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Seminars in Cutaneous Medicine and Surgery

Light-Emitting Diodes (LEDs) in Dermatology

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Light-emitting diode photobiomodulation is the newest category of nonthermal light therapies to find its way to the dermatologic armamentarium. In this article, we briefly review the literature on the development of this technology, its evolution within esthetic and medical dermatology, and provide practical and technical considerations for use in various conditions. This article also focuses on the specific cell-signaling pathways involved and how the mechanisms at play can be put to use to treat a variety of cutaneous problems as a stand-alone application and/or complementary treatment modality or as one of the best photodynamic therapy light source.
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Light therapy is one of the oldest therapeutic modalities used to treat various health conditions. Sunlight benefits in treating skin diseases have been exploited for more than thousands of years in ancient Egypt, India, and China. Solar therapy was later rediscovered by Niels Ryberg Finsen (Fig. 1, Fig. 2), a Danish physician and scientist who won in 1903 the Nobel Prize in Physiology or Medicine in recognition of his contribution to the treatment of diseases, notably lupus vulgaris. Phototherapy involving the use of an artificial irradiation source was born.[1]

It was only many years later that light therapeutic benefits were uncovered again using other segments of the electromagnetic spectrum (EMS) with visible and near-infrared wavelengths. In the late 1960s, Endre Mester, a Hungarian physician, began a series of experiments on the carcinogenic potential of lasers by using a low-powered ruby laser (694 nm) on mice. To his surprise, the laser did not cause cancer but improved hair growth that was shaved off the animal's back for the purpose of the experiment. This was the first demonstration of "photobiostimulation" with low-level laser therapy (LLLT), thereby opening a new avenue for medical science. This casual observation prompted him to conduct other studies provided support for the efficacy of red light on wound healing. Since then, medical treatment with coherent-light sources (lasers) and noncoherent light (light-emitting diodes, LEDs) has expanded. The use of LLLT and LEDs is now applied to many thousands of people worldwide each day for various medical conditions.

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LED photobiomodulation is the newest category of nonthermal light therapies to find its way to the dermatologic armamentarium and will be the focus of this review. Initial work in this area was mainly developed by National Aeronautics and Space Administration (NASA). NASA research came about as a result of the effects noted when light of a specific wavelength was shown to accelerate plant growth. Because of the deficient level of wound healing experienced by astronauts in zero-gravity space conditions and Navy Seals in submarines under high atmospheric pressure, NASA investigated the use of LED therapy in wound healing and obtained positive results. This research has continued and innovative and powerful LEDs are now used for a variety of conditions ranging from cosmetic indications to skin cancer treatment (as a photodynamic therapy light source).

LED Technology

LEDs are complex semiconductors that convert electrical current into incoherent narrow spectrum light. LEDs have been around since the 1960s but have mostly been relegated to showing the time on an alarm clock or the battery level of a video camera. They have not until recently been used as sources of illumination because, for a long time, they could not produce white light—only red, green, and yellow. Nichia Chemical of Japan changed that in 1993 when it started producing blue LEDs which, combined with red and green, produce white light, opening up a whole new field for the technology. The industry has been quick to exploit it. LEDs are based on semiconductor technology, just like computer processors, and are increasing in brightness, energy efficiency, and longevity at a pace reminiscent of the evolution of computer processors. Emitted light are now available at wavelengths ranging from ultraviolet (UV) to visible to near infrared (NIR) bandwidth (247 to 1300 nm).

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Figure 1 Niels Ryberg Finsen (1860-1904). Courtesy of the Clendening History of Medicine Library, University of Kansas Medical Center.

LED arrays are built using diverse methods each hinging on the manner in which the chips themselves are packaged by the LED semiconductor manufacturer. Examples of packaged, lensed LEDs are t-pack LED and surface mount LEDs (Figs 3-5). These packages can be affixed to a heat-sinking substrate by using either a "through hole" mounting or surface mounting. Through hole mounted devices are often referred to as t-pack LEDs. Importantly, it is also possible to procure wafers of bare, unpackaged chips, also called "dice." By using automated pick-and-place equipment, some manufacturers take such individual chips and affix them to printed circuit boards, creating so-called "chip-on-board" LED arrays. LED array is thus assembled on a printed circuit board. The pins or pads or actual surfaces of the LED chips are attached to conductive tracks on the PCB (printed circuit board). Assemblies built from t-pack LEDs are often unsatisfactory in that they do not always provide sufficiently uniform lighting, are not well heat-sinked, and they are bulky due to the size (several millimeters) of each t-pack device. Nonetheless, for certain applications, t-packs prove to be the most appropriate, cost-effective solution. However, when t-packs cannot provide the required performance, however, chip-on-board emerges as the answer.

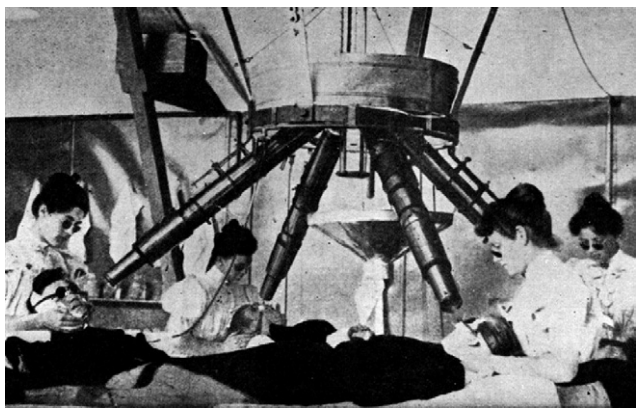

Figure 2 Finsen's phototherapy. Due to expense of carbon arc lighting, single lamp directed light through four water-cooled focusing lenses, allowing several patients to be treated simultaneously. Each patient had nurse attendant to focus light to single small region for up to 1 hour. (Reprinted from Bie V: Finsen's phototherapy. BMJ 1899;2:825)

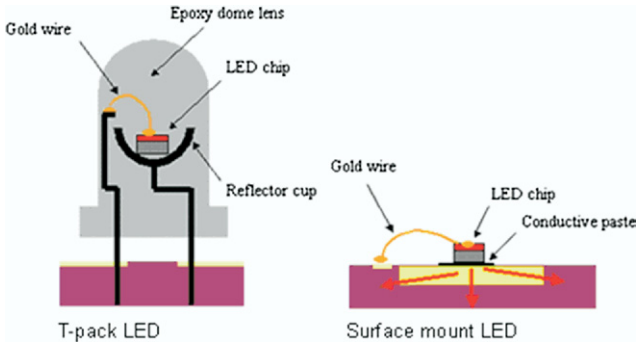

Figure 3 LED technology. The red arrows indicate the flow of heat. Courtesy of Stocker Yale, Inc.

A significant difference between lasers and LEDs is the way the light energy is delivered [optical power output (OPD)]. The peak power output of LEDs is measured in milliwatts, whereas that of lasers is measured in watts. LEDs provide a much gentler delivery of the same wavelengths of light compared to lasers and at a substantially lower energy output. LEDs do not deliver enough power to damage tissues and do not have the same risk of accidental eye damage that lasers do. Visible/NIR-LED light therapy has been deemed a non-significant risk by the Food and Drug Administration and has been approved for use in humans. Other advantages over lasers include the possibility to combine wavelengths with an array of various sizes. LED disperses over a greater surface area than lasers and can be used where large areas are targeted, resulting in a faster treatment time.

Mechanism of Action

In the same way that plants use chlorophyll to convert sunlight into plant tissue, LEDs can trigger natural intracellular photobiochemical reactions. To have any effect on a living biological system, LED-emitted photons must be absorbed by a molecular

Figure 4 A t-pack LED.

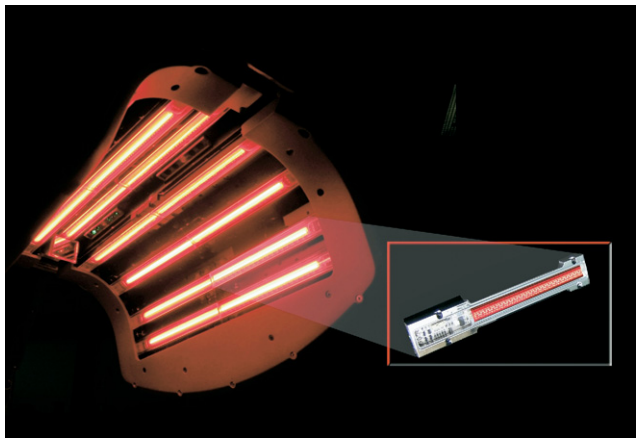

Figure 5 Linear chip-on-board LEDs.

chromophore or photoacceptor. Light, at appropriate doses and wavelengths, is absorbed by chromophores such as porphyrins, flavins, and other light-absorbing entities within the mitochondria and cell membranes of cells.

A growing body of evidence suggests that photobiomodulation mechanism is ascribed to the activation of mitochondrial respiratory chain components resulting in the initiation of a cascade of cellular reactions. It has been postulated that photoacceptors in the red to NIR region are the terminal enzyme of the respiratory chain cytochrome *c* oxidase with 2 copper elements. The first absorption peak is in the red spectrum and the second peak in the NIR range. Seventy-five years ago, Otto Warburg, a German biochemist, was given a Nobel prize for his ingenious work unmasking the enzyme responsible for the critical steps of cell respiration, especially cytochrome oxidase governing the last reaction in this process. Two chemical quirks are exploited: carbon monoxide (CO) that can block respiration by binding to cytochrome oxidase in place of oxygen, and a flash of light that can displace it, allowing oxygen to bind again.

Nowadays, it has been reported that cells often use CO and, to an even greater extent, nitric oxide (NO) binding to cytochrome oxidase to hinder cell respiration.[2] Mitochondria harbor an enzyme that synthesizes NO. So why would cells go out of their way to produce NO right next to the respiratory enzymes? Evolution crafted cytochrome oxidase to bind not only to oxygen but also to NO. One effect of slowing respiration in some locations is to divert oxygen elsewhere in cells and tissues, preventing oxygen sinking to dangerously low levels. Fireflies use a similar strategy to flash light (see section "Pulsing and Continuous Modes"). Respiration is about generating energy but also about generating feedback that allows a cell to monitor and respond to its environment. When respiration is blocked, chemical signals in the form of free radicals or reactive oxygen species are generated. Free radicals had a bad reputation, but now they can be considered signals. The activity of many proteins, or transcription factors, depends, at least in part, on free radicals.[3] These include many proteins such as those involved in the p53 cell-signaling pathway. Further, to bring free radical leak under control, there is a cross-talk, known as retrograde response, between the mitochondria and genes in the nucleus for which we are just beginning to explore the mechanism at play.[4,5] If we can better modulate this signaling, we might be able to influence the life or death of cells in many pathologies as it is more and more demonstrated in its antiaging effects on collagen metabolism.

A recent discovery has revealed that NO eliminates the LLLT-induced increase in the number of cells attached to the glass matrix, supposedly by way of binding NO to cytochrome c oxidase.[6] Cells use NO to regulate respiratory chain processes, resulting in a change in cell metabolism. In turn, in LED-exposed cells like fibroblasts increased ATP production, modulation of reactive oxygen species (such as singlet oxygen species), reduction and prevention of apoptosis, stimulation of angiogenesis, increase of blood flow, and induction of transcription factors are observed. These signal transduction pathways lead to increased cell proliferation and migration (particularly by fibroblasts), modulation in levels of cytokines (eg, interleukins, tumor necrosis factor-α), growth factors and inflammatory mediators, and increases in anti-apoptotic proteins.[7]

The photodissociation theory incriminating NO as one of the main players suggests that during an inflammatory process, for example, cytochrome *c* oxidase is clogged up by NO. LED therapy would photodissociate NO or bump it to the extracellular matrix for oxygen to bind back again to cytochrome c oxidase and resume respiratory chain activity. Understanding the mechanisms of cutaneous LED-induced specific cell-signaling pathway modulation will assist in the future design of novel devices with tailored parameters even for the treatment of degenerative pathologies of the skin.

Optimal LED Parameters

In LED, the question is no longer whether it has biological effects but rather what the optimal light parameters are for different uses. Biological effects depend on the parameters of the irradiation such as wavelength, dose (fluence), intensity (power density or irradiance), irradiation time (treatment time), continuous wave or pulsed mode, and for the latter, pulsing patterns. In addition, clinically, such factors as the frequency, intervals between treatments and total number of treatments are to be considered. The prerequisites for effective LED clinical response are discussed hereafter.

Well-Absorbed Deeply Penetrating Wavelength

Light is measured in wavelengths and is expressed in units of nanometers (nm). Different wavelengths have different chromophores and can have various effects on tissue (Fig. 6). Wavelengths are often referred to using their associated color and include blue (400-470 nm), green (470-550 nm), red (630-700 nm) and NIR (700-1200) lights. In general, the longer the wavelength, the deeper the penetration into tissues.[8-10] Depending on the type of tissue, the penetration depth is less than 1 mm at 400 nm, 0.5 to 2 mm at 514 nm, 1 to 6 mm at 630 nm, and maximal at 700 to 900 nm.[10]

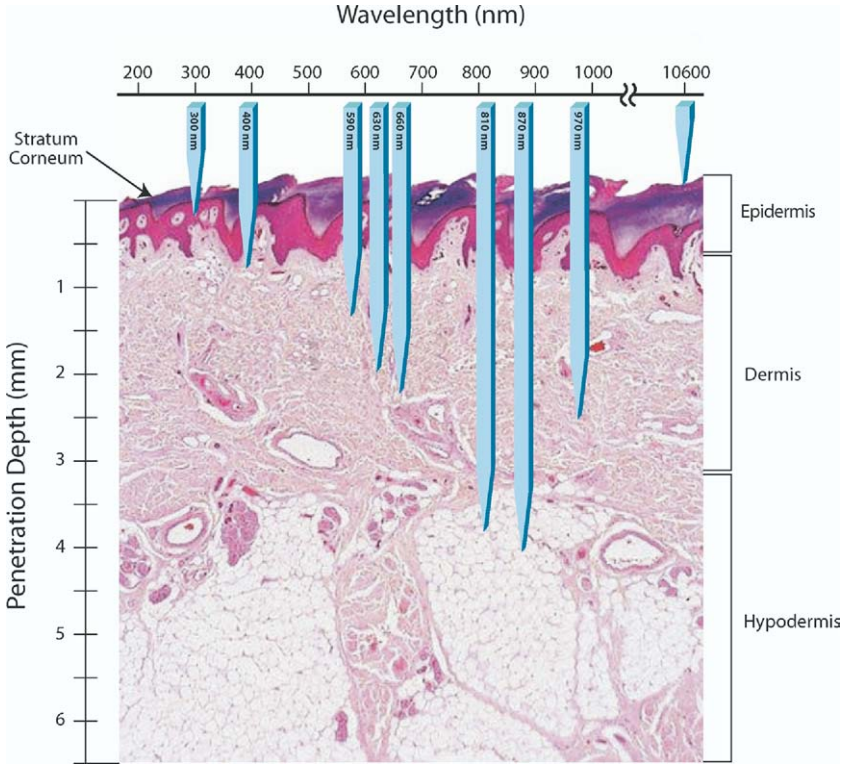

Figure 6 Optical penetration depth.

The various cell and tissue types in the body have their own unique light absorption characteristics, each absorbing light at specific wavelengths. For best effects, the wavelength used should allow for optimal penetration of light in the targeted cells or tissue. Red light can be used successfully for deeper localized target (eg, sebaceous glands), and blue light may be useful for the treatment of skin conditions located within the epidermis in photodynamic therapy (PDT) (eg, actinic keratoses). To reach as many fibroblasts as possible, which is often the aim of LED therapy, a deeply penetrating wavelength is desirable. At 660 nm, for instance, light can achieve such a goal reaching a depth of 2.3 mm in the dermis, therefore covering fibroblasts up to the reticular dermis. The wavelength used should also be within the absorption spectrum of the chromophore or photoacceptor molecule and will often determine for which applications LEDs will be used. Because cytochrome *c* oxidase is the most likely chromophore in LLLT, 2 absorption peaks are considered in the red (~660 nm) and NIR (~850 nm) spectra.[6]

Two major wavelength boundaries exist for LED applications: at wavelengths <600 nm, blood hemoglobin (Hb)

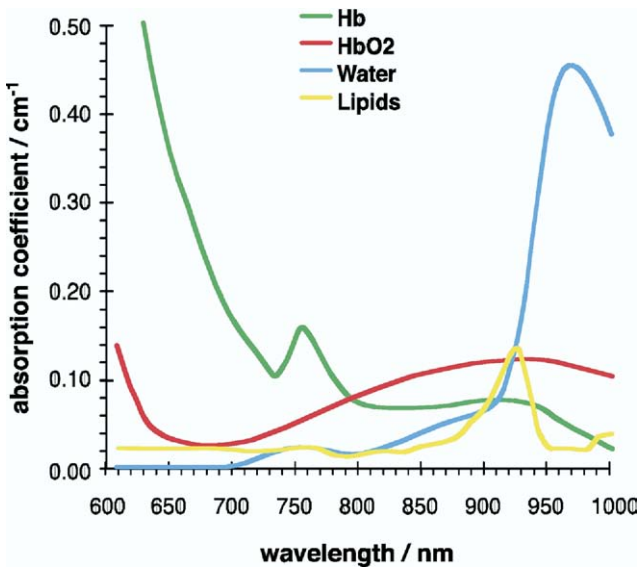

Figure 7 Main tissue constituents absorbing in the 600–1000 nm spectral range. Adapted with permission from Taroni P, Pifferi A, Torricelli A, et al: In vivo absorption and scattering spectroscopy of biological tissues. Photochem Photobio Sci 2:124-129, 2003.

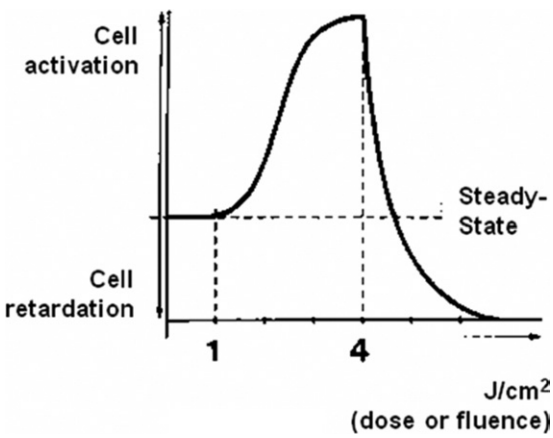

Figure 8 Schematic representation of Arndt-Schulz curve.

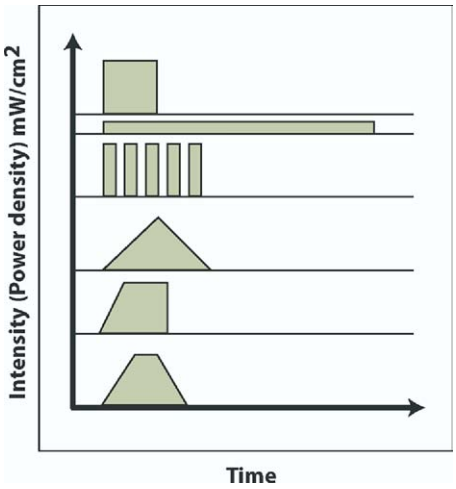

Figure 9 Different light delivery patterns with similar fluence.

is a major obstacle to photon absorption because blood vessels are not compressed during treatment. Futhermore, at wavelengths >1000 nm, water is also absorbing many photons, reducing their availability for specific chromophores located, for instance, in dermal fibroblasts. Between these 2 boundaries, there is a valley of LED possible applications (see Fig. 7).

Fluence and Irradiance

The Arndt-Schulz law states that there is only a narrow window of opportunity where you can actually activate a cellular response using precise sets of parameters, i.e. the fluence or dose (see Fig. 8). The challenge remains to find the appropriate combinations of LED treatment time and irradiance to achieve optimal target tissue effects. Fluence or dose is, indicated in joules per cm^2 (J/cm^2). The law of reciprocity states that the dose is equal to the intensity × time. Therefore, the same exposure should result from reducing duration and increasing light intensity, and vice versa. Reciprocity is assumed and routinely used in LED and LLLT experiments. However, the scientific evidence supporting reciprocity in LED therapy is unclear.[11]

Dose reciprocity effects were examined in a wound healing model and showed that varying irradiance and exposure time to achieve a constant specified energy density affects LED therapy outcomes.[12] In practice, if light intensity (irradiance) is lower than the physiological threshold value for a given target, it does not produce photostimulatory effects even when irradiation time is extended. Moreover, photoinhibitory effects may occur at higher fluences.

In Fig. 9, different light delivery patterns are shown. Interestingly, they are all of the same fluence but over time, the energy of photons does not reach the biological targets in the same way. This may alter the LED biological response significantly. The importance of pulsing will be discussed in the next section.

Certainly a minimal exposure time per treatment is necessary—in the order of several minutes rather than only a few seconds—to allow activation of the cell machinery; otherwise, tissue response is evanescent and no clinical outcome is expected. The ideal treatment time has to be tailored according to the skin condition or degree of inflammation present at the time of treatment.

Pulsing and Continuous Modes

Both pulsed wave and continuous wave (CW) modes are available in LED devices, which add to the medical applicability. The influence of CW versus pulsing mode, as well as precise pulsing parameters (eg, duration, interval, pulse per train, pulse train interval), on cellular response has not been fully studied. To date, comparative studies have shown conflicting results.[13] In our own experience, sequentially pulsed optical energy (proprietary pulsing mode with repeated sequences of short pulse trains followed by longer intervals) has been shown to stimulate more collagen production than CW mode.[14]

Under certain conditions, ultra-short pulses can travel deeper into tissues than CW radiation.[15,16] This is because the first part of a powerful pulse may contain enough photons to take all chromophore molecules in the upper tissue layer to excited states, thus literally opening a road for itself into tissue. Moreover, too long a pulse may produce cellular exhaustion whereas too short a pulse may deliver insufficient energy for a biologic effect to occur. Targeted molecules and cells may-on a smaller scale than selective photothermolysis-have their own thermal relaxation times.[14]

The NO photodissociation theory could also be part of the answer, especially the need for pulsing characteristics during LED therapy. Interestingly, fireflies use such pulsing phenomenon. There, oxygen reacts with the luciferyl intermediate to produce a flash of light. The glory is that the flash switches itself off. Light dissociates NO from cytochrome oxidase, allowing oxygen to bind again. Then, the mitochondria consume oxygen once more, allowing the luciferyl intermediate to build up until another wave of NO arrives.[17]

Precise Positioning of Treatment Head

Very precise positioning or working distance is mandatory to ensure optimal beam delivery intensity covering the treatment area so as to achieve maximum physiological effects. Accurate positioning ensures that the proper amount of photons is delivered to the treated skin to avoid hot or cold spots in the treatment field. This is especially important in photobiology as a required amount of energy must be delivered to the target to trigger the expected cell response. If insufficient photons reach the target, no cell response will result. Some LED devices even provide optical positioning systems to allow reproducible treatment distance within precise limits (±3 mm).

Timing of Treatments Outcomes

There are some indications that cellular responses after light irradiation are time dependent. A recent study suggests that responses such as ATP viability can be observed directly (1 hour) after the irradiation, whereas other responses such as cell proliferation require at least 24 hours before the true

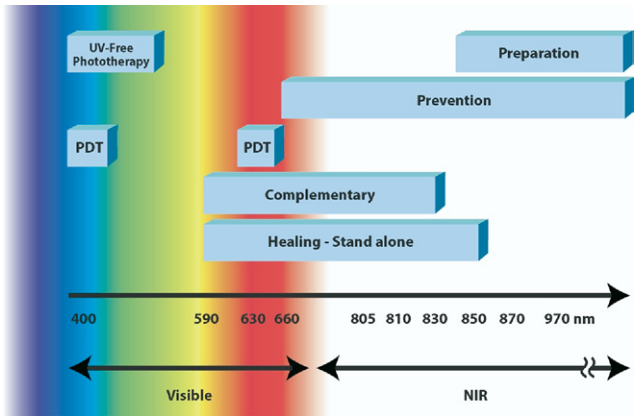

Figure 10 Current and promising LED applications as a function of wavelengths.

effect can be observed.[18] It is thus important to establish time-dependent responses to adequately assess photomodulatory effects. Fibroblasts in culture show physiological cyclical patterns of procollagen type I up-regulation and metalloproteinase-1 (MMP-1) down-regulation that can be emphasized by LED treatments every 48 hours.[19]

State of Cells and Tissues

The magnitude of the biostimulation effect depends on the physiological condition of the cells and tissues at the moment of irradiation.[20] Compromised cells and tissues respond more readily than healthy cells or tissues to energy transfers that occur between LED-emitted photons and the receptive chromophores. For instance, light would only stimulate cell proliferation if the cells are growing poorly at the time of the irradiation. Cell conditions are to be considered because light exposures would restore and stimulate procollagen production, energizing the cell to its own maximal biological potential. This may explain the variability in results in different studies.

Effects of LED

LED therapy is known for its healing and antiinflammatory properties and is mostly used in clinical practice as a supplement to other treatments such as nonablative thermal technologies. Different LED applications can now be subdivided according to the wavelength or combination of wavelengths used (see Fig. 10). LED therapy can be used as a standalone procedure for many indications, as described herein. A summary of recommended LED parameters for various clinical applications are presented in Table 1.

When reviewing the literature, one needs to keep in mind that results from different studies may be difficult to compare because the potential effects of variation of treatment parameters (eg, wavelength, fluence, power density, pulse/continuous mode and treatment timing) may vary from one study to the next. Moreover, there is the possibility that the photobiomodulatory effects are dissimilar across different cell lines, species and patient types. We will now discuss current LED applications.

Wound Healing

Early work involving LED mainly focused on the wound healing properties on skin lesions. Visible/NIR-LED light treatments at various wavelengths have been shown to increase significantly cell growth in a diversity of cell lines, including murine fibroblasts, rat osteoblasts, rat skeletal muscle cells, and normal human epithelial cells.[21] Decrease in wound size and acceleration of wound closure also has been demonstrated in various in vivo models, including toads, mice, rats, guinea pigs, and swine.[22,23] Accelerated healing and greater amounts of epithelialization for wound closure of skin grafts have been demonstrated in human studies.[24,25] The literature also shows that LED therapy is known to positively support and speed up healing of chronic leg ulcers: diabetic, venous, arterial, pressure.[26]

According to our experience, LED treatments are also very useful after CO_2 ablative resurfacing in reducing the signs of the acute healing phase resulting in less swelling, oozing, crusting, pain, and prolonged erythema thereby accelerating wound healing (see Fig. 11). It is important to keep in mind that to optimize healing of necrotic wounded skin, it may be useful to work closer to the near infrared spectrum as an increase in metalloproteinases (ie, MMP-1, debridment-like effect) production accelerates wound remodeling.

Inflammation

Free radicals are known to cause subclinical inflammation. Inflammation can happen in a number of ways. It can be the result of the oxidation of enzymes produced by the body's defense mechanism in response to exposure to trauma such as sunlight (photodamage) or chemicals. LED therapy brings a new treatment alternative for such lesions possibly by counteracting inflammatory mediators.

A series of recent studies have demonstrated the antiinflammatory potential of LED. A study conducted in arachidonic acid-treated human gingival fibroblast suggests that 635 nm irradiation inhibits PGE 2 synthesis like COX inhibitor and thus may be a useful antiinflammatory tool.[27] LED photobiomodulation treatment has also been shown to accelerate the resolution of erythema and reduce posttreatment discomfort in pulsed dye laser (IPL)-treated patients with photodamage and to prevent radiation-induced dermatitis in breast cancer patients.[28,29] Patients with diffuse type rosacea (unstable) (see Fig. 12), keratosis pilaris rubra, as well as postintervention erythema (eg, IPL, CO_2) (Fig. 11) can benefit from a quicker recovery with complementary LED therapy. (See also section on wound healing).

Because LED is known to reduce MMPs, it might be useful in conditions in which MMPs are implicated. One such case is lupus erythematosus (LE). LE is a heterogeneous autoimmune disease associated with aberrant immune responses including production of autoantibodies and immune complexes and specific MMPs have been implicated in its etiol-

Table 1 LED Parameters for Various Clinical Applications Used in our Practice

Applications	Wavelength (nm)	No. of Treatments	Irradiance (mW/cm^2)	Fluence (J/cm^2)	Treatment Time (min;sec)	Interval Treatment Time (hours)	Mode (Pulsed/CW)
Wound healing	660 & 850 combination	3-12	50 (minimal)	4	2:40	24-72	Sequential pulsing**
Inflammation/erythema/edema (diffuse type rosacea, post- procedure erythema (eg, IPL, CO_2)	630-660	3-12	50 (minimal)	4	2:40	48-72	Sequential pulsing
PDT	405-630	3+	50-100	>50	13-45	3 weeks	CW or pulsed
Photorejuvenation	630-660	12	50-100	4	2:40-16	48-72	Sequential pulsing
Sunburn prevention*†	660-970	ad 7	50	4	2:40-15	24-48	Sequential pulsing or CW
PIH prevention*†	870-970	ad 8	50-80	45-96	15-20	24-48	Sequential pulsing or CW
Scar prevention*	805-970	Multiple	50-80	45-72	15	24	CW
Photopreparation	870-970	3 (before every PDT Treatment)	>80	72-100	15	Pre-PDT (q 3 weeks)	CW
Photoregulation	660-850	Long-term	8-50	4-7,5	5-16	24-48	Sequential pulsing
UV-free phototherapy	405-850	Depends on inflammatory disease	30-50	27-135	15-45	48	Sequential pulsing or CW

*Sunburn, PIH, and scar-prevention methods = Photoprophylaxis.

**Sequential pulsing mode with proprietary pulsed characteristics (50% duty cycle).

†LED treatments should be preferably performed in the week before UV insult or skin trauma to better prevent sunburn or PIH, respectively.

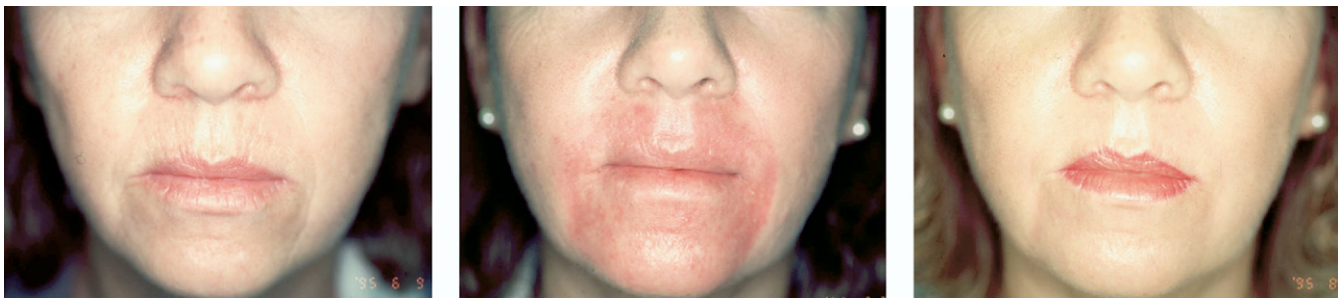

Figure 11 Pictures of a 47-year-old caucasian patient before CO_2 laser resurfacing, and 1 week and 3 weeks post procedure after 4 LED treatments given 48 hours apart.

ogy. MMP inhibition through LED treatments may reduce lupus-induced damage in inflamed tissues.

Photorejuvenation

In aged photo-damaged human skin, collagen synthesis is reduced with a concomitant elevation of matrix MMP expression.[30] Hence, a possible strategy for treating and preventing the clinical manifestations of skin aging is the restoration of the collagen deficiency by the induction of new collagen synthesis and reduction of MMP.

Using a variety of LED light sources in the visible to NIR regions of the spectrum, in vitro studies have revealed that LED can trigger skin collagen synthesis with concurrent reduction in MMP. A significant increase in collagen production after LED treatment has been shown in various experiments, including fibroblasts cultures, third-degree burn animal models, and human blister fluids, and skin biopsies.[14,31-34] In clinical studies, the increase in collagen production with concurrent MMP-1 reduction has been seen in association with improved appearance of photodamaged skin. Table 2 shows currently available LED sources for skin rejuvenation.

Photoprophylaxis or Photoprevention

Photoprophylaxis is a novel approach that we were the first to introduce—to the best of our knowledge—in the use of LEDs for the prevention of cutaneous manifestations after a trauma. If LED therapy is administered several times prior to a UV insult, a mechanical trauma such as a CO_2 laser treatment or a surgery, one may prevent undesirable consequences such as sunburn, postinflammatory hyperpigmentation (PIH), or hypertrophic scarring, respectively. These LED-preventative modalities will be discussed hereafter.

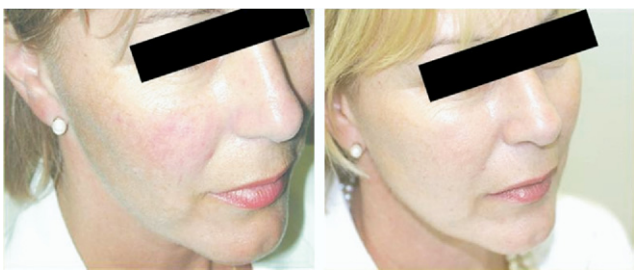

Figure 12 Picture of a female patient before and after complementary LED treatments for diffuse-type rosacea.

Sunburn Prevention

Beyond the repair of previous UV insults to the skin, visible to NIR light might offer protection against upcoming photodamage. It has been suggested that protective mechanisms against skin UV-induced damage may be activated by IR exposure in a number of in vitro studies using primary-culture human fibroblasts.[35,36] Therefore, LED treatment could stimulate skin resistance to UV damage.

Results from our own laboratory testing suggest that LED 660 nm treatment before UV exposure provides significant protection against UV-B induced erythema.[37] The induction of cellular resistance to UV insults may possibly be explained by the induction of a state a natural resistance to the skin (possibly via the p53 cell signaling pathways) without the drawbacks and limitations of traditional sunscreens.[38] These results represent an encouraging step toward expanding the potential applications of LED therapy and could be useful in the treatment of patients with anomalous reactions to sunlight such as polymorphous light eruption or lupus.

Postinflammatory Hyperpigmentation Prevention

PIH is a frequently encountered problem and represents the sequelae of various cutaneous disorders as well as therapeutic interventions especially on Asian and dark complexion patients. A preventative and complementary approach to thermal laser induced PIH using LED therapy is possible. According to unpublished work performed in our laboratory, the use of LED 660 nm therapy can prevent or treat PIH. On the basis of photographic analysis and melanin content measurements, most patients can achieve substantial reduction or absence of PIH lesions in the LED-treated areas (versus con-

Table 2 LED Sources Used for Noninvasive Skin Rejuvenation

Wavelength (nm)	System Name	Manufacturer
590	GentleWaves	Light Bioscience
630	Omnilux Revive	Phototherapeutics
660	LumiPhase-R	OpusMed

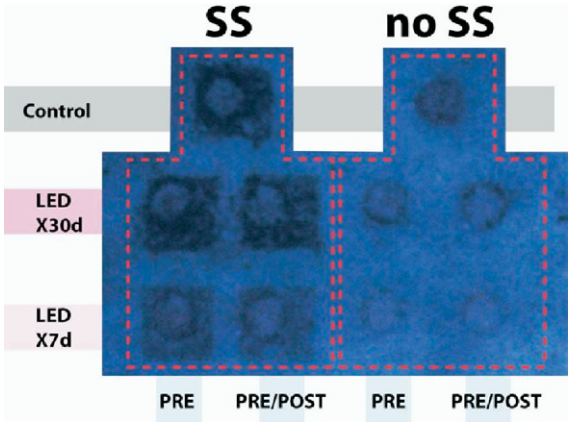

Figure 13 UV photography of skin taken 30 days after (SS) UV irradiation on areas pretreated for 7 days or 30 days with LED and control. The 7-day LED treatment before UV insult appears to be the best regimen to prevent PIH.

trol). In our hands, from 1 to 8 treatments delivered during a 1- to 2-week period prior to trauma will provide significantly less pigmentary response at the site of the trauma, especially if the area has been irradiated by UV posttrauma (by a sun simulator; Fig. 13). This could have tremendous implications since more than half of the planet (Asians and dark-complexioned people) is prone to such a postinflammatory pigmentary response.

Scar Prevention

Hypertrophic scars and keloids can form after surgery, trauma, or acne and are characterized by fibroblastic proliferation and excess collagen deposition.[39] An imbalance between rates of collagen biosynthesis and degradation superimposed on the individual's genetic predisposition have been implicated in the pathologenesis of these scar types. It has recently been proposed that interleukin (IL)-6 signaling pathways play a central role in this process and thus, that IL-6 pathway inhibition could be a promising therapeutic target for scar prevention.[40,41] As LED therapy has been shown to decrease IL-6 mRNA levels,[42] it may potentially be preventing aberrant healing. A recent study conducted by our research group revealed significant improvements on the treated versus the control side in appearance and outline of scars (Fig. 14).[43]

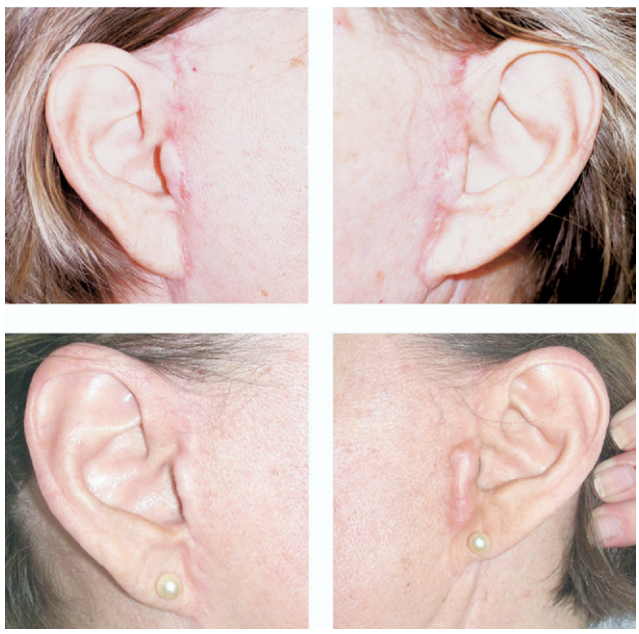

Figure 14 Patient after facelift preauricular scar revision (upper) and 12-month follow-up (lower). Left: LED-treated side X30 days post-surgery; Right: control (no LED).

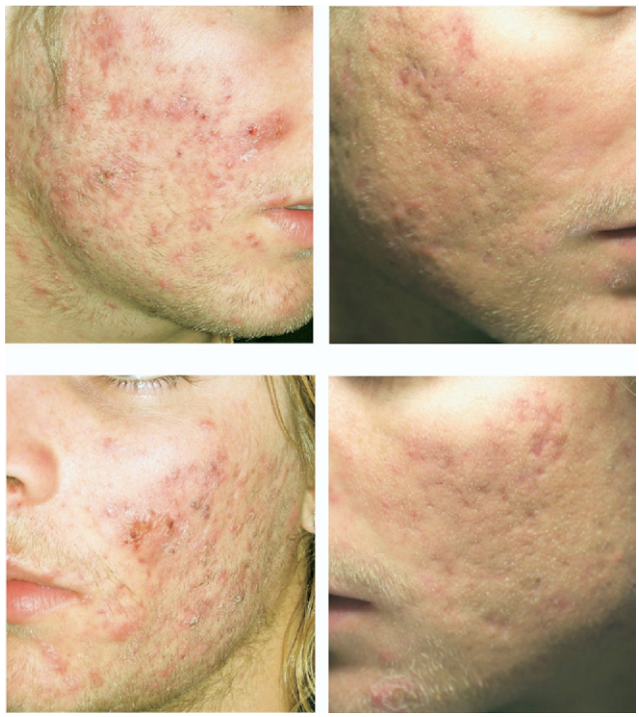

Figure 15 Nineteen year-old male patient before and 4-weeks after PDT for control right hemiface (upper panel) and LED-pretreated left hemiface with no residual inflammatory lesion on his cheek pretreated (lower panel).

Photopreparation

Photopreparation is another new concept that we have been working on that characterizes a way to enhance the delivery, through a substantially uniform penetration, of a given compound in the skin resulting in more active conversion of such topical agents (ie, ALA to PpIX) in targeted tissues. Radiant IR photopreparation increases skin temperature, which may lead to an increase in pore size (diameter) for enhanced penetration of a given topical in the pilosebaceous unit.

The efficacy of aminolevulinic acid photodynamic therapy (ALA-PDT), for instance, is dependent on ALA absorption and remains one of the main challenges of PDT. We have recently showed that increasing the skin temperature for 15 minutes with radiant IR (CW LEDs emitting @ λ 970 nm, irradiance 50 mW/cm^2, total fluence 45 J/cm^2) before ALA-PDT in the treatment of a cystic acne patient significantly

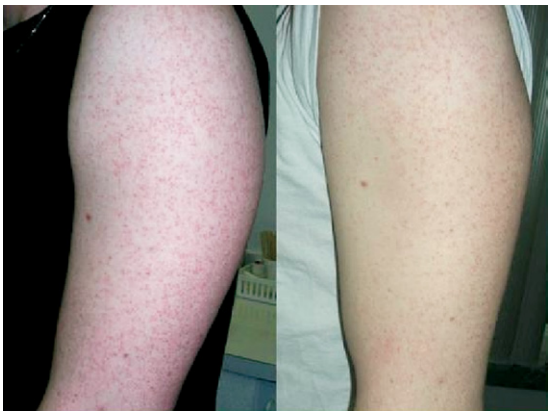

Figure 16 A 24-year-old patient with KPR after 2 months of daily treatments with 660/805 nm home use LED device.

decreased the number of cystic lesions in comparison with the non IR-heated side (Fig. 15).[44]

Photoregulation

Photoregulation involves an exciting new 2-level (importance of dermal–epidermal communication via cytokines) approach that we have evaluated with success to enhance the biological effects of a given topical. The main goal of this application would be to synergistically optimize any bioactive compound trajectory/route to ultimately up-regulate specific gene expression with simultaneous down-regulation of undesired ones via cell signaling pathways. In the esthetics industry, we believe such a method—even though still in its infancy—will become applicable in such applications as home-use skin rejuvenation and the treatment of inflammatory acne, hyperpigmentation disorders, oily skin, hyperhidrosis, eczema, etc.

UV-Free Phototherapy

UV radiation phototherapy has been used for decades in the management of common skin diseases.[45] However, there are side effects associated with UV deleterious effects as well as several contra-indications, including the long-term management of children and young adults and patients receiving topical or systemic immunosuppressive drugs. The primary effectors of UV phototherapy in the treatment of various skin conditions bear similarities with some of those associated with blue LEDs and IR phototherapy with LEDs, including singlet oxygen production and modulation of interleukins.[46,47] This provides a unique opportunity to explore the use of LED in skin conditions where UV therapy is used without the downside of inherent side effects. This approach has been termed UV-free therapy.

For instance, the mode of action of UVA phototherapy for atopic dermatitis was found to involve the induction of apoptosis in skin-infiltrating T-helper cells through a mechanism that requires the generation of singlet oxygen.[48] A recent study demonstrated that visible light (400-500 nm) can be successfully used for the treatment of patients with atopic eczema.[49] In our hands, even resistant KPR (keratosis pilaris rubra) may respond to LED therapy in the visible-NIR spectrum (Fig. 16). These promising results introduce a wide range of new potential application for LED.

Photodynamic Therapy (PDT)

PDT can best be defined as the use of light to activate a photosensitive medication that is applied to the skin prior to treatment. The PDT light source has a direct influence on treatment efficacy. Nowadays, the importance of treatment parameters of this light source is unfortunately greatly underestimated. High-end LED devices meet this challenge and can be used as the light source of choice for PDT (Table 3). Thus, PDT can serve as a treatment that complements other skin rejuvenation therapies or topical agents used to enhance collagen production. The use of a dual wavelength (red and blue) LED light source enhances PDT results for acne and other sebaceous disorders.[50] Red wavelength (630 nm) can reach the sebaceous glands and blue (405 nm) light photobleaches any residual protoporphyrin IX (PpIX) in the epidermis, thereby reducing posttreatment photosensitivity (Fig. 17). The way light photons are delivered seems to hold part of the answer for more effective PDT. Hence, dose rate is becoming one of the important criteria as opposed to total dose (fluence). Also, it is now suggested to avoid peak power effects on the photosensitizer—so-called thermal effects—that are usually encountered with light sources (thermal technologies) such as IPLs and lasers (ie, PDL). PDT frequent indications, both cosmetic and medical, are described in Table 4. LED technology clearly brings several advantages to

Table 3 Fluorescent and High end LED Systems for PDT

	Model		
Device Parameters	**Blu-U**	**LumiPhase-R/B**	**Omnilux Revive**
Wavelength (nm)	Fluorescent tubes 417	LED 405/630 (R/B)	LED 633
Power density (mW/cm²)	10	150/60 (R/B)	105
Working distance gauge	No	Optical Positioning System on both R & R/B Models	No
Treatment time (sec)	1000	160-1000	1200-1800
PDT light source	Yes	Yes	Yes

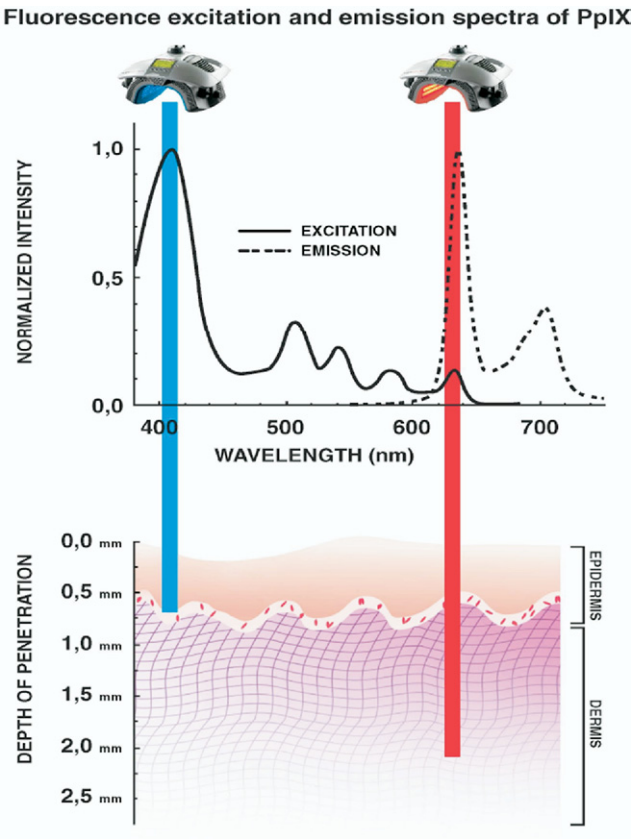

Figure 17 Dual-wavelength treatment head combines blue (405 nm) and red (630 nm) light to activate Protoporphyrin IX (PpIX).

enhance PDT clinical efficacy: progressive photoactivation of photosenstizers, large uniform beam profile, reduced procedural pain, and multiple wavelengths available.

Other Potential Applications

Rapidly emerging areas in light-based therapy include the treatment of cellulite and hair loss. Both conditions are very prevalent for which acceptable treatment options are lacking. Genetic, hormonal, and vascular factors have been implicated etiologies. Cellulite manifests as herniations of the subcutaneous fat into the dermis. It has been suggested that light therapy can improve the appearance of cellulite through the contracture and increase in deep dermal collagen, resulting in skin tightening and hypothetically providing a stronger dermo-subcuticular junction barrier to herniation.[51] A recent study demonstrated that cellulite responded positively to an anticellulite gel combined with red/NIR LED light exposure.[52] Light-based treatment (laser and LED) has also been shown to promote hair regrowth and increased hair tensile strength.[53] These effects are thought to be due to the dilation of blood vessels and increase in blood supply to hair follicles.

Table 4 Most frequent PDT Indications in Dermatology

Medical PDT	Cosmetic PDT
Actinic Keratosis (intended use)	Acne (inflammatory type)
Basal Cell Carcinoma	Sebaceous gland disorders
Bowens Disease	Oily skin
	Photodamage

Safety

LED is safe, nonthermal, nontoxic and noninvasive, and to date, no side effects have been reported in published literature. Caution must be emphasized especially for epileptic and photophobic patients especially if LEDs are pulsed.

Conclusion

We are now part of an exciting era in which complex subcellular reactions can actually be influenced favorably with the help of sophisticated configured LED ballistic photons to obtain excellent outcomes in a variety of skin conditions. Safer than sunlight, this new low level light therapy allows for the treatment of patients without pain, downtime or side effects. On the basis of sound photobiology principles, scientific and clinical studies conducted so far have shown promising results. The future seems limitless for LED therapy with innovative methods such as photoprophylaxis, photopreparation, and home use photoregulation although many challenges lie ahead. Future research should focus on investigating specific cell-signaling pathways involved to better understand the mechanisms at play, search for cellular activation threshold of targeted chromophores, as well as study its effectiveness in treating a variety of cutaneous problems as a stand alone application and/or complementary treatment modality or as one of the best PDT light source.

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