Chapter 12

Photobiological Basics and Clinical Indications of Phototherapy for Skin Rejuvenation

Robert Glen Calderhead and Yohei Tanaka

Additional information is available at the end of the chapter

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Abstract

Sunlight is essential to almost all forms of life for both light and heat. Plants need sunlight for photosynthesis, and man and animals alike need plants for many vital purposes. The sun featured many Millennia ago not only as a deity but also as a therapeutic source, so phototherapy is by no means a recent phenomenon. Niels Finsen's therapeutic arc lamp system in the early 1900s replaced the sun as a therapeutic source. Since then, many light sources have been successfully applied for phototherapy, with laser diodes and light-emitting diodes the most efficient. This chapter will explore what phototherapy is, and examine its important role in the fast-developing indication of skin rejuvenation. Systems used in phototherapy will be discussed and compared. Photobiological basics and light/tissue interaction underlying the process will be examined, together with the importance of treatment parameters. The wound healing process, on which skin rejuvenation rests, will be dissected with a discussion of the optimum wavelengths to photoactivate the skin cells, leading to the clinical indications in photorejuvenation.

Keywords: phototherapy, photobiomodulation, low level light therapy (LLLT), laser diodes (LDs), light-emitting diodes (LEDs), skin rejuvenation, wound healing, mitochondrion

1. Introduction

The authors believe that the first question we need to ask, and answer, is; what is 'photo-therapy'? The word is a compound derived from *phos*, *photos*, Greek for 'light' and from modern Latin *therapia*, from Greek *therapeia* 'healing,' from *therapeuein* 'minister to, treat medically.' In its broadest meaning, it is therefore the use of light to treat someone or

something. The modern accepted definition is 'the use of low incident levels of photon energy at a particular wavelength, targeting tissue to achieve a clinically useful local or systemic effect, but without the creation of heat (athermal) or damage (atraumatic).' We can compare that with 'photosurgery,' where heat and damage are deliberately created in tissue to achieve the desired clinical result.

Other terms have evolved which can be found in the literature. 'Photobiomodulation' was recently adopted as a MeSH (Medical Subject Headings) term, part of the US National Library of Medicine's controlled vocabulary thesaurus, which is used for indexing articles for MEDLINE, PubMed Central and so on. However, equally useful, and well-used in the literature, is the term 'low level light therapy,' with its acronym LLLT. This was born in 1988 with the publication by John Wiley and Sons of Chichester, UK, and authored by Ohshiro and Calderhead, of the pivotal and first volume on the clinical use of laser therapy, 'Low Level Laser Therapy; A Practical Introduction' [1]. The authors of the current chapter like to use both terms, with 'photobiomodulation' (PBM) being used to describe how low incident levels of photon intensity interact with the target at a cellular and subcellular level, and the term 'LLLT' being used to describe the therapeutic application and final result of PBM. Based on that, the reader will mostly see LLLT talked about in this chapter.

There are some other inaccurate terms which have been coined, mostly as marketing-driven language, which the reader may come across in the literature, including 'soft laser,' 'cold laser,' low power laser' and so on. One can see how a thermal reaction attracts the name 'cold laser,' but in actual fact, the lasers used for LLLT, either defocused surgical lasers or laser diodes, run very hot and require a lot of cooling, so they are not 'cold lasers.' 'Soft laser' is attractive as it gives the idea of a gently acting laser, but again, inappropriate scientifically speaking. It is true that many LLLT systems, laser- or LED-based, deliver output powers in milliwatts (mW), so it is tempting to call them 'low power' lasers. When we consider these misnomers, please realize that the most important consideration for both the scientist and the clinician is the **therapeutic reaction** in the tissue to the incident light that occurs at a level below the damage threshold of the target cells to give the PBM effect which delivers the LLLT-mediated therapeutic result: the system used to obtain this low level of reaction is, however, unimportant. A 50 W CO_2 laser is not a 'low power' laser, but if defocused to a 10 cm spot size, in the treatment of a nonresponsive leg ulcer, for example, the incident power density, or irradiance, is actually only 635 mW/cm^2, under 1 W/cm^2. On the other hand, an 830 nm 60 mW laser diode (LD)-LLLT system can be focused to a 50 μm spot on the retina by the human eye. The incident intensity in this case is in excess of 3000 W/cm^2. In the first example, the 'high level' laser, target tissue will not be heated at all: in other words, phototherapy. In the second example, the 'low level laser,' the retinal tissue will be severely damaged with ablation and vaporization: in other words, photosurgery. In short, the 'level' in LLLT has therefore got nothing to do with the device used to produce the incident light; it is, rather, the **level of reaction** in the target cells which must be below the cellular damage threshold. This is illustrated in **Figure 1** and the legend thereto.

In 1988, light-emitting diodes (LEDs) were available and were very bright, but they were drastically low-powered with an unstable and extremely divergent output. Furthermore,

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they emitted at a very broad waveband, so it was possible to source a 'red' LED, but it was very difficult to find a narrow-band 633 nm LED (**Figure 2**), essential when targeting wavelength-specific chromophores. 'Chromophore' is in general the term given to tissue, cellular or subcellular targets for incident light energy at specific wavelengths. The clinical efficacy of LEDs at that time was thus extremely limited. Ohshiro and Calderhead had to concentrate their research and clinical findings on laser sources, both to some extent defocused continuous wave (CW) surgical lasers, for example, 10,600 nm carbon dioxide (CO_2) and 1064 nm neodymium-yttrium aluminum garget (Nd:YAG) lasers, very low-output lasers such as the 632.8 nm helium neon (HeNe) laser, but especially on specific-use gallium aluminum arsenide (GaAlAs) laser diodes incorporated in laser therapy systems, developed by Ohshiro in conjunction with Matsushita Electronics, and emitting at

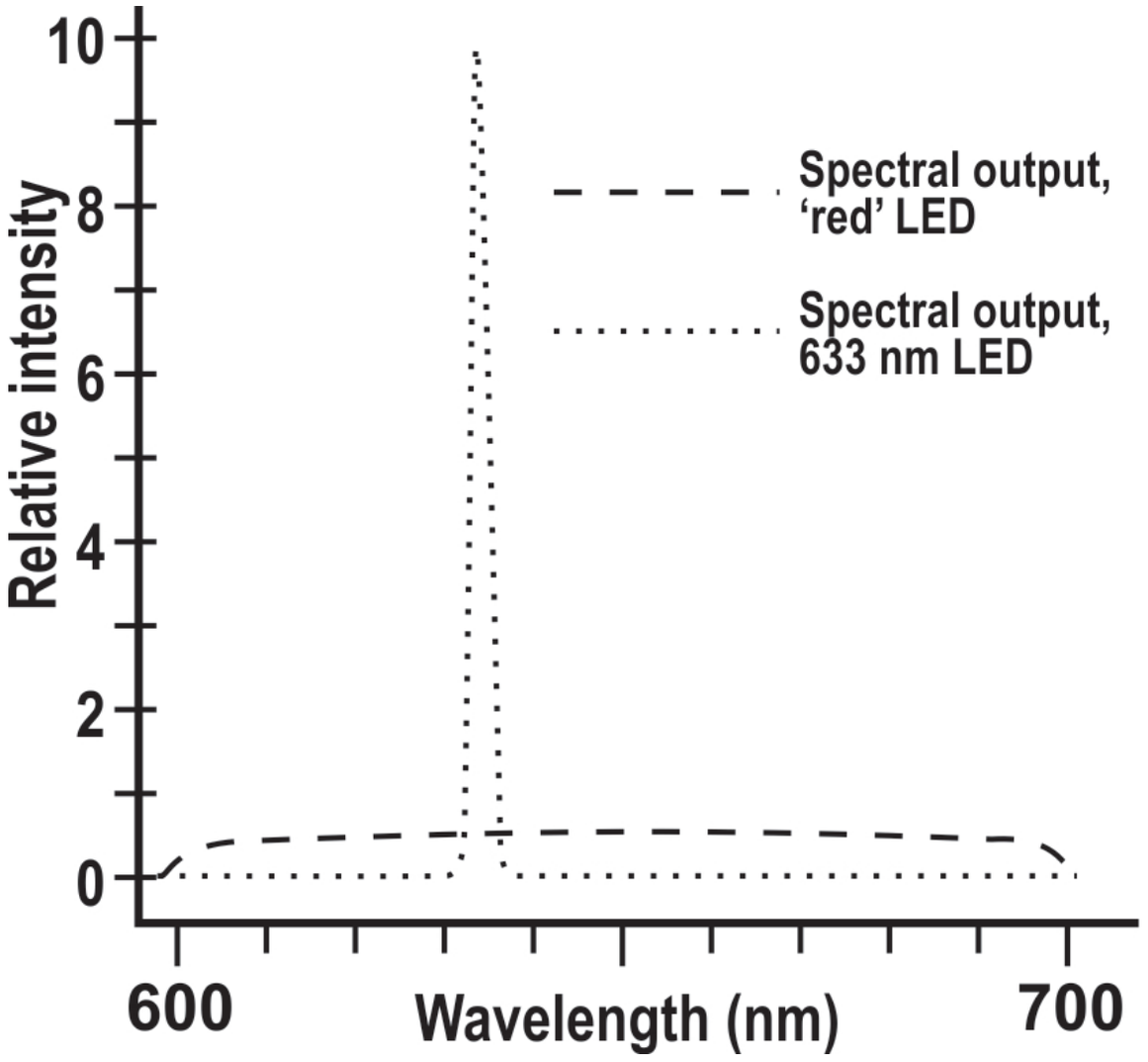

Figure 1. Difference in spectral distribution and relative output power (photon intensity) between an old-generation broad bandwidth red light-emitting diode (LED) and the new generation type, emitting in the example shown at 633 ± 5 nm. With the new generation LEDs, even though they are non-coherent, more than 90% of the photons are emitted at the rated wavelength with a very narrow bandwidth, conferring quasimonochromaticity on the beam.

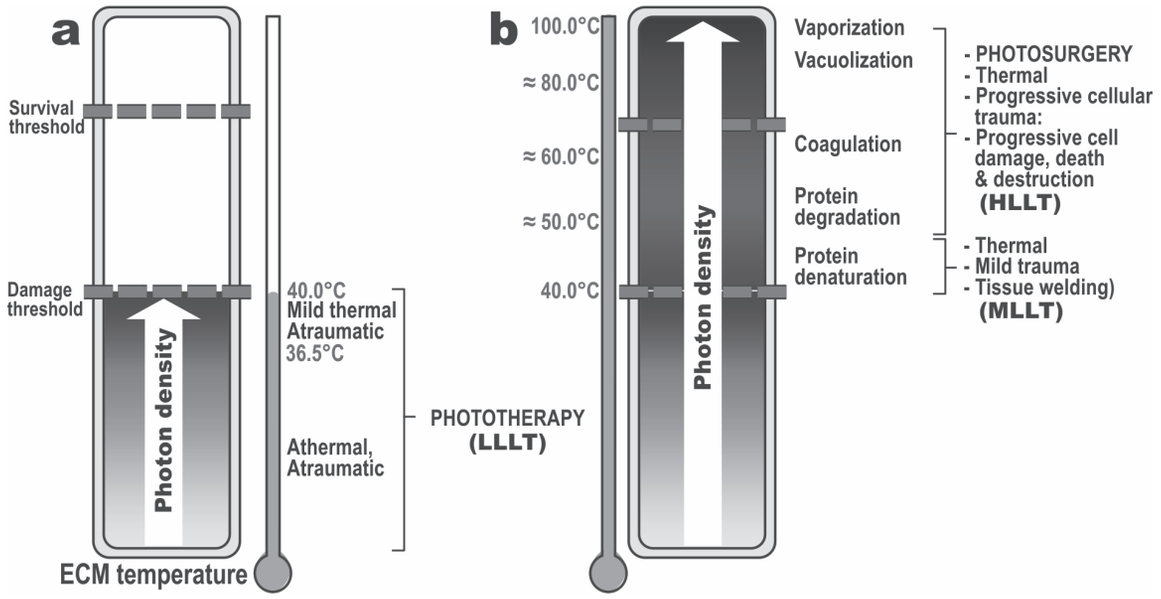

Figure 2. Schematic representation of a cell irradiated with two different irradiances, one low, one high, with the cell's arbitrary damage and survival thresholds indicated, showing changes in the extracellular matrix (ECM) temperature on the thermometer images. In (a), as the intensity of the absorbed incident photon energy increases, cellular activity is enhanced (photobiomodulated): the result of this is characterized as athermal and atraumatic LLLT. In (b), the continuing increase in incident photon intensity raises the level of reaction in the cell, and the internal temperature, beyond the damage threshold: although damaged, however, the cell is still alive. This is classed as mid level laser treatment (MLLT) following Ohshiro's classification system [Ohshiro T: A new effect-based classification of laser applications in surgery and medicine. Laser Ther, 1996; 8: 233–239]. As the temperatures in the target tissue rise to around 60°C, more intensive damage occurs as ECM collagen coagulation begins resulting in necrosis. Temperatures continue to rise with even higher intensities until tissue temperatures reach 100°C and the tissue is ablated with the vaporization of cellular and extracellular water. This is classed as high level laser treatment, HLLT, or photosurgery.

830 ± 3 nm. Low-level laser therapy thus became LLLT, but with the advent of clinically useful LEDs, as will be discussed in Section 3 below, low-level *laser* therapy became low level *light* therapy but with the acronym left as LLLT [2]. Please see Section 3 below for a detailed discussion of what lasers, laser diodes and light-emitting diodes are, and how they are used in LLLT.

2. Nothing new under the sun

LLLT is often thought of as 'new,' only some three decades old or so, and even the laser itself is not long over its half-century, having been first successfully demonstrated by Dr Theodore Maiman in 1960 [3]. The use of light in medicine dramatically precedes laser treatment by not just centuries, but by millennia. In Ancient Egyptian friezes from around 4000 BC, the sun is depicted as delivering rays to man, dogs and plants, with each ray ending in a little hand, 'patting' the target. In addition, in front of the face of the Pharaoh, the sun's ray ends in the ankh, the symbol for life (**Figure 3**). This illustrates the sun as the source of light and life. In addition, it is written in papyrus records that a herb similar to parsley was crushed and rubbed onto depigmented skin, probably a form of vitiligo,

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Figure 3. A portion of a frieze from Egypt's Tell el-Amarna, showing the Pharaoh Amenhotep IV in the rays of the sun (deified as Aten), where the 'patting' hands and the ankh symbol at the end of the rays can be clearly seen.

which in dark-skinned Ancient Egyptians must have been quite stigmatic. The area was then exposed to the full force of the sun, and the activation of the coumarins in the crushed parsley by the shortwave blue component of sunshine instigated a very strong photosensitive reaction resulting in severe sunburn. This was followed, at least partly, by postinflammatory hyperpigmentation, the much feared PIH following today's laser treatment, thus hopefully repigmenting the depigmented area.

Almost 2 millennia later, Hippocrates of Kos, the 'Father of Medicine,' was of the opinion that sunshine was one of the fuels of life, because his fellow Greeks, basking in Sunshine most of the year round, were of a much better and happier disposition than the barbarians to the north, which Hippocrates attributed to the fact that the northerners did not get enough sun.

Treatment using the sun is referred to as heliotherapy, from the Greek *Helios*, 'the sun.' However, the definition became a little broader, also involving exposure to specific wavebands, not necessarily from the sun. For many years, it was really only the sun that was powerful enough, and one of the treatments for 'melancholia' involved shutting the patient in a room with many windows to let in natural light, with red curtains to increase the ant-melancholic component of sunlight. One famous patient was King George III of the UK (1760–1820), who in his later years was believed to suffer from severe 'melancholia' and was shut in red-curtained rooms for treatment. It is now believed that he actually had a form of the blood disease porphyria, so this treatment probably exacerbated his condition and it is probably no wonder the poor monarch was known as 'Mad King George.'

At the turn of the twentieth century, man's dependence on the sun as a therapeutic light source was broken by the brilliant Danish scientist and clinician, Niels Finsen, who developed an artificial light source based on light energy emitted by an electric arc lamp, from which all heat had been filtered out. He was particularly successful for his work using this lamp on lupus vulgaris, for which he won the Nobel Prize for Medicine in 1903. Finsen did not enjoy

good health, and died in 1904. However, his vast interest in phototherapy inspired by his own experiments into the use of sunshine and particular filtered wavelengths for treating his own Niemann-Pick disease [4], lived on, and the Finsen Medal is awarded to outstanding contributors to phototherapy up to this day.

More recently, blue light phototherapy (460–490 nm) has been routinely used in the treatment of neonate hyperbilirubinemia, that is, jaundice in newborns, in whom the bilirubin in the bloodstream has not been sufficiently filtered out by the mother's placenta.

However, one of the largest examples of a breakthrough for a unique medical light source came in 1960, with the successful oscillation of the first ruby laser by Dr Theodore Maiman. The major difference between laser energy and other filtered light sources is the coherent nature of laser energy, comprising monochromaticity (one single wavelength), temporal and spatial phase of the photons in the laser beam, and the ability to collimate a laser beam so it can travel large distances with minimal divergence.

Maiman's laser was based on a ruby crystal, and as the laser medium usually gives its name to the laser, it became known as a ruby laser. In the 5 short years from 1660 to 1965, almost all of the lasers used today in surgery and medicine were swiftly developed, including the 1046 nm neodymium:YAG (and other members of the YAG family), the argon laser (488 and 514.5 nm), the 10,600 nm carbon dioxide (CO_2) laser and the helium neon (HeNe) laser. Visible red and near-infrared (near-IR) semiconductor (diode) lasers were also developed. The clinical potential of this unique pure light source was quickly realized, as was of course the military implications. Ophthalmology was the first field to explore the use of the laser for retinal disorders in the mid-60s, followed quickly by dermatology for removal of cutaneous lesions. Both these specialities used the selective but destructive photocoagulative power of the visible light lasers, particularly the green 514.5 nm band of the argon laser, and the 694.3 nm band of the ruby laser. The CO_2 laser became a powerful 'light scalpel' for comparatively blood-free and precise incisional, excisional and ablative indications in a variety of specialities, including oto-rhino-laryngologists, neurosurgeons and gynecologists.

However, an interesting anomaly was quickly noted by those using the CO_2 laser in particular, in that patients complained of less postoperative pain, shorter-lasting erythema and almost equally good wound healing following laser surgery as compared with the cold scalpel. It was thought at first that it was the heat generated by the laser that brought about this serendipitous occurrence, but it was gradually realized it was the 'L' component of laser that was the causative element … the light, not the heat. In 1969, Professor Endrè Mester practicing in Semmelweis University, Budapest, Hungary, published a pivotal paper in Hungarian on the use of the athermal and atraumatic 5 mW HeNe laser to treat over 1000 cases of severely recalcitrant crural ulcers, followed by an English overview in 1971 [5]. Astonishingly, he achieved a cure rate of better than 80%, with less than 2% of the patients not responding at all [6]. This was the birth of modern-age phototherapy, so that Prof Endre Mester is regarded rightly as the Father of Phototherapy. Finally, something new had been found under the sun after all.

Smaller and for-purpose laser sources were developed enabling the delivery of low incident levels of photon energy at wavelengths found useful in cellular biomodulation, in particular

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laser diodes. More recently, a new generation of light-emitting diode was developed by the Space Medicine Laboratory in the National Aeronautics and Space Administration (NASA) in the USA, and LEDs are taking their place as useful and verified phototherapy light sources. All of these will be explored in the next section.

3. Phototherapy devices

The main devices used in modern state-of-the-art phototherapy have already been mentioned in the previous sections. These are filtered polychromatic non-laser light sources, such as xenon lamps and (more rarely) incandescent lamps; defocused continuous wave surgical laser systems, such as the CO_2 and Nd:YAG laser, although more rarely these days; dedicated low-irradiance laser diode-based systems; and made-for-purpose LED-based systems.

3.1. Filtered lamps

There are a number of filtered non-laser light sources available for phototherapy practice, based on high-intensity xenon or other continuous-output gas-based lamps. These offer greater photon intensities than incandescent lamps and also require much less in the way of cooling. The filters are typically in the blue, yellow, red and near-infrared (near-IR) range, with bandwidths in tens of nanometers or less. The spectral output from these systems is heavy in the near-IR waveband and then tends to trail off through the visible to the UV-A band. The pattern of a typical spectral output is seen in **Figure 4**. The entire output power is spread over the entire emitted spectrum. There are two possible methods to filter the light to obtain the desired 'color.' A narrow bandwidth cut-off/cut-on filter for example, used to obtain a small 10–20 nm band at the desired wavelength, for example, around 633 nm which is a popular wavelength for activating cellular activity, as will be explained later. The reader will however appreciate that this will dramatically reduce the available photon intensity to give an irradiance of a very few mW/cm^2, given that the output through the entire visible waveband from 400 to 700 nm is comparatively low in the first place. Another method is to cut-off the unwanted shorter wavelengths. A cut-off filter rated at 630 nm will allow light energy all the way from the near-IR components up to around 630 nm, but will cut off all wavelengths shorter than that. The emitted light is still a polychromatic waveband and therefore not really suitable for any indication requiring wavelength selectivity for the target chromophore. However, many of those who use these lamps find them effective, but very long exposure times are needed to achieve the desired final dose in even a few joules per square centimeter (J/cm^2).

3.2. Defocused surgical lasers

When Ohshiro and Calderhead started researching the field of phototherapeutic indications in the late 1970s, the only dedicated low output laser system available was the helium neon (HeNe), delivering milliwatt ranges at 632.8 nm. The HeNe laser was the system used by Mester in his early papers, and it was these data from Mester that first encouraged Ohshiro

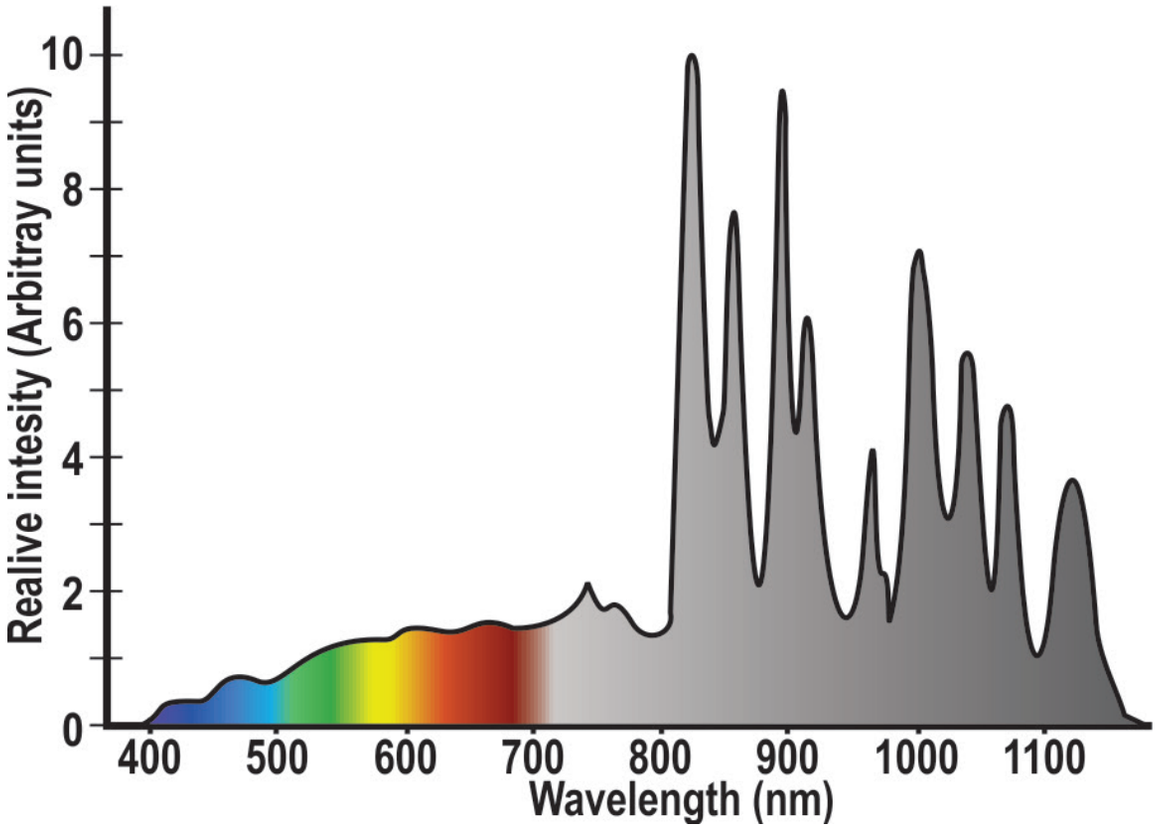

Figure 4. Approximate representation of the polychromatic spectral spread of a typical unfiltered continuous operation xenon lamp. The envelope of the lamp contains an ultraviolet filter to remove potentially harmful UV wavelengths. The majority of the output lies in the near-IR (from approximately 700 nm upwards). Some lamps apply the full spectrum in therapeutic practice. Others use cut-off filters to cut out the unwanted shorter wavelengths. However, all longer wavelengths are still delivered up to the cut-off point, that is, still polychromatic light, unless a cut-on filter is also applied to remove the unwanted longer wavelengths.

and then Calderhead to investigate the potential of the use of low incident levels of light energy for first pain attenuation, and then wound healing. Ohshiro had established a pain clinic in his Tokyo Clinic, and, in addition to the HeNe laser, he first looked at the 1064 nm wavelength of the continuous wave Nd:YAG laser, chosen because of its deeper penetration than 632.8 nm, and comparatively low absorption in melanin and blood. In addition, the HeNe laser tended to be rather low-powered, necessitating longer treatment times to achieve good results.

By defocusing the usual output of his CW Nd:YAG laser, delivered by a selectable variety of larger spot sizes, extremely practical and very low incident irradiances of less than 1 W/cm^2 could be delivered with good efficacy for pain attenuation of both acute and chronic pain. To compare the Nd:YAG with the HeNe, to produce a useful incident dose or energy density of 15 J/cm^2, an approximately 20 s exposure with the Nd:YAG was needed: over 15 min treatment was needed to get the same dose with a 15 mW/cm^2 HeNe.

The defocused CO_2 laser as a pain attenuation and wound healing device also attracted some attention in the late 1980s and early 1990s, but like the Nd:YAG system, they are large and expensive devices, and need a great deal of ancillary equipment and adaptation for regular

use as phototherapy systems. Furthermore, technology advanced rapidly so that CW Nd:YAG lasers were quickly supplanted by more adaptable and versatile Q-switched and long-pulsed systems, and CW CO_2 lasers lost favor in the face of the much more precise superpulsed and ultrapulsed systems, followed by the fractionated approach. Having said that, small CW CO_2 lasers still occasionally attract attention in the literature for wound healing applications [7], although there have been no reports for defocused CO_2 laser systems for skin rejuvenation.

3.3. Laser diode-based therapeutic systems

As mentioned, Ohshiro's Nd:YAG laser was a large and expensive piece of equipment, so he worked with an electronics company in Tokyo to develop a much smaller, dedicated semiconductor-based laser therapy system for phototherapy. First tried was the gallium arsenide (GaAs) diode, but it could not be run at continuous wave without severely overheating, so finally the gallium aluminum arsenide diode was developed and found to be ideal. The first system to be trialled was a battery-operated 15 mW GaAlAs system, delivering around 500 mW/cm^2, and a controlled study on pain attenuation was published in 1981 comparing the efficacy of the GaAlAs diode system with the defocused CW Nd:YAG system in pain entity and age-matched patients at the same dose. Despite its small size, the diode laser proved to be at least as effective as the Nd:YAG system [8].

The first commercial laser therapy system was jointly developed by Ohshiro and Matsushita Electronics (National Panasonic,) and launched as the first of the 830 nm Panalas® systems in 1981. Ohshiro did not stop thinking about improving both systems and treatment techniques, as well as looking at underlying mechanisms. In 1988, Ohshiro launched a new GaAlAs diode laser based system, delivering 60 mW, the OhLase-3D1®, and that has evolved to the present day. Also in 1988, Ohshiro and Calderhead put all of their thoughts together in having the volume already mentioned above, 'Low-Level Laser Therapy: A Practical Introduction' published by John Wiley and Sons. In the same year, the journal *Laser Therapy* was announced by John Wiley of Chichester, and the International Laser Therapy Association (ILTA) was formed, all championing Low-Level Laser Therapy. LLLT was well and truly born and has continued to grow and develop up till today. The agreed MeSH term may be photobiomodulation, but if 'LLLT' is entered into PubMed as a search term, the reader will find over 4400 entries! A very large percentage of them are actually on clinical or research facets of LLLT and phototherapy, rather than any other laser-associated aspect.

LLLT systems based on laser diodes (LDs) remain extremely popular and are manufactured by a number of reputable companies worldwide. Some of them have USA FDA and other national regulatory body clearances. Because of the beam geometry of LD chips, the treatment area is usually punctal in nature with a spot sizes ranging from less than 1 mm^2 to defocused systems offering 1 cm^2 or so, but not a lot larger than that. Treatment techniques are therefore based on point by point approaches. To cover a larger area, quite useful for treating larger wounds, for example, an array of LDs could be considered. In reality, GaAlAs diodes run quite hot, so good heat sink design is need to keep even single LDs running cool. Too much heat in the chip will cause a change in the rated wavelength, and that would not meet the criterion of precisely targeting wavelength-dependent chromophores. It is therefore difficult

to run arrays of LDs without some form of aggressive cooling. Light-emitting diodes (LEDs), on the other hand, do not run so hot and are much easier to cool than LDs. For such planar arrays, LEDs are the answer, which leads us into the next subsection.

3.3.1. Enter the light-emitting diode

When LLLT was dependent on LDs for the light source, as in the many publications appearing in the late 1980s and early 1990s, LEDs were commercially available. However, although they were certainly cheap and cheerful, ideal for indicator lamps, traffic signals and Christmas trees, they were on the other hand totally inappropriate for medical application because of their low and unstable output powers, extreme divergence and wide bandwidths. As said already, we could source red LEDs, but not 633 nm LEDs (*cf* **Figure 2** above and legend). Very expensive superluminescent diodes (SLEDs) were available offering almost laser-like bandwidths, but even these proved significantly inferior to LD-LLLT systems when compared side by side in controlled animal studies and could still only be applied point by point [9]. All this changed in 1988, however, when Professor Harry Whelan and his NASA Space Medicine Colleagues succeeded in developing what became known as the 'NASA LED' [10]. These LEDs were many-fold more powerful than their older generation cousins, typically 5 orders of magnitude more powerful in fact; they had much narrower divergence offering high photon intensities; they were remarkably stable; and probably the most important development, they were quasimonochromatic, offering spectral outputs with more than 95% of the photons at the rated wavelength. In other words, although they were still noncoherent, non-laser light sources, they offered laser-like precision for targeting wavelength-specific chromophores in tissue, cellular and subcellular targets. Finally, a real breakthrough had been made to provide a practical, clinically useful new light source for phototherapy, capable of being mounted in large area planar arrays. Whelan and his colleagues went on in the following 2 years to demonstrate that their new near-IR wavelength LEDs were clinically viable in an in vivo wound healing model [11]. In the first few years of the New Millennium serious and scientifically proven, LED-based systems were developed first for hands-free large area PDT for non-melanoma skin cancers using the 633 nm wavelength [12], followed by LED-only acne treatment using the combination of the visible blue 415 and 633 nm wavelengths [13], skin rejuvenation and accompanying histochemical and ultrastructural extracellular matrix changes with 830 nm near-IR and 633 nm wavelengths [14], sports medicine and pain attenuation with the 830 nm wavelength [15], and so on. LED-LLLT was well and truly demonstrated to work, and work well. All of the above wavelengths, with the exception of the 415 nm wavelength, fell within Karu's phototherapeutic window for effective cellular photoactivation with visible and near infrared lights sources, laser or non-laser [16]. Thus, it is when the reader examines these 4400-plus PubMed results for LLLT, that he or she will find more and more very serious papers demonstrating a growing solid body of evidence for both clinical and basic research into LED-LLLT among the laser-based literature.

Figure 5 schematically illustrates the differences in the patterns of emission from lasers, laser diodes, light-emitting diodes and filtered non-coherent lamps as used in phototherapeutic indications, including the rejuvenation of photo- and chronologically aged skin. **Figure 6** shows examples of commercially available laser diode-based, lamp-based and light-emitting diode-based systems used worldwide for LLLT.

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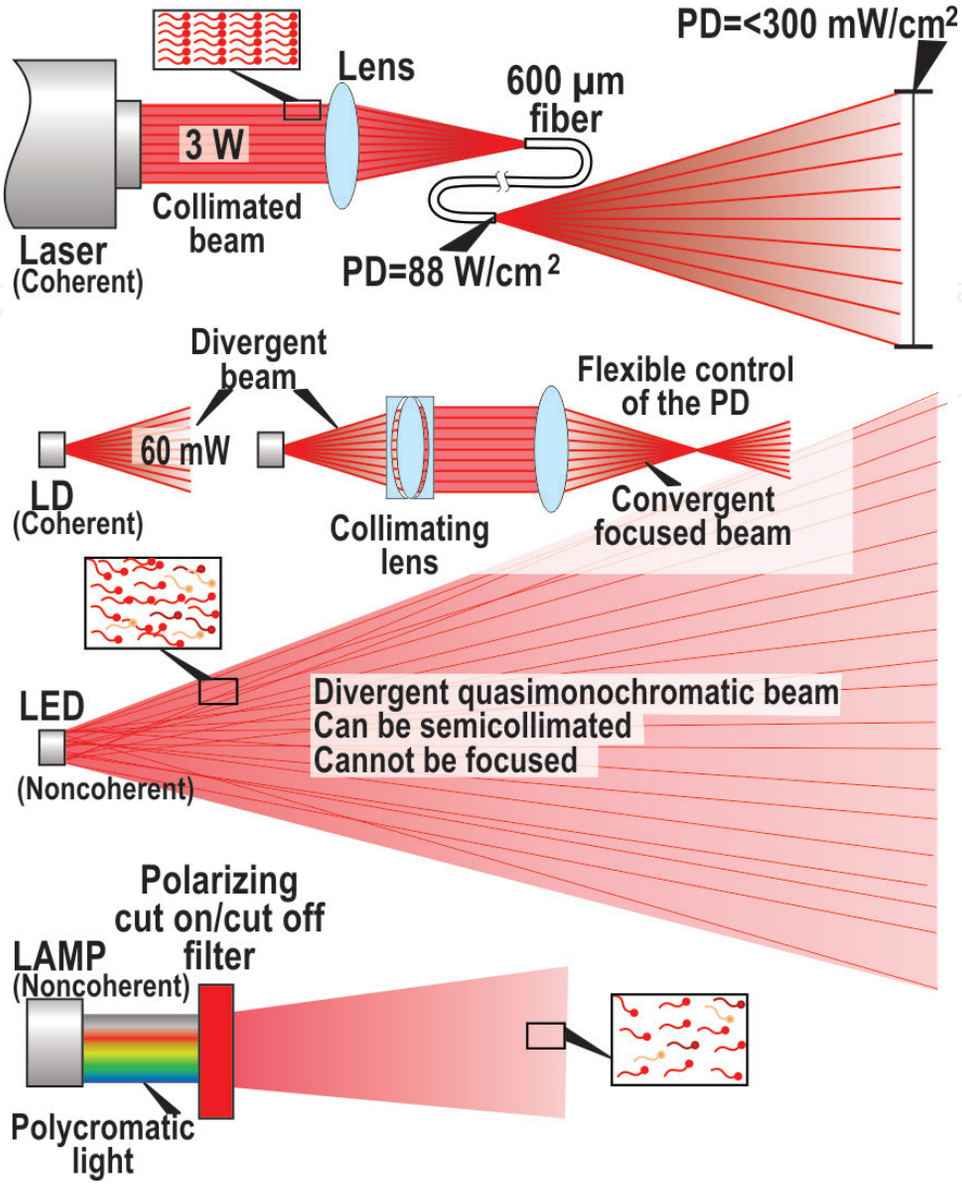

Figure 5. LLLT sources compared. Although not used these days, of historical interest is the defocused CW 1064 nm Nd:YAG. The optimum method was to couple the beam from the laser into an optical fiber. This could be any length, so the laser could be well away from the treatment room, and even several treatment rooms could be serviced with the one laser. The beam emerging from the distal end of the fiber is divergent and multimode, giving a uniform intensity across the beam. By using different beam sizes, the desired irradiance could be selected. Laser diodes (LDs) by their nature emit a defocused elliptical beam. The angle of divergence is high so it is normal to have the beam collimated (just like the ubiquitous laser pointer), because an LD is still a laser. The beam can then be focused within the handpiece of the system, so that either a convergent beam or a divergent beam can be used to give the ideal irradiance at the tissue, depending on the distance between the lens and the target tissue. The divergent beam is inherently safer. LEDs are also highly divergent, but emit noncoherent light. The better quality new generation LEDs are, however, quasimonochromatic, emitting all of their photon energy more or less at the rated wavelength, and no color filter is required. They can be semicollimated to decrease the angle of divergence and increase the irradiance, but they cannot be perfectly focused like a laser. They can be mounted in large planar arrays to irradiate a large area of tissue in a hands-free manner. The polychromatic lamp type system requires a filter to filter out (cut off) the unrequired shorter wavelengths, leaving only the wavelength wanted for treatment. To make this light output as similar as possible to an LED, the filter, however, needs to be very precise (i.e., narrow band), and it needs to have a cut on element to remove the unwanted longer heat-producing IR light. This means that the photon intensity at tissue is rather low, and longer exposures are required to give a reasonable dose.

Figure 6. Examples of current phototherapy systems. Top left: laser diode (LD)-LLLT systems. The upper example shows a pen-type probe, near-IR system (Thor Probe, Thor Lasers, UK). This is connected a mains-operated control console. The lower example is a battery-operated 830 nm LD-LLLT system (OhLase-3D1 HT1, JMLL, Japan). In both cases, the treated area is very small, and the systems are used in a punctal fashion in contact mode, separating the treated points by a few millimeters or so. Top right: filtered polychromatic filtered lamp LLLT system (Bioptron, Switzerland). A larger area of tissue can be treated in a hands-free manner. The yellow cut-off filter is illustrated here. Bottom: free-standing 830 nm LED-LLLT system (HEALITE II, Lutronic, Korea). The large treatment head can be adjusted to treat anybody contour from the back, to the face, to an arm or leg, again in a hands-free manner.

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4. Wavelength: the prime parameter in phototherapy

The first law of photobiology states that absorption must occur before there can be any reaction. This might appear to be self-evident, but what actually governs absorption of light in a target, and indeed, what decides the chromophore, or target, for that light? The reader would be excused for thinking it is the output power of the light source, but it is in fact the wavelength. This is particularly critical in phototherapy. Photons travel through space in straight lines, but with a sinusoidal waveform. Wavelength is a measurement of how far a photon will travel in one complete cycle, and is measured in nanometers (nm), one billionth of a meter, or fractions and multiples thereof. Light energy comprises a very small section of the very extensive electromagnetic spectrum which runs from ultrashort cosmic rays in femtometers and below all the way to wavelengths of kilometers for electrical energy (**Figure 7**). Knowing the wavelength of an LLLT system lets us understand if we can see the light it emits or not (visible or invisible light), and if we can see it, what color it is.

Figure 8 is a composite of three main concepts centered around wavelength. In the central part of **Figure 8**, the visible spectrum (400–700 nm) and a portion of the invisible near-IR spectrum can be seen (700–1010 nm), as part of a photospectrographic data set captured from polychromatic 'white' light which had been shone through a human hand in vivo [17]. The wavelength is indicated on the x-axis in nanometers (nm), and the optical density (OD) ranges from 3 to 8.5 (logarithmic units) on the y-axis. The higher the OD, the more dense the target is to specific wavelengths of the incident light. The upper portion of **Figure 8** schematically represents the relative penetration of selected wavelengths into skin, based on the OD findings of the central portion. The shorter wavelength visible light at blue (415 nm), green (532 nm) and yellow (590 nm) offers poor penetration into skin in vivo. From 590 nm yellow, it is only 43 nm to 633 nm red, but penetration increases by almost 3.5 orders of magnitude, more than 1000 times better than yellow. That is a critical difference in penetration which is highly wavelength dependent. Deepest penetration is achieved around 830 nm in the near infrared. In general, as wavelength increases, tissue penetration also increases.

The lower section of **Figure 8** offers an explanation as to why these wavelength-mediated differences in penetration exist. Here are shown the absorption spectra of three of the biological chromophores in living skin: melanin normally in the epidermis; blood (oxy- and deoxyhemoglobin) in the dermis and water throughout the skin. From this, the strong affinity of the shorter visible wavelengths for blood and melanin precludes light at these wavelengths reaching much beyond the superficial papillary dermis. If the target for the phototherapy is, for example, fibroblasts, then these wavelengths will not reach the target … no absorption, no reaction. Red light at 633 nm penetrates much better because it has much less absorption in both blood and melanin, and even less so at 830 nm. Beyond 830 nm, water starts to become of interest as a chromophore, and penetration into tissue starts to fall off quite rapidly after 1000 nm. This is why, apart from the now more or less extinct defocused 1064 nm beam of the CW Nd:YAG or the very occasional use of defocused CW CO_2 energy, no phototherapeutic light source is reported with a wavelength over 1000 nm.

The blue 415 nm is at the peak of the Soret band and is not only highly absorbed in melanin and blood, and it is right at the peak of the absorption spectrum of porphyrin. This wavelength is

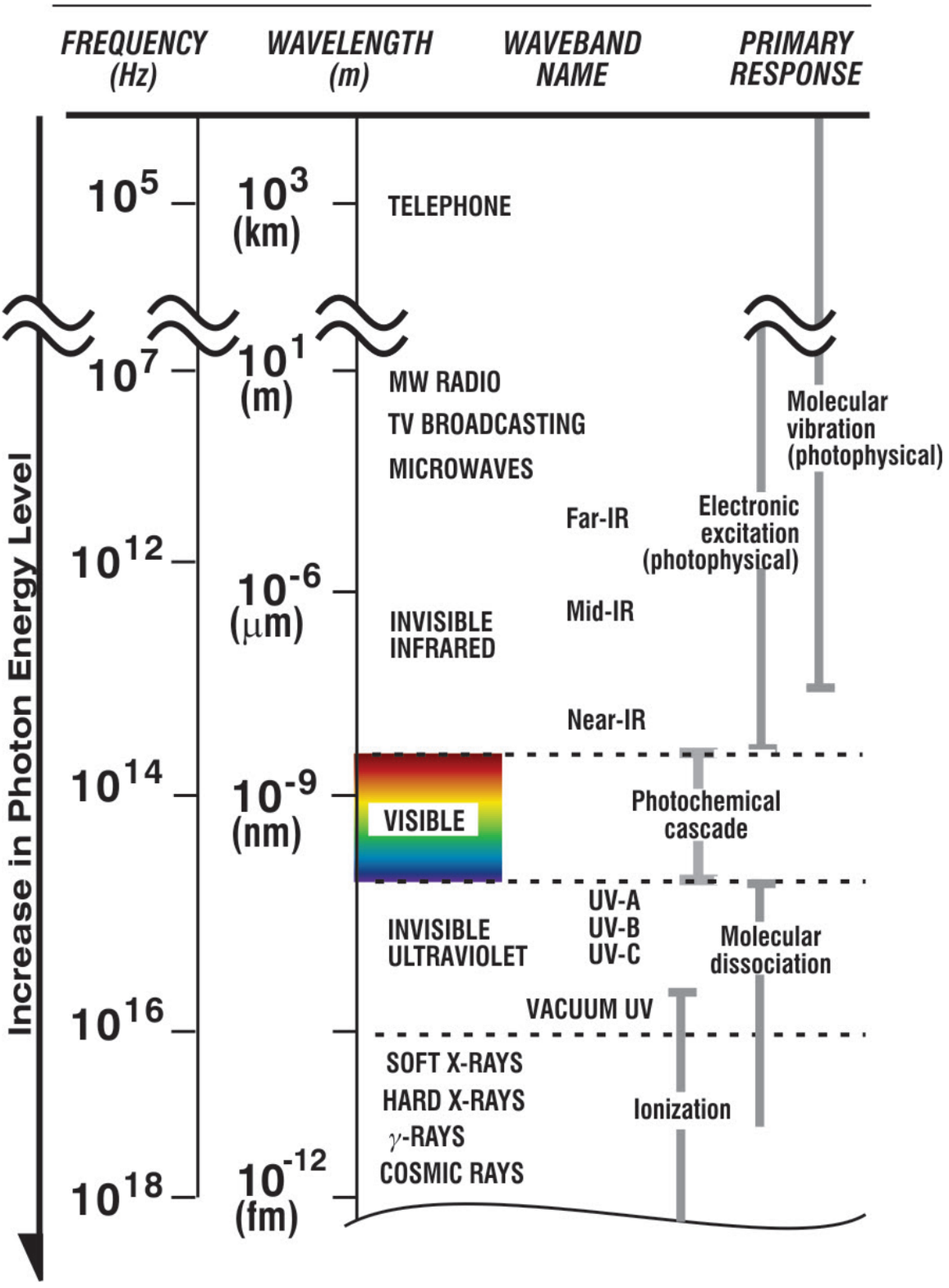

Figure 7. The electromagnetic spectrum (EM) covers a vast range of energy radiation types extending from the shortest cosmic waves (wavelengths measured in femtometers [fm] or shorter), through ultraviolet and visible radiation (nm), infrared radiation (μm) to the broadcasting waveband (m) and even mains current and wired telephone transmission (km).

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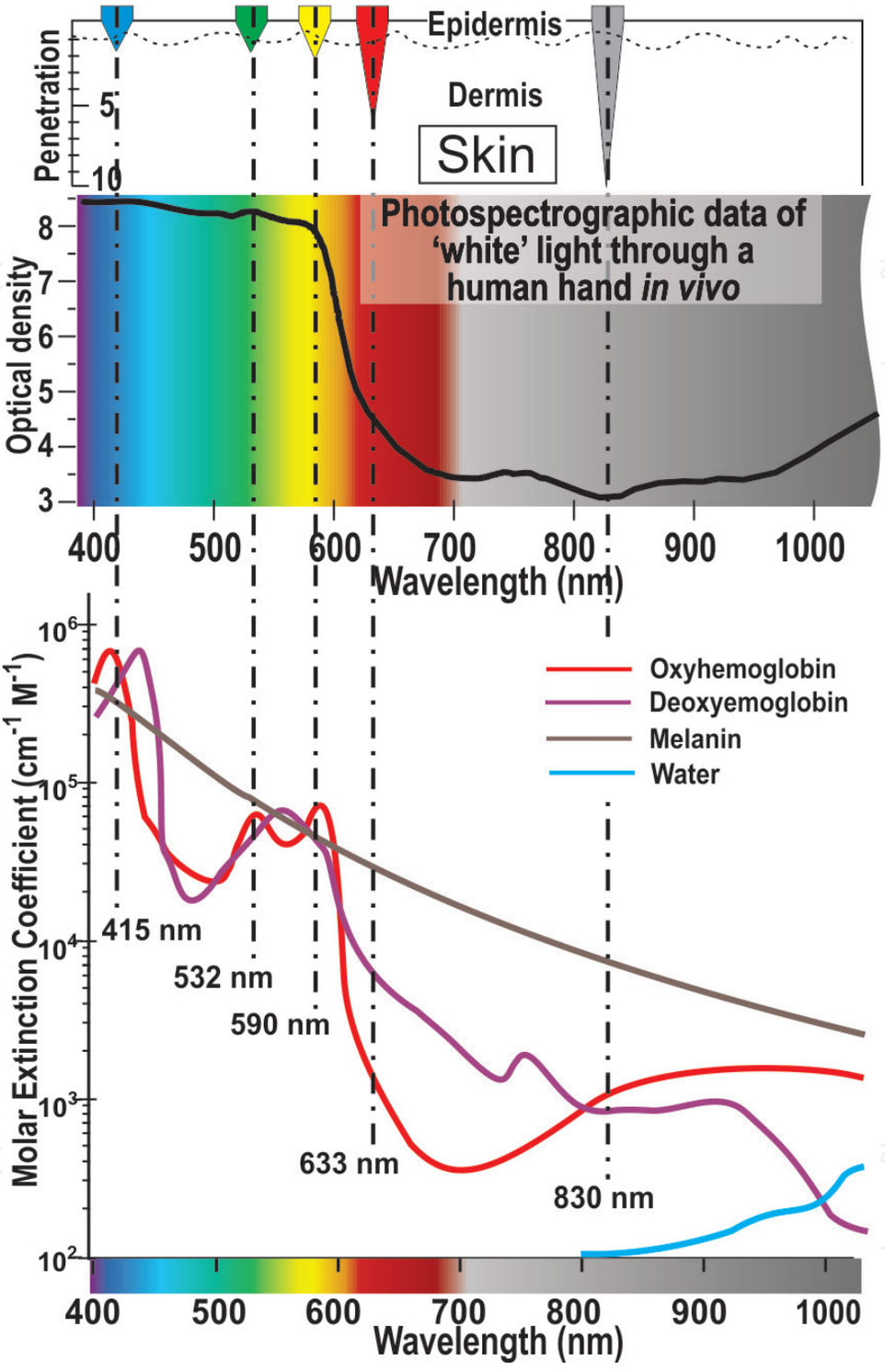

Figure 8. Several aspects illustrating the importance of wavelength in phototherapy. The central image shows photospectrometric data measured from penetration through a human hand in vivo. Based on the computer-derived trace on that part of the figure, the upper section illustrates relative penetration of selected wavelengths into the skin. Coupled with these, the lower section shows the absorption spectra of some biological chromophores, or targets, namely melanin, blood and water. Note the wavelength selectivity in these chromophores, and how that helps to determine the depth of penetration of different wavelengths into a living target as well as determining the target itself. Please see the text for further details.

popular as part of combination blue and red light (or near-IR) treatment of active inflammatory acne vulgaris [18]. The causative bacterium, *Propionibacterium acnes*, is known to harbor protoporphyrin IX (PpIX) and coproporphyrin III when it is active. By selectively targeting these porphyrins with light at 415 nm through endogenous photodynamic therapy (PDT), reactive oxygen species are rapidly generated within the *P. acnes*, and they are forced into apoptosis through oxidative stress [19]. With *P. acnes* damaged and destroyed, the inflammatory cycle of acne vulgaris is partially broken. No other wavelength is therefore appropriate for targeting the endogenous porphyrins in *P. acnes*. However, acne is recognized as a multifactorial disease with a strong inflammatory component, only partly associated with *P. acnes*, and both visible red (e.g., 633 nm) and near-IR light (e.g., 830 nm) have powerful antiinflammatory properties [20, 21]. If either of these wavelength therefore follows the 415 nm treatment some 48 h later, the remaining causes of the inflammation are targeted with deep penetration into the dermis, and an all-round approach to treating acne with blue and red (or infrared) light has been developed and well-reported [13, 22]. Here is an example where only a particular wavelength, or wavelengths, can affect a particular target, and in a multi-targeted disease a combination of wavelengths is therefore effective.

It can thus be stated that, in LLLT, wavelength governs both absorption, and penetration. However there is one other important factor which is connected with these two and that is intensity, consider **Figure 9a**. Two wavelength-specific targets exist in the upper dermis. An LLLT system, but with the incorrect wavelength, tries to treat target 1. The wavelength is incorrect, there is no absorption, and therefore, there is no reaction. Target 2 is irradiated with the correct wavelength, absorption occurs, and a reaction is successfully elicited. This is what the discussion above has been saying. Now look at **Figure 9b**: the targets are the same, but they are in the deeper dermis. An LLLT system irradiates the area over target 3, and the operator knows that the wavelength is correct. Unfortunately, there is insufficient photon intensity to get enough photons down through the dermis to the target: there is no absorption, hence no reaction. The operator therefore takes an LLLT system with a higher photon intensity and treats the area. The photons now reach the target 4 and are absorbed, and the desired reaction is achieved. So, although wavelength is key, if there is insufficient photon intensity from the light source giving low irradiance, or a too high angle of divergence diluting the irradiance, then the photon intensity at the target will not be sufficient to get the optimum reaction. In theory, one photon can activate one cell, but in practice, the cell needs to be bombarded with several photons, that is, multiphoton absorption, before the optimum level of reaction is reached. Sometimes having the right wavelength is just not enough.

This problem is associated more with LEDs than with LDs, because the photon intensity of LDs is many times higher than LEDs, given that LDs are coherent with all photons exactly the same wavelength, and in phase, exactly in step in temporally and spatially, like a regiment of identically clad soldiers marching in perfect time. The disadvantage of LD-LLLT is that it needs to be applied manually, point by point, in the contact mode, whereas LED systems have planar arrays which can cover large areas. Another way to ensure that as large a volume of tissue is involved is to maximize the scattering effect in tissue, and wavelength determines how well the light will scatter. Longer wavelengths scatter much better than shorter ones, in other words 830 nm scatters better than 640 which scatters better than 530 nm: **Figure 10** compares the penetration and scattering power of a 530 laser pointer (5 mW) with that of a

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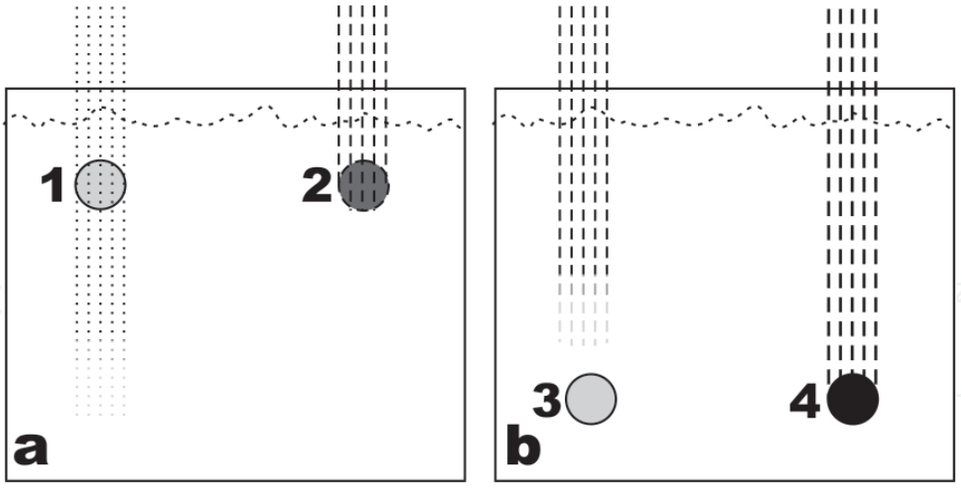

Figure 9. (a) The wavelength of light irradiating target 1 is inappropriate resulting in no absorption, therefore no reaction. On the other hand, target 2 is irradiated with an appropriate wavelength, and absorption occurs with a reaction. (b) The same targets are now deeper in the dermis. The same light source is used again, but the intensity is insufficient so not enough photons reach the target: no reaction. When the same light source is used at a higher intensity, the target is reached and a reaction is achieved.

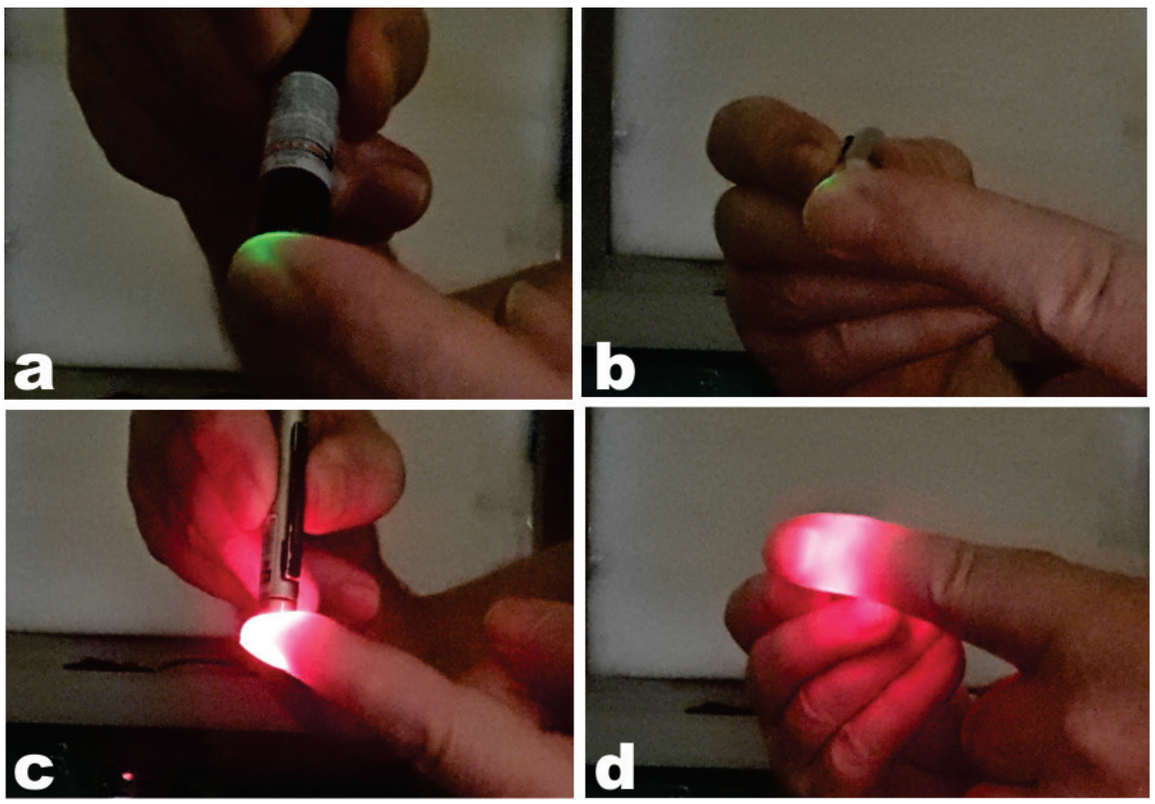

Figure 10. A green 530 nm 5 mW laser pointer compared with a red 640 nm 3 mW pointer. (a and b). Proof that green light, even laser energy, at 530 nm from a laser pointer neither penetrates deeply into a living finger nor does it scatter, even when placed near the thinner part of the fingertip. (c and d) On the other hand, the less powerful red laser light penetrates right through the finger and out the other side, even when placed a little bit further down the finger where there is bone as well (d). Note the scattering effect, transilluminating the whole lateral width of the finger. Note also the red light seen on the hand holding the pointer: that is illustrating powerful backscatter from the irradiated tissue.

640 nm laser pointer (3 mW). That figure illustrates very well that red light around 633 nm is capable of penetrating into living tissue deeper than 1 cm … the thickness of the author's (RGC) finger!

Scattering occurs when photons encounter different optical characteristics in the target and are pushed off their straight trajectory. They can be scattered forwards, laterally and backwards: actually, with enough photon intensity, it's a mixture of all three, and it is an excellent way to ensure that the largest possible area of tissue is affected by the incident light. In the case of laser energy, it is well understood that larger spot sizes minimize lateral and back scattering outside of the beam path in tissue and therefore get deeper absorption with more photons. Of course, the intrinsic absorption depth depends above everything else on the wavelength, but we can make science work for us to maximize that depth, and ensure multiphoton absorption in the target.

5. Light and tissue interaction

Unlike the situation in laser surgery, at the incident photon intensities associated with LLLT, there is no photothermally mediated effect. All effects take place at athermal, or almost athermal levels, and with no damage to cells or their organelles, or surrounding tissue. The key to the efficacy of LLLT in redressing the skin damage cause by the combination of photoaging and chronological aging lies in how the target cells, and other tissues, use the energy which is delivered to them by the incident photons, following absorption. As stressed in the previous section, there has to be absorption so that the little packet of energy carried by each photon is passed on to the energy pool of the target cells. The interaction between incident light and tissue is therefore at both the subcellular, cellular and tissue levels.

It was mentioned in passing in the previous section on wavelength that visible light and near-IR light actually have different primary mechanisms of action when absorption occurs in the target tissues. On referring back to **Figure 7**, there is a column titled 'Primary response.' For neither visible nor infrared light is photobiomodulation actually the primary response, but is rather the end result of the effect following the intermediate reactions associated with the primary response. As Karu has postulated [16], the basic stages of the LLLT-mediated reaction can be described as follows:

- Absorption (photoreception) occurs (by necessity … no absorption, no reaction) leading to the primary response.
- This induces the second stage, signal transduction and amplification.
- And leads to the ultimate stage of photobiomodulation (the photoresponse).

5.1. Visible light: primary photochemical reaction

For visible light, the primary response is photochemical in nature, with the main photoreceptor being the end terminal enzyme of the respiratory chain of the cellular mitochondria,

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cytochrome c oxidase, CCO, well demonstrated by Karu [16, 23]. The mitochondrion is arguably the most essential organelle for the cell, indeed for the entire organism, as its function is to act as the energy factory for the cell and surrounding tissue. The nucleus may be the heart and soul of a cell, but hearts and souls need energy to function, and that's the task of the mitochondrion. Mitochondrial CCO has an action spectrum which runs from the yellow through the red waveband (580–700 nm) with the peak around 630–635 nm. This made the helium neon (HeNe) laser at 632.8 nm an ideal phototherapy research tool, and almost all of Karu's and others' research on photobiomodulation in the 1970s to the end of the 1990s centered on the HeNe as the light source of choice. Now with quasimonochromatic LEDs available as a clinically useful light source, photoeffects of the 633 nm LED have also been well reported. The energy released by absorption of the incident photons in the CCO starts a photochemical cascade, resulting in the creation of adenosine triphosphate (ATP), simply described as follows: ATP synthase (ATPsy) with the coenzyme nicotinamide adenine dinucleotide (NAD) is triggered to combine inorganic phosphate (Pi) with adenosine diphosphate (ADP) to synthesize adenosine triphosphate (ATP). ATP is the fuel of the cell, and the organism. As part of this process, minute amounts of nitric oxide (NO) are released, NO being a powerful signaling compound with beneficial properties in tissues. In addition, calcium ions (Ca^{2+}) and protons (H^{+}) are also released into the cytosol, two very powerful additional signaling compounds. As the levels of these signaling compounds increase in the cytosol, the membrane transport mechanisms, in particular the sodium-potassium pump ($Na^{+}K^{+}$-ATPase), are stimulated into action resulting in interexchange of materials between the cellular cytosol and the extracellular fluid. At the same time, the message reaches the nucleus, and the final stage of photoresponse is reached: the cell is fully photoactivated. Photoactivated cells, if damaged or compromised, can repair themselves or be repaired; photoaged skin and wounded skin are examples of tissues with damaged or compromised cells. If the cells have a function to perform, for example, macrophages or fibroblasts, they will perform their job better and faster. If more of the cells are required, mitosis will be stimulated, or others will be recruited in. One, two or all three of these things can happen in photoactivated tissues. It is a powerful process.

On the other hand, light energy at 830 nm in the near-IR induces a completely different primary response, which is photophysical in nature rather than photochemical, as pointed out by Smith [2]. This comprises vibrational and rotational changes in the electrons of the atoms making up the molecules of the membranes of the target cells. This instantly activates the membrane transport mechanisms and intra- and extracellular exchange begins. The cellular energy requirements for this are very high, so the mitochondria are swiftly co-opted into action: at the same time, not only the cellular membranes, but also the membranes of the cellular organelles including the mitochondria are activated by near-IR wavelengths, so a secondary chemical ATP cascade is swiftly induced. Rather than being the primary photoresponse as with visible light, it therefore becomes part of the second stage of signal transduction and amplification with near-IR light, but the end result is exactly the same as for visible light: a photoactivated cell. The same three possible responses exist: repair, functional improvement or cell recruitment. Regarding the particularly interesting effect of LLLT at both visible and near-IR wavelengths on compromised or damaged cells, they

actually and surprisingly respond many times better to LLLT than normal cells do, as has been commented on by many researchers [24]. As the cells found in photoaged skin are in various states of damage and are compromised to at least some degree, this aspect of the reaction to LLLT is of great interest in the photorejuvenation process in all affected cell types and extracellular matrix components. **Figure 11** schematically summarizes the effect of visible and near-IR LLLT on target cells. **Figure 12** takes us beyond the photoresponse, the endpoint achieved by both visible and near-IR light, and with a flow chart takes us through the various processes and complex interactions which have already been elicited and which lead to wound healing, as dealt with in a later section together with the antiinflammatory response [25]. The chart also shows the steps to pain attenuation which is also something that LLLT can achieve, but out with the scope of this chapter although it may be of interest to the reader.

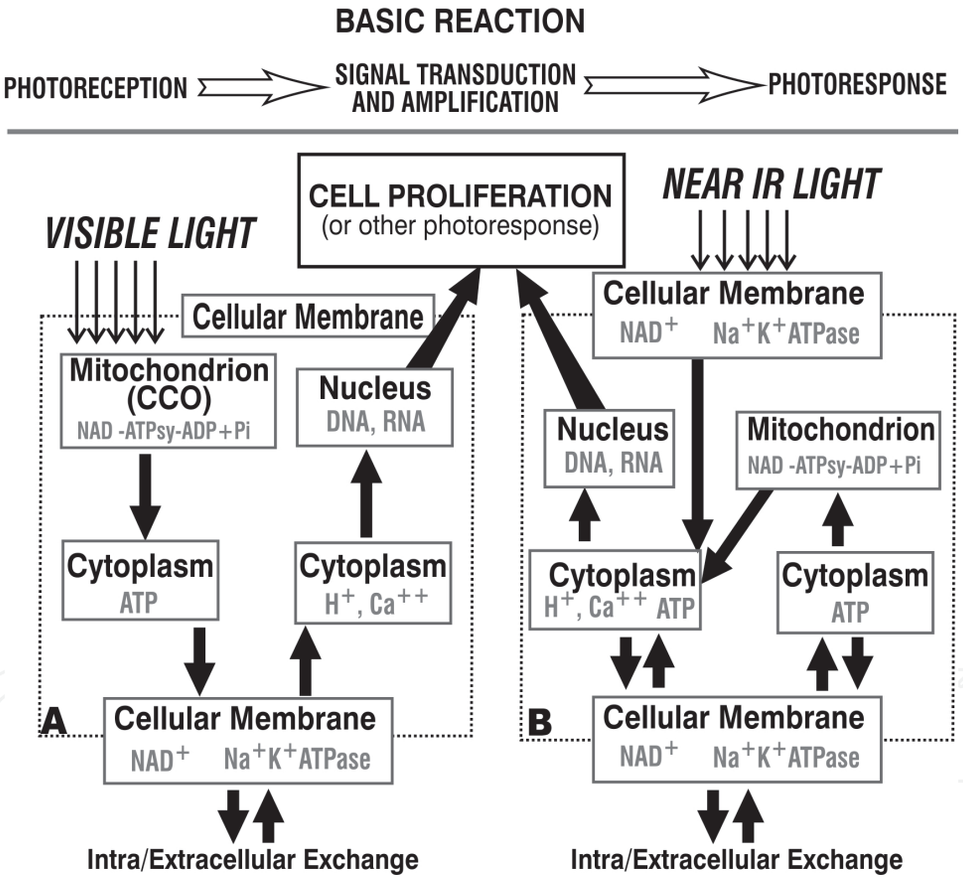

Figure 11. Primary and secondary photoresponse of target cells to visible and near-IR light. (A) Visible light penetrates through the cell membrane and is absorbed in cytochrome c oxidase in the mitochondrion respiratory chain, initiating a photochemical cascade with production of adenosine triphosphate. (B) Near-IR light, on the other hand, is mostly absorbed by the membrane itself, immediately initiating the membrane transfer mechanisms through a photophysical reaction. This leads to a secondary chemical cascade. See the text for further details (CCO, cytochrome c oxidase; NAD, nicotinamide adenine dinucleotide; NAD^+, oxidized form of NAD; ATP, adenosine triphosphate; ATPsy, ATP synthase; ADP, adenosine diphosphate; Pi, inorganic phosphorus; Ca^{2+}, calcium ion; H^+, proton; Na^+K^+ATPase, sodium-potassium pump [cell transport mechanism]).

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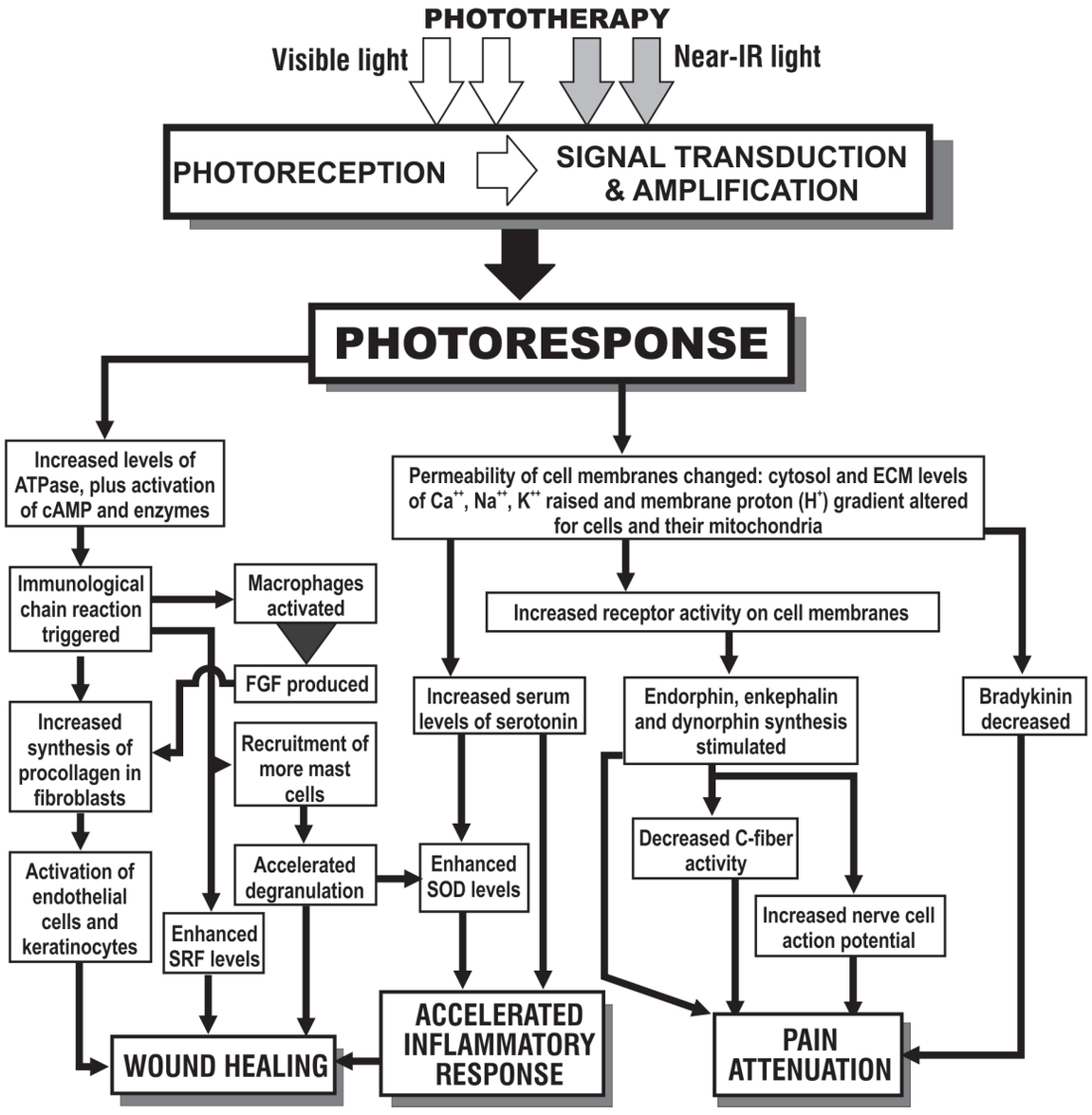

Figure 12. What happens after the photoresponse has been achieved and the target cells are photoactivated? This flowchart explores the already elicited steps on the pathway to wound healing, including the antiinflammatory effect of LLLT. These effects are mostly elicited with 830 nm (from Refs. [25, 26]. Used with permission of the publishers). ATPase, adenosine triphosphatase; cAMP, cyclic adenosine monophosphate; ECM, extracellular matrix; Ca^{2+}, calcium ion; K^{2+}, potassium ion; H^{+}, proton; FGF, fibroblast growth factor; SOD, superoxide dismutase; SRF, serum response factor.

5.1.1. Parameters involved in this interaction

The critical parameter has already been discussed above, namely the wavelength. What wavelength is required will depend largely on what targets are to be treated. In the case of rejuvenation of photoaged skin, the major target will be the cells in the epidermis and dermis whose function is to maintain the integrity of these structures. The next section will look at these cells in some detail, with a note regarding which wavelength or wavelengths have been

examined for efficacy in achieving photomodulation in these cells. The other two parameters, which are also important, are the irradiance or power density measured in W/cm^2, and the dose or energy density, measured in J/cm^2.

The power density (PD) describes the actual power incident on the tissue per unit area. The output power on its own is a good guide to what the system is capable of delivering, but it does not become meaningful until the unit area the energy is irradiating is also brought into the equation: the area targeted by any system is called the spot size, from which the irradiated area can be calculated. For LD-LLLT systems, the spot size can be rather small with the diameter measured in mm, although there are some systems that deliver a defocused spot of 1 cm in diameter or more using an optical fiber delivery system. Typical output powers for these systems range from a few mW up to 1000 mW, 1 W. The irradiation pattern for LDs is an ellipse, with a longer and a shorter axis, so measuring the area is not as simple as that of a circular spot for which the area is calculated using the formula pi (π, 3.142) times the square of the radius (r) of the spot in centimeters, written as πr^2, expressed in cm^2. It is important to remember to use the radius, one-half of the diameter, rather than the diameter itself. To calculate the PD, the output power in watts is divided by the irradiated area in cm^2, giving W/cm^2, or mW/cm^2. In the following example, an LD-LLLT system delivers 1000 mW with a spot size of 1 cm: the power is thus 1.0 W and the radius is 5 mm, 0.5 cm, which when squared becomes 0.25 multiplied by 3.142, to give the area as 0.786 cm^2. Dividing the power by the area gives us the PD, 1.27 W/cm^2 in this example. The typical range of power densities can be from 15 mW/cm^2 or lower, up to as high as 5 W/cm^2 or even higher. It is possible to go up to a PD of 10 W/cm^2 without seeing any appreciable rise in the temperature of the irradiated tissue, but the exposure time becomes much shorter as will be discussed under energy density below. For elliptical spot sizes treated with an LD-based system, the area of an ellipse is calculated by πab, where a is the radius of the longer axis and b the radius of the shorter axis (expressed in cm). If the spot size is 2 mm x 1 mm, then the area will be ($3.142 \times 0.1 \times 0.05$) = 0 .0157 cm^2. A 60 mW LD-LLLT system with that spot size would thus have a power density of 3.82 W/cm^2. These examples give PDs (irradiances) on the high side, but which are still valid power densities to achieve athermal LLLT.

Having worked out the power density, the next consideration is how long will this be incident on the target tissue, referred to as the exposure time and measured in seconds (s). By multiplying the PD by the exposure time, the energy density (ED) or dose is calculated in J/cm^2. Quite often the energy of a system is stated in J. One joule is 1 W for 1 s, but without the unit area irradiated by that energy, the value is totally useless for anyone trying to replicate the experiment. The correct way to report any such LLLT experiment is to give all of the parameters, namely output power, spot size or irradiated area and the exposure time. Both the PD and the ED can then be calculated, and the same parameters can be replicated by anyone wishing to conduct the same treatment, with hopefully the same result. Once an ideal dose in J/cm^2 has been determined, then the irradiation time necessary to achieve that dose can be calculated for any system once the PD is known, by dividing the ED in J/cm^2 by the PD expressed in W. If 60 J/cm^2 is determined to be the optimum dose, then for an LLLT system delivering 100 mW/cm^2, the treatment time will be $60 \div 0.1 = 600$ s = 10 min. The higher the PD of the system, the shorter the irradiation time to achieve the same dose: a 500 mW/cm^2 system

will take 2 min, and a 3 W/cm^2 system will take only 20 s to deliver 60 J/cm^2. However, caution is required when only the dose (ED) is considered without thinking of the PD. When a dose of 60 J/cm^2 is achieved over 30 ms with a PD of 2000 W/cm^2, the effect will be photosurgical, with heat and damage occurring in the tissue. On the other hand, if the same dose (60 J/cm^2) is delivered with a PD of 100 mW/cm^2 over 10 min, the effect will ne athermal and atraumatic, in other words LLLT, but the dose is the same. If we use a pharmaceutical analogy, the PD is the medicine, and the ED is the dose. As any pharmacist will tell you, if the medicine is not correct, there is no use in playing around with the dose.

In the case of LED-based systems, or the filtered lamp type of system, we are often at the mercy of the manufacturer regarding the rated irradiance of their system unless we have access to the sophisticated type of integrating sphere power meter needed to measure this output. In both types of system, a divergent cone of light is delivered: LEDs by their very nature emit a divergent ellipse-like cone, whereas the light from the lamp filter is a simple divergent cone. This means that the area irradiated by the light will increase as the light source is drawn away from the target, thereby reducing the incident PD by an inverse square ratio. This is illustrated in **Figure 13** comparing a single collimated LD, a single LED an LED panel and several panels in an articulated array, ideal for treating contoured biological targets, for example, the face, to give uniform intensity over the entire surface. It is therefore important to ascertain at what distance the manufacturer has calculated the irradiance (almost always in mW/cm^2). One of the advantages of LED systems, but which make calculation of the PD extremely difficult without actual measurement with a suitable power meter, is the fact that the intersecting LED beams create a phenomenon known as photon interference. **Figure 13** shows this schematically. A greater photon intensity is delivered at a distance from the surface of the LEDs in the array than actually at the surface of the array, that is, directly in front of the LEDs with no distance between them and the target tissue. For this reason, those LED mask-type facial photorejuvenation systems available on the market, and some hand-held systems designed to be used in contact with the target tissue, are not maximizing the effect of the LEDs mounted in the mask or applicator, because the full potential of the LEDs is not being realized by not creating a distance between the LEDs and the target tissue. This is not to say that these direct contact systems will not have any effect: there will be some absorption, therefore there will be a reaction, but it will not be as effective clinically as when the LED array is some centimeters from the target tissue. A recent study measured the irradiance of a commercially available 830 nm LED-LLLT system at various points from adjacent to the LEDs themselves to several cm away [26]. At some 10 cm away from the arrays, the actual irradiance in mW/cm^2 had gradually increased to be significantly higher than that measured at the LEDs themselves, because of the photon interference phenomenon, and remained high up to 17 cm from the panels before there was any noticeable drop off in intensity. Interestingly in this study, at 20 cm the measured irradiance was equal to that at 3 cm distance. The photon intensity of LED planar arrays is a function of the total area of the active array and the placing of the LEDs. From a certain distance between the array and the tissue: the array is not seen by the tissue as individual LEDs, but as a fairly homogeneous single irradiator.

When the benefit of photon interference is combined with the powerful scattering effect of red and particularly near-IR light in tissue (*cf* the scattering power of red *vs* green in **Figure 10**),

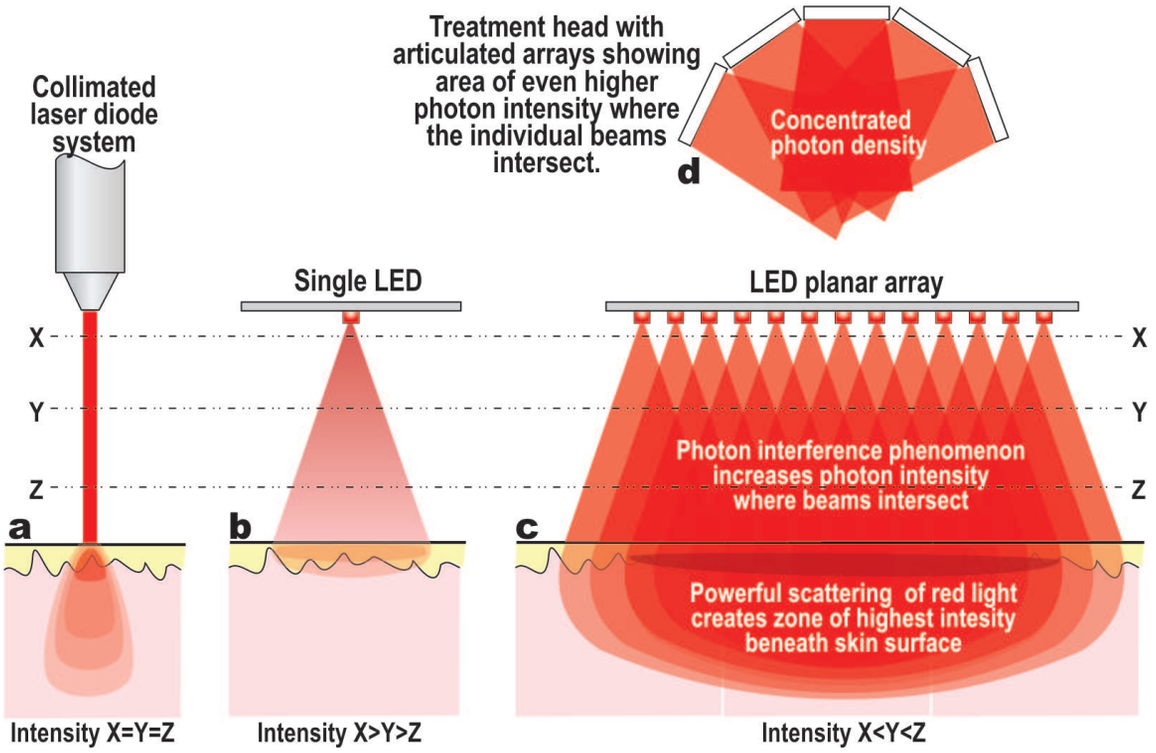

Figure 13. Different beam patterns above and in tissue compared among an LD and LEDs. (a) LD-based LLLT system showing a collimated, coherent beam without too much loss of intensity. Deep penetration is achieved in tissue because of the coherent nature of the beam and high photon intensity. Good scattering causes concentrated intensity in the target tissue just beneath the skin surface. (b) A single LED with a noncoherent divergent beam, losing in intensity as the beam diverges. Poor penetration is achieved with extremely low photon intensity in very superficial skin. (c) An array of LEDs showing intersection of each beam causing the photon interference phenomenon, increasing the photon intensity as the beams show multiple intersection as they near the tissue. Deeper penetration is achieved in the target because of the enhanced photon intensity, with scattering of the red light causing the zone of highest intensity in the target tissue beneath the skin surface. (d) Treatment head comprising 5 LED panels, articulated to allow adjustment to follow the contour of a curved target, for example, the face. Where the beams from all the panels intersect, a zone of even higher photon intensity is created to enhance treatment efficacy.

an interesting phenomenon has been noted whereby the highest photon intensity in the target tissue is actually beneath the surface, exactly where it is required, as the cellular targets for LED-LLLT lie at the stratum basale in the epidermis and in the dermal matrix. The same phenomenon of photon interference does not occur with the filtered light sources as many of these incorporate a polarizer in the lens, and therefore, a highly significant drop-off in intensity occurs concomitantly with the increasing distance between the lamp/filter and the target tissue, similar to the single LED seen in **Figure 12b**.

5.2. Cellular targets for light-tissue interaction

The following **Table 1** summarizes the main cellular targets for LLLT, and all can participate in some way to help to turn back the skin aging clock during the process of LLLT photorejuvenation.

The majority of these cells are the key players in the wound healing process. What has the wound healing process to do with photorejuvenation of skin? The answer is … everything, and that will be made clear in the next section.

Cell	Location/function	Effective wavelength(s)	Photobiomodulation-boosted activity
Keratinocytes [27]	Epidermis: Stratum basale Germinative cells ('mother keratinocytes'), producing constantly upward-moving daughter keratinocytes making up the stratum spinosum. Also known for plentiful cytokine synthesis	590 nm 633 nm 830 nm	590 nm and 633 nm: target CCO in the abundant keratinocyte mitochondria to boost intra-and extracellular ATP, Ca2+ and H+. Improve tight cell adhesion in stratum spinosum and enhance cellularity of daughter keratinocytes. Improve quality of epidermis through efficient daughter keratinocyte production by mother keratinocytes. Synthesize multiple pro- and antiinflammatory cytokines, some of which drop down into the dermis and react with fibroblasts, macrophages and mast cells 830 nm: act on keratinocyte function via photophysical interaction with membrane. End result same as for 590 nm and 633 nm End result: a fresh-looking and plump epidermis, an essential component in skin photorejuvenation
Melanocytes [28–30]	Epidermis: Stratum basale Melanin-producing dendritic cells (in melanosomes), with pigment-darkening as melanosomes proceed out along dendrites for incorporation in daughter keratinocytes as granules	633 nm 830 nm 415 nm	Both 633 nm and 830 nm have been shown to regulate the tyrosine-tyrosinase oxidation process, reduce excess amounts of pigment-darkening tyrosinase and quantities of tyrosinase-related proteins (TyRPs) 1 & 2. Normalization of dopa and dopamine, associated with over- and underactivity of tyrosinase. Some reports on 830 nm repigmentation of systemic vitiligo lesions 415 nm has shown the potential to help with repigmentation of depigmented areas through action on the melanocyte End result: can be normalization of any abnormal pigment synthesis and over-darkening activity as well as the potential to repigment depigmented areas
Fibroblasts [14, 30–32]	All layers of the dermis Most important cells for producing and monitoring structural components of the extracellular matrix (ECM, collagen and elastin fibers). Also produce and regulate the ECM lubricating ground substance	590 nm* 633 nm 830 nm	633 nm, 830 nm: LLLT-irradiated fibroblasts produce better quality collagen (mostly type I), better elastin and replenish the ground substance. Photoactivated fibroblasts also more efficiently keep homeostasis of the dermal extracellular matrix through balancing levels of lytic enzymes (matrix metalloproteinases, MMPs) and protective enzymes (tissue inhibitors of MMPs, TIMPs). LLLT-treated facial skin showed plump, fibroplasic fibroblasts with good collagen bundles compared with unirradiated and sham-irradiated skin End result: much better structured ECM with plump, well-oriented collagen bundles (better sheer strength), and new elastic fibers (better ability for skin to reform after deformation)
Mast cells [30, 33, 34]	Exist throughout the ECM, usually found clustered around blood vessels Basophilic granulocytes which play a role during allergic and wound repair activity through release of pro- and antiinflammatory granules, cellular chemotactic agents, trophic factors and superoxide dismutase (SOD), a powerful endogenous antioxidant	830 nm 633 nm (lesser extent)	When irradiated during LLLT with 830 nm in particular, mast cells are stimulated to release their granules in several stages into the ECM, which normally only happens following wounding or as part of an allergic response. First stage is proinflammatory, which peaks and then quenches the inflammatory stage of wound healing. Second stage is antiinflammatory to hasten movement from the inflammatory stage into proliferative stage, and release of chemotactic factors to recruit more reparative cells, plus release of trophic factors to support these cells. Finally mast cells release SOD which remains in the ECM and acts as a protective agent against future oxidative stress, for example, UV radiation-mediated as part of the extrinsic aging process End result: mast cell degranulation accelerate the usual wound healing phases, allowing a quicker interphase transition between inflammation and proliferation, thus the remodeling stage starts earlier and works more efficiently to give good alignment and better orientation of new fibers, especially in the Grenz zone just under the dermoepidermal junction

Cell	Location/function	Effective wavelength(s)	Photobiomodulation-boosted activity
Macrophages [35–38]	Free-floating in the ECM throughout all layers of the dermis Phagocytic cells whose task is to maintain the cleanliness of the ECM by removing all detritus, such as denatured fibrous fragments, cellular and other debris. An important point si that during phagocytic action, they release fibroblast growth factor (FGF), ideal for fibroblasts during the proliferative stage of wound healing	830 nm 633 nm (lesser extent)	LLLT with 830 nm in particular, although 633 nm has also been trialled, has been shown to photoactivate macrophages to work harder and faster through more efficient target identification and chemotaxis, to internalize their collected debris better and return to their task faster. When photoactivated, macrophages were shown to release at least an order of magnitude more FGF, thus making the ECM a better and more favorable environment for fibroblasts during the proliferative stage End result: with a cleaner and clearer ECM, the skin condition is maintained better. Fibroblasts are able to do their job in a more favorable environment thanks to the presence of trophic factors
Neutrophils [39–42]	White blood cells (granulocytes, part of the polymorphonuclear cell family) found when required anywhere in the dermis First line of defense by the immune system against invading pathogens. They engulf their target and kill it through oxidative stress via the release of singlet oxygen species. Associated with trophic factor release, particularly transforming growth factor (TGF) α and β	830 nm	Neutrophils are normally associated with an attack by invading pathogens or as prophylactic protection immediately after wounding. When irradiated with 830 nm, neutrophils are recruited into normal skin. Even although there are no pathogens for them to kill, they still release trophic factors beneficial to the wound healing process as a whole End result: more trophic factors added to the ECM to assist other cells during either the wound healing process or as part of their normal duties

CCO, cytochrome c oxidase.

*Only from in vitro studies, but very limited in vivo by extremely poor penetration.

Table 1. Target cells for phototherapy, their biological location, the wavelength(s) to which they respond best and a description of their activity when photoactivated.

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5.3. Blood supply as a target for LLLT photorejuvenation

There is no point in encouraging the skin cells to thrum along nicely unless these cells are receiving nutrition and oxygen and that is the function of the dermal vasculature. Both 633 and 830 nm have been associated with supportive activity for the blood vessels in the dermis [42–47]. The interaction between blood vessels and LLLT is therefore of equal importance to the interaction between LLLT and the skin cells. Because of its deeper penetration, and possibly because it delivers a photophysical primary response to the endothelial cells, 830 nm has a good body of literature supporting a strong interaction with the blood supply, delivering a higher flow rate and volume and thus bring oxygenation and nutrition to the ECM. In addition, where there have been circulatory problems, LLLT has restored circulation such as in ischemia animal models, and Raynaud's patients [47, 48]. It has been suggested that the LLLT acts directly on the vessel walls, but there is also a reaction involving the parasympathetic system, inducing further extended vasodilation. In one study involving patients with the athetotic type of cerebral palsy, patients in a state of sympathetic hypertension with very poor blood supply to the peripheral circulation as assessed by real-time fine plate thermography received one single 830 nm LLLT session on acupuncture points on the chest. Within 5 min, thermography revealed increasing body warming which remained highly significant in the extremities at 90 min after the single treatment [49].

This effect on the parasympathetic system, our 'rest and digest' or 'rest and relax' nervous system is important as a destressor, as stress is also a contributory factor to the aging of the skin. In particular with the 830 nm LED-LLLT system, it is often noted that patients quickly fall asleep during photorejuvenation sessions and wake up feeling refreshed. Within 5–10 min, a gentle warming of the face is also felt as the microvasculature brings more blood to the superficial dermis through vasodilation. The latter is without a doubt a physical beneficial phenomenon, whereas the former is more of a psychosomatic benefit. However, if patients feel more relaxed, and in fact, their faces have been treated with LLLT photorejuvenation; the importance of the psychosomatic benefits cannot be ignored, mostly due to the improved vascular supply following parasympathetic system stimulation by, in particular, 830 nm LLLT.

6. Wound healing: the basis of photorejuvenation

As stated above, the wound healing process underpins good skin rejuvenation. When the photoaged and intrinsically aged skin is studied carefully, the onslaught from environmental factors such as air pollution, ultraviolet-related oxidative stress, smoking for those who smoke, or even for those who are forced to exist in a smoky atmosphere, nutritional factors and even the water in which we wash our skin and drink takes an enormous toll on the ordered structures of the extracellular matrix and the level of activity of the cells populating it. Photoaged skin is every bit as compromised as wounded skin, and so one of the optimum and most elegant ways to fight this skin damage, most of which is due to sunlight, is to use the beneficial side of light through application of LLLT: in other words, apply photorejuvenation.

When the aims of photorejuvenation are considered carefully, the reader will see clearly that the end results of the wound healing process and photorejuvenation are synonymous. We need new and well-organized collagen fibers and bundles, efficiently remodeled to give optimum orientation, body and strength to the skin including a nicely linearly oriented Grenz zone coursing under the dermoepidermal junction, and adding support to the epidermal appearance. We need the degraded elastotic elastic fibers replaced with newly synthesized elastin forming new, viable elastic fibers to return the reforming and tightening properties to sagging photoaged skin. We need fresh and well-hydrated ground substance, to lubricate and oxygenate the components of the ECM. We need toned up and active fibroblasts to deliver all three of these goals just mentioned, and to regulate the homeostasis of the ECM supported by hard-working macrophages to maintain ECM health through keeping it free of clogging debris. Furthermore, above this restored and youthful ECM, we need a clear, luminous epidermis, with good basement membrane function to support and nourish the activities of the germinative and other cells in the stratum basale; well-convoluted papillary processes are also needed to give as large a supporting area as possible at the dermoepidermal junction, and above the epidermis, we need a well-ordered stratum corneum to provide good skin barrier function without excess sebum. With application of LLLT, all of these can be achieved through the athermal and atraumatic action of LLLT on the target cells, particularly if LLLT is used in combination with moisturizing and nutrifying creams and sera with the added protection of a daily regimen using a good UVA/B sunscreen.

The wound healing cells have been introduced in **Table 1**, namely, the mast cells, macrophages and neutrophils during the immediately post-wound inflammatory process; the fibroblasts and endotheliocytes (to repair damaged blood vessels or for neovascularization) during the proliferative stage; and the transformational cells during the long remodeling stage, fibroblast to myofibroblast transformation and fibroblast to fibrocyte dedifferentiation. All these cells occur at their different stages, and in different numbers. If we can marry LLLT with these potential targets, then we can get more efficient wound healing, and faster, without compromising the process in any way. The wavelengths which have shown efficacy for each cell type are listed in **Table 1**. In general, 830 nm near-IR is the favorite, followed by 633 nm visible red, and LED-based systems are in the ascendency compared with LD-based systems, simply because the LED systems are capable of irradiating a large area in a hands-free manner. If we can get efficient wound healing, then we can most certainly extrapolate the same benefits to the indication of phototherapy for photorejuvenation of the aging skin.

A PubMed search using 'LLLT' and 'Wound healing' brings up over 700 titles in a vast range of wound types, and surgical specialities. That is an impressive number. How does LLLT affect frank wound healing? In a study by Trelles and colleagues on the application of LED-LLLT after full face ablative resurfacing with the Er:YAG and CO_2 laser in 50 patients, 25 received LLLT after their resurfacing procedure, and 25 received sham treatment [50]. In the LLLT group, healing (as defined by full reepithelization and resolution of edema and erythema) occurred in an average of 6.1 days compared with 13.2 days in the non-LLLT group. In addition, all the usual side effects associated with full-face ablative resurfacing, edema, erythema, bruising and pain were significantly reduced in the LLLT group, with better than 92% of the LLLT patients being extremely satisfied with the procedure compared with 55%

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of the sham-LLLT group. A recent study by Min and Goo examined 830 nm LED-LLLT for a variety of skin wounds which had proved recalcitrant to normal healing, including severe inflammation, bacterial infection, viral infection, and Bell's palsy [51]. All cleared up in from 1 to 5 weeks with no visible scar formation, even in one case of a severe ischemic ulcer with a large defect. In a case report on contact irritant dermatitis caused by a home-use alpha-hydroxy peel, corticosteroids failed to reduce the inflammation for more than 5 weeks: 830 nm LED-LLLT in three sessions, 3 days apart, completely controlled it [25]. Moreover, 830 nm LED-LLLT has shown significant prophylaxis against hypertrophic scar formation postthyroidectomy in a controlled study [52]. To summarize, it can be argued that LLLT not only speeds up the wound healing process, but ensures that good quality wound healing is achieved, with prophylaxis against unwanted scar formation.

7. Clinical indications of phototherapy in skin rejuvenation

So, finally, having looked at some of the science and technology behind phototherapy, what about LLLT for photorejuvenation of the aging and aged skin? First the methods available need to be considered. Discussed earlier in this chapter were LD-based systems, LED-based systems, and filtered lamp-based systems. It has to be said that LD-based systems deliver higher photon intensities than LEDs, which in turn are in general much more intense than filtered lamp systems. LDs deliver coherent light at a precise wavelength. LEDs deliver non-coherent light, but with more than 95% of the photons at the rated wavelength, quasimonochromaticity, and with clinically useful photon intensity thanks to their treatment head design and photon interference among the LED beams. Filtered lamps deliver polarized light at a slightly broader bandwidth than LEDs because of the filter technology, but with rather low intensities requiring longer exposure times. Almost all LD-based systems require manual application in a point-by-point mode, and even those with some form of stand-based applicator can cover only a small area at a time. LED-based systems have large-areas planar arrays, the better systems having multiple articulated panels to enable uniform irradiation of curved areas of the body, such as the face: these are applied in a completely hands-free manner, covering large areas of the body in one session. Filtered lamp systems are also available with stands to hold the lamp in a hands-free manner, but have a smaller treatment area than LED systems, and cannot cover curved areas with uniform irradiance.

Based on the statements above, the authors therefore feel that, given the rise of popularity of LED-based phototherapy systems in the clinical world and also given the increasing body of LED-based evidence in the peer-reviewed literature [25, 53], the optimum phototherapy system for photorejuvenation should thus be the large array LED-based system. The wavelengths which have achieved the largest coverage in the literature are as follows: 415 nm, but only as part of acne phototherapy, so perhaps cannot be included in photorejuvenation; 633 nm visible red; and 830 nm. Of the latter two, several articles have examined the use of the wavelengths in sequential combination for photorejuvenation, with very good results. [14, 54, 55]. The regimen as it evolved called for the near-IR 830 nm to be applied first, then 2–3 days later the 633 nm visible red head was applied. This was repeated over 4 weeks. The

dose for the 830 nm component was usually 60 J/cm^2, and for the 633 nm was over the 100 J/cm^2 mark. All three studies had a follow-up period, ranging between 8 and 12 weeks during which no further treatment was given, subjects being allowed only to wash their faces with hypoallergenic soap without any other skin care preparation. In all studies, steady improvement was noted in the skin condition in the weeks after the final treatment. The ultimate study in photorejuvenation with LED-LLLT was that by Lee and colleagues [32], in which she compared 633 used on its own with 830 used on its own, the 830/633 nm combination and a sham treated control group. All subjects had only one-half of their faces treated. Lee not only took clinical photography, she also conducted histological, profilometric, ultrastructural and immunohistochemical assays to examine what was happening underpinning the very good results of her study at 12 weeks after the final treatment session. All the LED-treated groups were statistically significantly better than the sham group, and the treated sides were improved compared with the untreated sides: in the sham-irradiated group, there was no real improvement between the sides. It was anticipated that the combination group would show the best results, but in fact it was the 830 nm group who led in most of the assays. Skin elasticity at 2 weeks after the final treatment was significantly better for the 830 nm group, as was neocollagenesis and elastinogenesis. A strong Grenz zone was seen under a plumper and better organized epidermis, and fibroblasts in transmission electron microscopy were active and fibroplasic, surrounded by bundles of good quality collagen fibers. At 2 weeks after the final treatment, tissue inhibitors of matrix metalloproteinases (TIMPs) 1 and 2 were seen, suggesting a photoprotective effect, which was not seen in the sham or unirradiated specimens. The major finding for the subjects themselves was assessed via patient satisfaction. In all the treated groups, this grew significantly from immediately after the final session to 12 weeks after the session. The combination 830/633 nm group was significantly superior to the 633 nm only group. However, the most surprising finding was the much earlier and better satisfaction recorded by the 830 nm group.

So how does LED-LLLT help with rejuvenating the photoaged face? In short, LED-LLLT stimulates all phases of the wound healing process, but without causing any wound. It was shown that 830 nm LED in a human subject study in vivo recruited significantly more mast cells, macrophages and neutrophils into irradiated tissue 48 h after a single irradiation of one arm in all 8 subjects in the study, compared with the unirradiated arms [34]. Moreover, at 48 h the mast cells had mostly degranulated, compared with no degranulation at all seen in the contralateral untreated arm. Similar findings have also been observed in the mouse tongue model, although with 633 nm rather than 830 nm [33]. Additionally, ultrastructural assessment with transmission electron microscopy showed that the ECM in all the treated tissue specimens was in what appeared to be an inflammatory state with abundant interstitial spaces and the clear presence of perivascular edema. The findings resembled those after a wound, but there was no wound.

The authors surmised that the swift degranulation of the mast cells very soon after 830 nm LED-LLLT had dumped a slew of proinflammatory cytokines into the normal tissue during the first stage of excellulation of granules which had induced a wound-like response. More mast cells and macrophages were then recruited in via chemotactic signals released by the granules, together with neutrophils, none of the latter being found in any of the fields in the specimens

from the unirradiated arms. In other words, a quasi-wound had been formed with a strong inflammatory response, but without heat or damage, and with no grossly visible aspects of any of the traditional signs of wounding, calor, rubor or dolor. The wound healing process teaches us that, after inflammation, comes proliferation, followed by remodeling. The authors concluded that the action of the 830 nm LED-LLLT on mast cells had elucidated the first stage toward photorejuvenation by creating the inflammatory response.

It could therefore be argued, based on the findings in the Lee study referenced above, and the speedy wound healing in other studies, that the continued regimen of LED LLLT, twice weekly over 4 weeks, accelerated the wound healing process underpinning the rejuvenation of both the ECM and the epidermis in a stepwise manner, enhancing the fibroblast activity in the proliferative stage, and allowing the remodeling stage to be entered earlier. That continued improvement seen in the Lee study following the end of the actual treatment in all three treatment groups, but particularly in the 830 nm group, was the visible result of the remodeling process working on the newly laid down collagen fibers in the dermis during the proliferative stage, supported by the fresh elastinogenesis. On the other hand, it took time, 12 weeks in fact, to see the optimum results. This shows how important it is to prepare patients to be patient when planning photorejuvenation with low level light therapy. LED-LLLT certainly works, but it works from the inside out and takes time. However, concomitant use of good skin care preparations and establishment of a daily UVA/B sunscreen regimen would accelerate results and quite possibly maintain them even longer.

As to the optimum wavelength, in a review on the efficacy of LED-LLLT, Kim and Calderhead came down firmly in favor of the 830 nm wavelength [25]. Calderhead and colleagues reviewed 830 nm LED-LLLT both in stand-alone and in adjunctive indications and came to the same conclusion [56]. In a recent invited review for *Clinics in Plastic Surgery*, Calderhead and Vasily examined the efficacy of LED-LLLT in the aging face, and again pointed to the overall efficacy of the 830 nm wavelength [57]. Having said that, 633 nm has shown interesting results on induction of fibroplasia in fibroblasts in a human in vivo model, so cannot be discounted [32]. As long as there is absorption there will be reaction, and remember that the key to absorption to achieve effective photorejuvenation is primarily wavelength.

8. Innovations in photorejuvenation

The previous sections in this chapter have dealt mostly with very narrow-band light sources in photorejuvenation as part of photomedicine, concentrated on non-coherent but quasimonochromatic LEDs and coherent LDs at specific wavelengths. However, one of this chapter's authors (YT) has recently launched exploration into a new concept of potentially phototherapeutic light having built up an impressively large body of evidence. Tanaka offers an innovative approach to photorejuvenation, namely comparatively broad band near-IR with a cut-on/cut-off water filter to exclude certain wavelengths in that IR waveband.

A specific band of near-IR energy (1100–1800 nm together with a water-filter that excludes wavelengths 1400–1500 nm) has been demonstrated by Tanaka to induce various biological

effects through a broad range of clinical, histological, and biochemical investigations [58–72]. Tanaka reported that water-filtered broad-spectrum near-IR can promote up-regulation of genes related to type I collagen synthesis, including LARP6 and COL1A1, which achieves skin tightening and skin rejuvenation [72]. This exciting development of a specific broad-band IR waveband is also associated with deep penetration of the water-filtered waveband into the dermal ECM, targeting both cells, subcellular components and the vascular plexus.

Tanaka also reported that water-filtered broad-spectrum near-IR induces long-lasting vasodilation that may prevent vasospasm and be beneficial for ischemic disorders [65]. Near-IR also relaxes and weakens dystonic and hypertrophic muscles to reduce wrinkles and myalgia [60, 61]. The ability of LLLT at 830 nm to activate the parasympathetic system and counteract sympathetic hypertension was noted above as reported by Asagai and colleagues [49], so this new approach pioneered by Tanaka may also have far-reaching benefits in the treatment of athetotic tonic spasm in profoundly affected cerebral palsy quadriplegic patients. Near-IR is an essential tool in cancer detection and imaging and induces drastic non-thermal DNA damage of mitotic cells, which may be beneficial for treating cancer [66, 67]. Activation of stem cells by near-IR energy may be useful in regenerative medicine [62, 68, 70, 73].

Although the underlying mechanisms of various biological effects by water-filtered broad-spectrum near-IR have not been clearly elucidated, the potential of this innovative approach may be also significant, and the range of its applications in the medical field is expected to be wide [70]. Therefore, further studies in this area are needed to more accurately investigate the biological effects of water-filtered broad-spectrum near-IR phototherapy and photorejuvenation, and to evaluate its potentially large contribution as a new component in the low level light therapy armamentarium.

9. Conclusions

The authors of the present chapter are of the clear opinion that LLLT is a valuable tool for the aesthetic clinician in rejuvenating the photoaged face, but it is only one such tool. We further believe that LED-based systems are the best way to go because of their ease of use and hands-free delivery, compared with LD-based devices. We finally believe that 830 nm offers very interesting properties compared with other wavelengths, making it the wavelength of choice because of its superior depth of penetration, and larger number of cells and targets it has been shown to photoactivate. However, the novel indication of Tanaka's broad-band water-filtered near-IR must also be watched extremely closely, since this waveband penetrates well into the ECM and beyond and has been proved to target and photoactivate wound healing cells and the vascular plexi.

A great deal of work remains in exploring the exact mechanisms of LLLT action, although many pathways at subcellular and genetic levels have been and are being explored. The TGF-β/Smad signaling pathway is the latest to be explored in the collagen synthesis chain of events [74], coupled with up-regulation of genes related to type I collagen synthesis, including LARP6 and COL1A1 [72], and more will doubtless be uncovered. The more that

is known, the better can we use LLLT to target the correct pathways to help turn back the skin's aging clock in photorejuvenation, from the inside out … fighting photodamage with reparative phototherapy. However, 'No man is an island, entire of itself' (*1624 Meditation 17*, from *Devotions Upon Emergent Occasions*, John Donne, 1573–1631): in the same way LLLT photorejuvenation cannot possible accomplish everything. Combination is without a doubt the key, and whereas LLLT as a stand-alone modality has a lot of promise in rejuvenating the not-so aged face, when we come to treat the seriously aged face, then LLLT will be an excellent adjunctive modality to the more aggressive laser and energy-based device treatments.

Just to leave the reader with a teasing thought, the authors have often seen the term 'photoantiaging' bandied about, when what people are really talking about is photorejuvenation, the central subject of this chapter. But what about 'true photoantiaging'? Suppose we clinicians and researchers start to apply pure LLLT, either with near-IR LEDs or broad-band water-filtered near-IR in younger patients in their late teens, for example … would that give us true 'photoantiaging' and remove or at least postpone the necessity for photorejuvenation later in life? It is an intriguing thought.

Finally, a group of authors, writing almost 10 years ago in *Lasers in Medical Science* on their years of experience in the use of light in facial rejuvenation, concluded that no single modality could accomplish all the complex events required for effective skin rejuvenation, and suggested that combination phototherapy was the best approach, amalgamated with other conventional modalities, and with an adjunctive epidermal care regimen [75]. There is indeed, nothing new under the sun.

Author details

Robert Glen Calderhead[1]* and Yohei Tanaka[2]

*Address all correspondence to: docrgc1213@gmail.com

1 Clinique L Dermatology, Goyang, South Korea

2 Clinica Tanaka Plastic and Reconstructive Surgery and Anti-aging Center, Nagano, Japan

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