. Translational research, according to public health authorities, attempts to bring new treatments and research knowledge into practice for patients for whom the treatments are intended.[27] For this reason, contemporary photomedicine research perfectly fits in the paradigm of translational research because it struggles with both objectives. Although considerable efforts have been dedicated to create new devices and treatment options in order to improve PBM, another important task is to make health professionals and patients more knowledgeable about it.

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Many clinical trials and laboratory studies have consistently shown good, reproducible results in conditions and diseases where drugs and surgery are failing, but PBM has not been widely adopted by mainstream medicine. The reason for this state of affairs depends on 'who you ask

- For scientists, it is a lack of mechanism, parameters, and dose evidence;
- For doctors, it is a lack of large, clinical-trial systematic reviews;
- For hospital administrators, it is a lack of reimbursement;
- For insurers, it is a lack of cost/benefit evidence;
- For industry representatives, it is excessive marketing hype and misinformation; and
- For development professionals, it is a lack of a clear path and sufficient funding to achieve clinical approval.

The basic science research of PBM incorporates physics, chemistry, and biology. Physics encompasses light—tissue interactions, tissue optics, and light-

source properties; chemistry looks at light absorption, chromophores, photomodulation of reactive oxygen species, and photochemical reactions; and biology covers cell signaling, transcription factors, and proliferation and migration in culture.

The translational research aspects of PBM concentrate on animal models of a broad range of diseases and conditions. Because medical conditions can have strong variations between different patients, it is useful that animal models can create a reproducible controlled environment for researchers. Some examples of conditions studied with animal models and treated with PBM are wound healing, pain, arthritis, inflammation, microbial infections, bone and tendon regeneration, traumatic brain injury (TBI), and some neurological diseases, such as Alzheimer's, Parkinson's, and strokes.

Light irradiation using a low power density has been reported as a noninvasive, noncarcinogenic, nontraumatic procedure that can provide a therapeutic benefit to many diseases and medical conditions, and that has been reported to have few (if any) side effects. In addition, PBM is used to improve human wellness with aesthetic and cosmetic applications, improvements in sports performance, and has diverse veterinary applications. The biomodulation achieved by PBM allows it to be applied in situations that can be apparently paradoxical because it can sometimes be used to stimulate cells and tissues, and in other situations it can inhibit the same biological effect. For this reason,. PBM is referred to by many researchers as a regulator or modulator because it restores the organism to homeostasis. Moreover, there is considerable evidence of the systemic effects of PBM, which means that application to one site of the body can produce an improvement of a condition in another distant .body part that did not receive light. Systemic effects can be explained by local effects of light that can be transferred to other sites through the circulating blood, via the lymphatic system; or via the nervous system. Moreover, the blockage of axonal nerve impulses can explain the decrease in pain sensation when PBM is delivered to specific points in the continuously connected nerve pathway from the painful site (periphery) to the central nervous system.

The stimulatory effect of PBM was used for one of the first clinical applications in wound healing because PBM promotes beneficial effects during all four phases of the wound-healing process (coagulation, inflammation, migration,[28] and remodeling[29]). These processes can be regulated by many growth factors and are connected with nitric oxide (NO) signaling. The release and production of NO

can be modulated by PBM.[3°]

An interesting example of the systemic effect of PBM was provided by Hopkins et al. when they conducted a randomized, triple-blind, placebo-controlled experiment wherein 22 healthy subjects had two standardized 1.27-cm^2 abrasion wounds induced on their anterior forearms. PBM (820 nm, 8 J/cm^2, 125-s duration, 700-Hz pulse rate) was applied on only one of the two randomly chosen wounds.[31] Evidence for a systemic blood (or carried by blood) effect of laser irradiation were obtained in follow-up testing (on days 6, 8, and 10) because it revealed that the laser group had smaller wounds than the sham group for both the treated and for the untreated wounds.[32]

Reduction of inflammation due to light therapy is one of the most well-accepted PBM effects.[33] It is evidenced by a decrease in chemical inflammatory mediators, such as prostaglandin E2,[31,34,35] leucocytes,[36] and tumor necrosis factor (TNFa).[37] PBM can modulate the pro-inflammatory response, increasing both the mRNA expression and the protein concentration of anti-inflammatory mediators, such as IL-10 (related to tendinitis) and heat shock protein-72 (HSP72) (related to rheumatoid arthritis). These anti-inflammatory effects are similar to the ones promoted by treatment with glucocorticoids (anti-inflammatory steroids). The anti-inflammatory and pro-inflammatory effects promoted by PBM are strong evidence that PBM acts as a homeostasis regulator in order to maintain balance between the anti- and pro-inflammatory responses.

There are many ways that PBM can decrease pain, including anti-inflammatory effects, neural blockade, stimulation of lymphatic activity, tissue repair, and reduction of muscle spasm. Each of these mechanisms has been studied in a translational manner from subcellular levels to clinical application. Lasers can relieve nociceptive and neuropathic pain by partially inhibiting nerve conduction and reducing afferent stimulation, mimicking some functions of local anesthetic injections.[29] In addition, PBM can produce a long-lasting pain decrease due to neuroplasticity, which is the capacity of neurons in both the peripheral and central nervous systems, to be modulated by increased or decreased afferent activity from the somatosensory nerves.[38] PBM has been successfully used for decreasing pain in various situations, such as arthritis, crystallopathies, tendinopathies, lateral epicondylitis, postoperative and myofascial pain, as well as muscle-skeletal pain in the neck, back, and shoulder.

Photobiomodulation with red and NIR light has been applied successfully to

ameliorate disorders of the cardiovascular and respiratory systems. Oron et al.[39] showed that laser irradiation caused an increase in newly formed blood vessels six days post myocardial infarction in rats. Many functions in vascular walls are regulated by NO, including the suppression of the inflammatory response, vasodilatation, angiogenesis, inhibition of apoptosis, and cell migration." The beneficial effect of PBM on lung function and the reduction of clinical symptoms have been demonstrated by blood irradiation or transcutaneous lung irradiation.[41] Recently, lasers and LED irradiation in the central nervous system have been reported to bring positive outcomes for acute and chronic strokes, traumatic brain injury, memory and mood disorders, and various neurodegenerative diseases, such as Parkinson's, Alzheimer's, and retinal degeneration.[21'22] Importantly, PBM shows no side effects in either animals or humans,[23-25] which is a much desired characteristic for a therapy carried out in the brain and central nervous system. In addition, red and NIR laser irradiation to the spinal cord have been demonstrated for treating spinal cord injuries, the restoration of traumatically injured peripheral nerves,[42] and systemic effects of PBM on crushed sciatic nerves.[43] The application of PBM associated with surgical operative procedures has been rising in importance: pre-surgery application (pre-conditioning[44]) decreases cell death and reduces wound dehiscence; PBM during the operation decreases the inflammatory process; and when used during post-operative care, can reduce the recovery time, especially in the elderly or patients with co-morbidities. These benefits can be observed even in large and complicated surgeries such as saphenectomy in diabetic patients.

Special emphasis must be given to the applications of PBM in dentistry because there is virtually no procedure in that field that will not respond positively to photobiomodulation; using a drill to prepare a restoration or an instrument for mechanical debridement starts an inflammatory response within the tissue and tooth pulp. PBM helps modulate the inflammatory response while reducing pain, making it a useful weapon in every dental practitioner's repertoire that can both ease the job of the practitioner and improve the patient's experience.

Wellness can be provided by PBM for aesthetic applications. The regeneration and stimulation effect of PBM promotes the resurfacing and rejuvenating of the skin. Moreover, it is a very well-established treatment for hair regrowth, and evidence is accumulating for fat reduction.

Sports medicine will benefit from PBM because both professional and

amateur athletes can better recover from intense exercise, and the process also aids training regimens. In the near future, sport agencies must deal with "laser doping" by at least openly discussing it because the aforementioned beneficial

Not less impressive is the use of PBM in veterinary medicine. PBM has been used for pets (companion animals) with essentially the same applications as mentioned for humans. In addition, it can be used to improve the reproduction of farm animals and prevent extinction of threatened species. Moreover, it is a side-effeet-free treatment for injured wild animals.

PBM is more than an alternative kind of medical treatment; it is a whole new method to control cellular processes and modulate living organisms by precise alterations in the chemistry of biomolecules. PBM enables the contemporary clinician or therapist who holds a modern and multidisciplinary outlook to fight against diseases and other disorders in both humans and other animals. Moreover, it is a possible way to stimulate or inhibit many different biological processes that occur in most (if not all) different living creatures. It could even be suggested that the photobiomo-dulation phenomenon is as old as life itself.

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