Research Article

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Innovative light sources for phototherapy#

https://doi.org/10.1515/bmc-2022-0020
received April 10, 2022; accepted May 3, 2022

Abstract: The use of light for therapeutic purposes dates back to ancient Egypt, where the sun itself was an innovative source, probably used for the first time to heal skin diseases. Since then, technical innovation and advancement in medical sciences have produced newer and more sophisticated solutions for light-emitting sources and their applications in medicine. Starting from a brief historical introduction, the concept of innovation in light sources is discussed and analysed, first from a technical point of view and then in the light of their fitness to improve existing therapeutic protocols or propose new ones. If it is true that a "pure" technical advancement is a good reason for innovation, only a sub-system of those advancements is innovative for phototherapy. To illustrate this concept, the most representative examples of innovative light sources are presented and discussed, both from a technical point of view and from the perspective of their diffusion and applications in the clinical field.

Keywords: light source, phototherapy, innovation, photodynamic therapy, photomedicine.

Introduction

The use of light for therapeutic purposes is an ancient practice. We have news of this through hieroglyphic, cuneiform, and alphabetical writings datable between 3000 and 500 BC. The first light source used was the sun, without any other means in between.

The applications of heliotherapy changed over time, but the sun remained the only source of light until 1700. In the second half of the eighteenth century, lenses or filters were introduced between the sun and the body, thus manufacturing the first instruments for phototherapy. It was only with the development of electricity that the first artificial light sources were born. In 1880, Thomas Edison's company started the commercial production of the first filament bulbs. In 1897, Niels Ryberg Finsen created the first artificial lamp for phototherapy (arc lamp with carbon electrodes) to replace sunlight filtered through glass media for his experiments on Lupus (Figure 1). These studies earned him the Nobel Prize in 1903 *in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science*. In 1927, a patent paved the way to produce fluorescent lamps filled with mercury vapours and an inner coating of Beryllium, soon replaced by fluorescent oxides. This technology has had great prominence in the phototherapy field up to the present day, with intensive use for various pathologies of dermatological importance. Nevertheless, the great innovation of the last century was the advent of coherent light sources, namely the invention of the ruby laser in 1960. Only 10 years later did the first semiconductor light sources appear (light-emitting diodes [LEDs]); together with lasers, LEDs represent the key technologies for the application of optical radiation to biomedicine. Today, light sources emit pulsed or continuous wave wavelengths, from UVC to infrared, for both therapeutic and diagnostic purposes. Since the first lamps, great progress has been made: in a century, we have gone from rudimentary instrumentation where metal and mechanics were predominant to the current semiconductor light sources and wearable illuminators. Improvements, of course, are remarkable also from the patient's perspective.

This manuscript is dedicated to Professor Silvia E. Braslavsky on the occasion of her 80th birthday.

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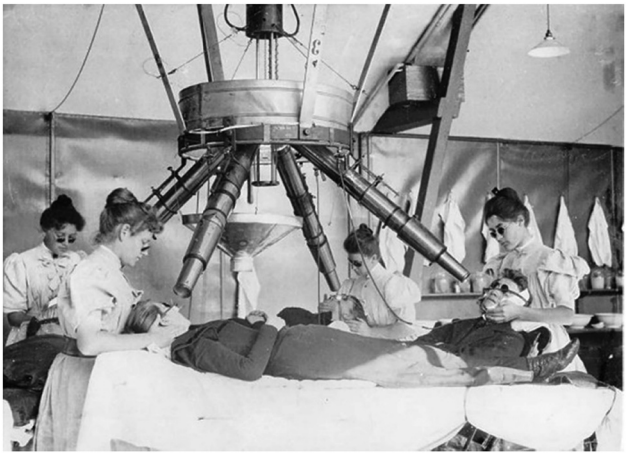

Figure 1: Phototherapy with a Finsen lamp at the Institut Finsen, Copenhagen, Denmark, circa 1900 (from https://rarehistoricalphotos.com/).

What makes a light source innovative?

In the first instance, we could think that innovation in light sources can be associated with improvements in one of the following interconnected characteristics: size, working principle, light quality, and the aggregation state of the light emitter. Let us analyse them briefly.

Size

Since their invention, lasers have made a tremendous impact on modern science and technology. Of current specific interest are the numerous advantages brought about by their miniaturization. In recent years, microlaser design and applications have greatly increased, especially in the case of whispering-gallery microlasers (WGMs) [1]. WGMs are generally made by dispersing dye molecules into a polymeric microstructure with a typical size of the order of tens of microns: laser emission is obtained upon optical excitation. A similar condition can be realized in certain organisms in nature that can synthesize fluorescent proteins (like the Green Fluorescent Protein). In these organisms, lasing within living cells can be carried out when an external optical excitation is provided, resulting in a "biological cellular laser" [2,3]. Remarkably, these cells remained alive even after prolonged action of laser operation.

WGMs have found several applications in biosensing [4,5]: light amplification and lasering to and from biological systems enable intracellular sensing [6], monitoring of contractility in cardiac tissue [7], detection of individual viral particles [8], and advancement of *in vivo* sensing [9,10].

On the other hand, organic LEDs (OLEDs) are probably the emitter type associated with the largest light sources ever realized (like the OLED screen display installed at the Dubai Aquarium & Underwater Zoo (UAE) at Dubai Mall), even if with no medical applications for the moment. In the future, these source types could be considered for performing total body phototherapy exposure. This is currently performed using LED sources and is especially applied to the case of neonatal jaundice [11,12].

The above light sources are extracorporeal or need an extracorporeal optical excitation source, which precludes their use for the treatment of internal diseases or deeply seated lesions within internal organs unless invasive systems, for example, optical fibres, are used for light delivery. As such, there is a great interest in the development of light sources that can illuminate the diseased region from within. One approach towards this goal is Bioluminescence Resonant Energy Transfer, which takes advantage of the natural phenomenon of bioluminescence to provide a cell-based light source, for example, based on the firefly luciferase bioluminescence [13,14].

Likewise, the development of nanotechnology has provided several types of inorganic nanomaterials that can effectively act as light sources for phototherapy applications [15]. Besides being often functionalized to acquire further targeting and/or photosensitizing properties, some of these *targeted nanomaterials* present a long-lasting luminescence afterglow or persistent luminescence, such as in the case of zinc gallogermanate or silicate hosts doped with different elements [16,17]. In most applications, a narrow particle size distribution is desirable; particle dimensions in the range of 50–300 nm are commonly prepared to prevent possible long-term toxicity [18].

Aggregation state

Nowadays, the most widespread light source types in medicine are based on solid or gaseous emitters, classified according to the aggregation state of the radiating species. Among the solid emitters, we can mention those based on semiconductors (e.g. diode lasers, LEDs, and OLEDs) as well as the solid-state lasers (e.g. Nd:YAG and Ti:Sapphire lasers). Among the gas-based sources, we mention the gas-discharge lamps and gas-based lasers (e.g. CO_2 and excimer lasers).

Innovation can be found in solid or gaseous sources covering new wavelengths or wavelength ranges, such as the case of far-ultraviolet C [far-UVC] [19] or mid-infrared [20].

Regarding liquid sources, the state-of-the-art is probably represented by liquid-dye lasers, but they are generally difficult to maintain and operate, and therefore, their usage is limited to very few cases. However, innovative and easy to operate optoelectronic devices based on liquid materials have recently been reported, such as light-emitting electrochemical cells (ECLs) [21] and liquid OLEDs [22]. The first ones are based on electrochemiluminescence, where the active layer consists of a mixture of an emitter and an ionic polyelectrolyte (Figure 2). For OLEDs, light emission is obtained by applying a voltage to a flux of liquid OLEDs inside a microchannel. Compared to solid ones, liquid emitters could allow the development of more flexible and effective protocols for light delivery, like in the case of cave organ illumination. This could be performed either by direct injection of the light-emitting liquid (provided it is biocompatible) or by use of ad hoc and transparent catheters with purposely designed geometry. Possible innovative sources based on a liquid emitter could also derive from aerosolized sources, presented later in the text.

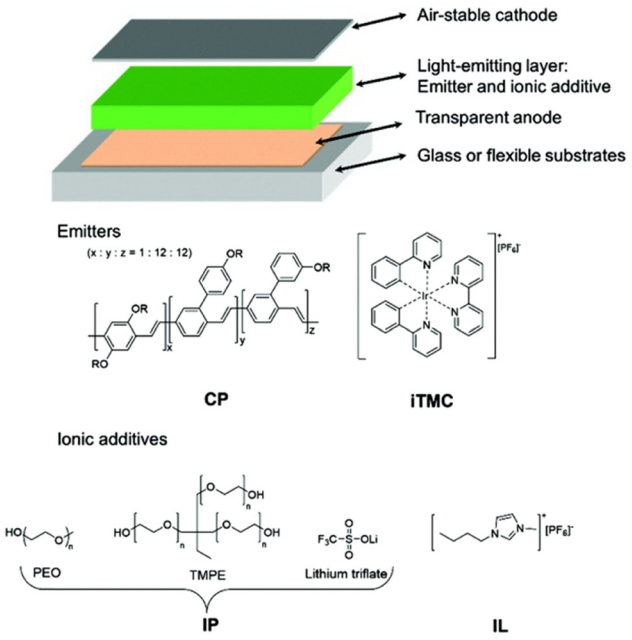

Figure 2: Sketch of ECLs and the chemical structures of different types of emitters and ionic additives. CP, conjugated polymer; ITMC, ionic transition-metal complex; PL, polyelectrolyte; and IL, ionic liquid. Image from ref. [21].

Working principle

The very first lamps were based on an incandescent filament, exploiting black body emission. These so-called thermal sources are still present (halogen and infrared-/near-infrared lamps) even if no significant technological innovations are noticeable in the medical application field. Non-thermal sources generally include different working principles, among which the most widespread ones are based on atomic, molecular, or interband transitions: fluorescent, excimer or arc lamps, LEDs, OLEDs, and coherent laser emission. The working principle itself could justify innovation in phototherapy if it represents the reason to overcome limitations of use in the clinical practice. This is especially true in all those cases where internal organs must be targeted. For example, as also illustrated in the following chapters, phosphorescence-based sources could be proposed as an alternative to "tethered sources" (e.g. fibreoptic delivered light): leveraging the delayed-emission principle, these sources are intrinsically non-invasive or minimally invasive, with limitations arising from the capacity to efficiently store energy and release it in due time. In the last few years, materials science has greatly advanced in designing and synthesizing new phosphorescent materials and in particular room-temperature phosphorescent materials, with many possible medical applications ranging from bioimaging to cancer and antibacterial therapy [23]. Similar considerations could be applied to bio-derived sources based on bioluminescence and using a "biochemical fuel" (e.g. ATP), which is or can be made available *in situ*. Ultimately, these sources are based on chemiluminescence, another case of an "old" working principle with possible new applications. A recent example can be found in the European project *Lumiblast*, where mitochondria-powered chemiluminescence is exploited to treat inaccessible tumours non-invasively [24,25]. A similar idea is being recently developed with applications in both therapy and detection of infectious agents and considering as well luminol-based self-luminescent systems [26].

Finally, other physical phenomena could be exploited in the coming years, namely light emission by triboluminescence (upon mechanical stimulation), acoustoluminescence (upon acoustic vibration of single crystals or granular media), and sonoluminescence (upon imploding bubbles in a liquid when excited by sound) [27]. Triboluminescence is generally considered an umbrella term for light emission resulting from mechanical stress, and as such, it includes both acousto- and sonoluminescence [28–30]. Its applications are now mainly in the fields of sensors, displays, and bioimaging devices [30,31].

Nevertheless, sonoluminescence has recently seen interesting and innovative developments in the therapeutic field [32,33], also due to the much greater penetration depth of sound in tissues with respect to optical radiation.

Medical needs

Over time, both technological and medical advancements have generated new needs to satisfy and new possibilities for further applications. As it is difficult to understand if and which of the two fields drives progress first, we must choose a perspective in which to frame our analysis. With this logic in mind, the needs coming from the clinical world are certainly a strong driving force to produce innovation and a good reason to define innovation as well: if a light source responds to an unmet clinical need, that source is innovative. Talking about therapy, examples of new medical needs are the following: decrease invasiveness, reach difficult districts, address new targets, define alternative therapeutic schemes, increase the facility of use and/or flexibility, increase the emitted power and/or available wavelengths, etc. A similar scheme, in principle, could also be applied to diagnosis.

In this perspective, attention is first driven to the application and then bounces back to the principles of light–tissue interaction and the technology producing the desired light emission characteristics to respond to that specific application. For example, thinking of the photochemical reactions at the basis of the photodynamic inactivation (PDI) of certain bacteria types, the infection localization in the stomach or the lungs calls for a light source that should be delivered inside those organs, effectively and possibly non-invasively. In dermatology, patient's pain is often one of the drawbacks of photodynamic therapy (PDT) treatments, which generates the need for a lower light dose rate and longer treatments, at the same time compatible with efficient point-of-care management. The result, in some cases, is the recommendation for daylight therapy, which makes the sun itself a (newly) innovative light source. In toxicology, preliminary research has considered a transesophageal fibreoptic illumination of the lungs for the photo-dissociation of carboxy-haemoglobin as a possible alternative therapy in the case of CO intoxication [34,35]. An increased CO elimination rate and a decreased CO uptake were demonstrated during poisoning in a murine model, together with a survival improvement in ongoing CO poisoning.

It is evident that each new request ("medical need") limits the number of the possible variables characterizing the light source and its emission. Fortunately, there are as many variables to play with. Thinking of light–tissue interaction [36], the rationale is to consider the plethora of light-induced effects (Figure 3) and maximize the desired one while minimizing the downsides, also considering the physics of light penetration in the biological matter and the presence of different absorbers (Figure 4) [37–39] to answer the following questions: Which main effect is sought (Figure 3)? Which wavelength or spectrum? Pulsed or continuous emission? Coherent or incoherent light? Which power and/or irradiance? Which illu-

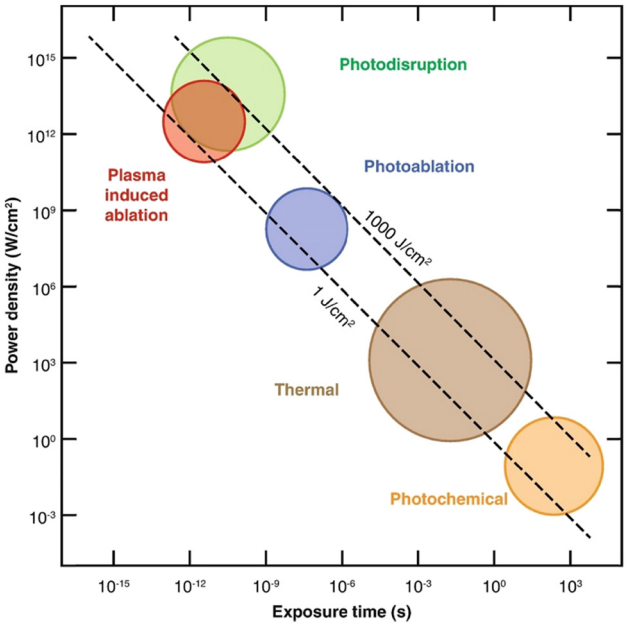

Figure 3: Light-induced effects in tissue. Image from ref. [36].

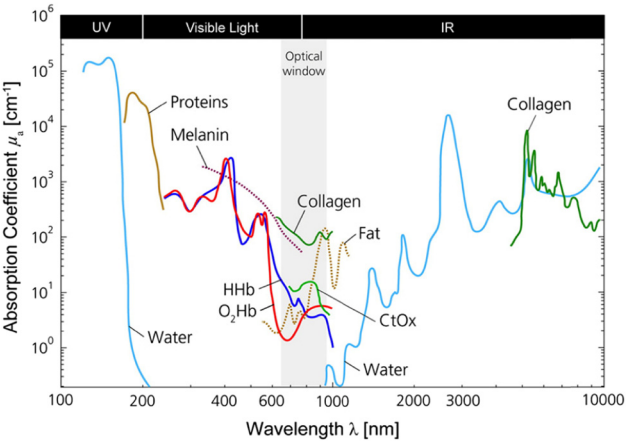

Figure 4: In human skin, a spectral region of minimal light attenuation, commonly referred to as the "optical windows," is observed between 600 and 1,300 nm. Image from ref. [39].

mination dimensions and/or depths? Which collateral effect? How to convey the light (e.g. free in the air, via an optical fibre, ingested, inhaled)?

Phototherapies have nowadays numerous therapeutic applications, starting from dermatology where light delivery is only limited by penetration issues in the target tissue; this corresponds to the best possible scenario for an *in vivo* application. For many years, other disciplines have been added such as ophthalmology, gastroenterology, pneumology, urology, and gynaecology, besides various applications in surgery (anticancer therapies) and clinical microbiology (microbial infections). The point here is to find where innovation is present and how it is driven by (old or new) medical needs. From a physical point of view, solving those needs means affording two main topics, namely the study of light-induced effects (Figure 3) and the role of light absorbers in tissues (Figure 4). For that, the light wavelength is one of the main parameters to care about. In therapy, its choice depends on the target chromophore(s) and desired penetration depth, in diagnostics on the molecule(s) to be investigated. In both cases, we must consider which depth in the tissues we want to reach. Then, light emission parameters must be chosen to define the various radiometric quantities such as energy, power, and irradiance, besides other parameters such as light delivery regime (pulsed/continuous) and pulse characteristics. Referring to Figure 3, photochemical and photothermal effects are associated with most of the innovations in the corresponding light sources. This is probably due to their non-destructive nature, which besides physics can best call for other disciplines (photochemistry, photobiology, and photomedicine) to come into play to drive, modulate, or synergize the induced biological effects. Among all, PDT and PDI are the most considered applications nowadays [40–42]. Here, it is worth mentioning that the same molecule (e.g. a photosensitizer) can intrinsically be used for both phototherapy and photodiagnosis, exploiting different and exclusive de-excitation pathways, namely those leading to reactive oxygen species formation and fluorescence, respectively [43–45].

Examples of innovative light sources

Based on the previous discussion, let us illustrate some examples of light sources which are innovative due to their ability to respond to new and/or unsatisfied medical needs.

Wearable sources

Wearable photonic devices have many applications in healthcare, including sensors for physiological monitoring, and light sources for phototherapy [46]. The first marketed devices consisted of LED arrays that directly irradiate the skin, but the rigid structure makes it difficult to determine the treatment dosage and avoid illumination hot spots. The development of flexible and conformable lighting technologies has allowed maximum treatment efficiency at lower power and longer treatment time. Liu et al. [47] reported a wearable, flexible, and lightweight array of 55 LEDs (Figure 5) designed to be worn on a knee for osteoarthritis phototherapy with a 0–13 mW/cm^2 irradiance at 630 nm. A more innovative approach has been developed by Farrell et al. [48] proposing a conformable device made by a 1 mm thick elastomeric membrane edge-lit by specially fabricated micro sized LEDs. Nanoparticle-based scattering films (polydimethylsiloxane membrane) are utilized to extract the light from the membrane; a uniform emission of 15 $\mu W/cm^2$ is reported over an area of 2 cm^2.

Compared to LEDs, OLEDs are very thin (thickness of <1 μm) and can emit light evenly over the entire surface. Their lightness and intrinsic conformability make them strong candidates for the next generation of wearable light sources. Notwithstanding, flexible OLEDs are already in the market and widely used for displays; their applications in photomedicine are still very limited. They usually require high voltage, cannot be fabricated on stretchable and robust flexible materials with free-form shape, and the generated light power does not reach the threshold for PDT applications. The recent improvement in efficiency, stability, and brightness have allowed the realization of extremely thin and flexible OLEDs able to resist in high humidity conditions, as in the case of a plaster [49,50]. These new technological achievements have paved the way for novel photomedical applications that have recently been investigated [51]. In ref. [52], Jeon et al. proposed a deformable and high-power parallel-stacked OLED able to produce more than 100 mW/cm^2 for PDT against melanoma (Figure 6). In ref. [53], the same author reports on OLED application in wound healing.

One of the biggest limitations that hinders the usefulness of wearable devices is a continuous power supply. Batteries must be small-size, lightweight, and biocompatible. To overcome this, efficient energy harvesters with better energy management are needed. A possible approach relies on self-powered generators such as the piezoelectric and triboelectric nanogenerators [54] that

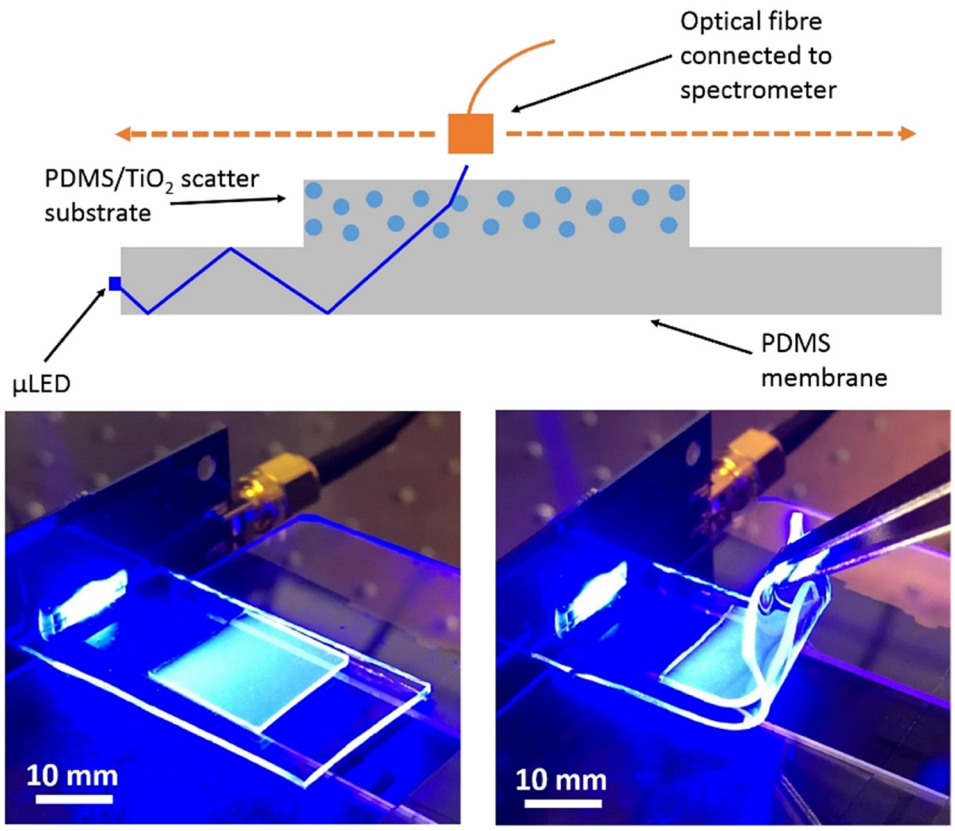

Figure 5: The top figure shows a simple sketch of the device: a thin elastomeric membrane with a scattering film on it is edge-lit by micro-sized LEDs. On the bottom part, two pictures of the device are shown. In particular, the uniform light emission and the device flexibility are clearly shown. Adapted from ref. [48].

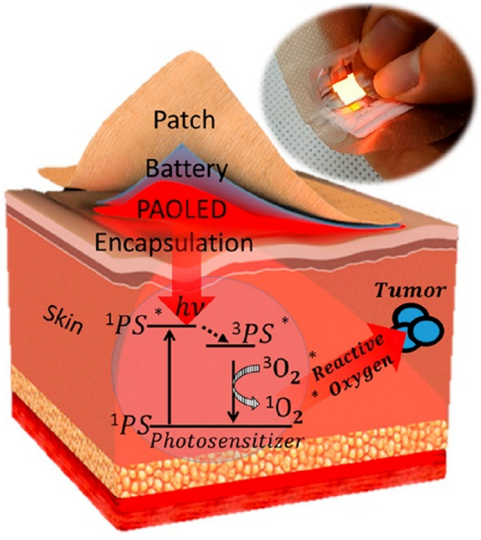

Figure 6: Parallel-stacked OLED (PAOLED) designed in the form of plaster. The schematic illustration of PDT treatment principle is also shown. Adapted from ref. [52].

convert mechanical energy harvested from the environment into electricity.

A different approach to wearable devices consists of using light-emitting fabrics based on optical fibres. Generally, optical fibres are used in telecommunication or transmission power applications, where they are requested to guide the radiation with minimal losses from one end to the other, thanks to the internal total reflection condition that takes place in the fibre core. Unlike most cases, optical fibre losses are rather requested to obtain the desired emission (illumination) geometry in phototherapy applications. Light leakage along the fibre is generally obtained via processing or macro bending of the fibre cladding [55–57]. In the first case, cladding micro-perforations allow light propagation from the fibre core to the environment. With macro bending (Figure 7, top), the fibre radius of curvature exceeds a specific critical value; this prevents total internal reflection from occurring in the core, leading to light emission along the fibre. Multiple bending can be kept in place while embedding the fibres in a stable structure, such as a textile (Figure 7, bottom). Mordon et al. [58] reported several applications of light-emitting fabrics by *in vitro* and *in vivo* experiments aimed at evaluating their

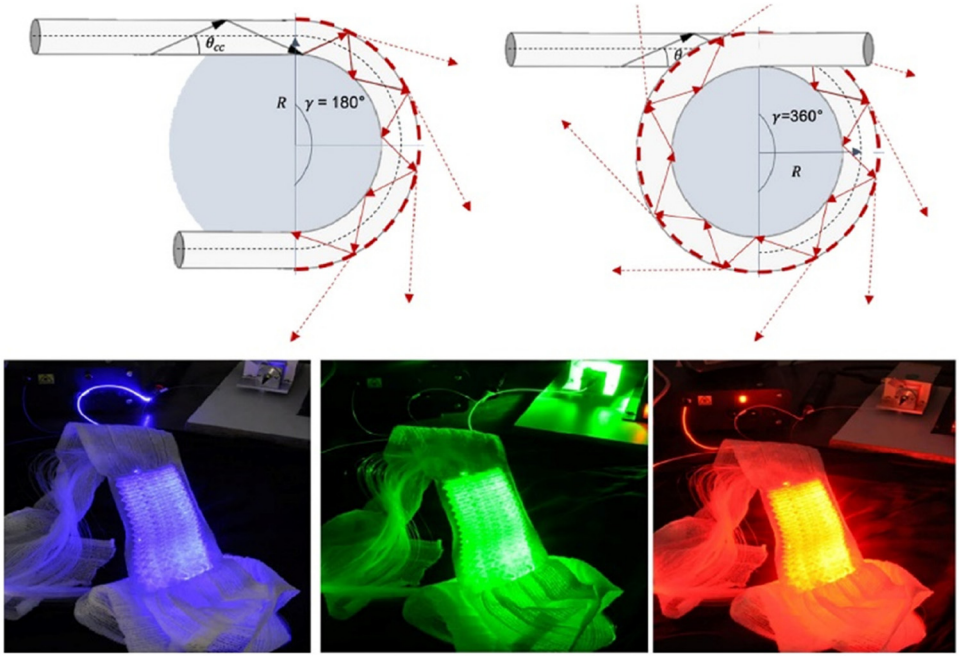

Figure 7: Top: when the radius of curvature *R* of a bended-optical fibre exceeds a specific critical value, leaking of the light propagating into the fibre is achieved. Bottom: bended fibre can be embedded in a textile structure, thus realizing a light-emitting fabric. Adapted from ref. [58].

efficacy for antitumoral PDT [59,60]. These light-emitting and plastic fabrics emit in the range 400–1,200 nm: using a 2.6 W 635 nm laser, they obtain an average irradiance of approximately 1 mW/cm^2 over a surface of about 660 cm^2 with almost 91% homogeneity. Other clinical applications include the treatment of actinic keratosis and the primary extramammary Paget's disease of the vulva [58]. Quandt et al. [61] developed a textile to be used as a wearable, long-term phototherapy device in the treatment of neonatal jaundice (hyperbilirubinemia), producing a homogeneous light emission within 4% variations. By designing a network of polymer optical fibres, they present the first example of direct manufacturing of phototherapeutic clothing realized without any post-processing of the textile material. The broad transmission spectrum of polymeric optical fibre, together with an adequate light source, should allow obtaining the needed power density requested for specific phototherapy applications.

One of the major limitations of the light delivery approach based on external, with respect to the body, sources is related to the limited light penetration depth in tissues. To overcome this restriction, percutaneous light delivery systems have been designed. The idea is to use a light-transparent material to create an array of microneedles, with a typical length of up to 2 mm, that can guide or focalize light through the skin, thus providing optical access to deep layers [62–64]. A different innovative approach to delivering light up to a 4 mm depth under the skin has been proposed by Hu et al. [65] with the development of a near-infrared rechargeable "optical battery" implant for irradiation-free continuous PDT (Figure 8). The battery is fabricated by a combination of an upconversion material with typical ultraviolet (UV)/blue emission, a UV rechargeable, persistent phosphor and a photosensitizer, assembled into a biocompatible material that can be solidified in any size and shape. Excitation of the upconversion material with just 5 s of 980 nm radiation allows the generation of 30 min persistent luminescence at 520 nm, after which a new "recharge" can be applied for the next 30 min treatment. *In vivo* experiments were performed on HT29 tumour implanted subcutaneously into mice, demonstrating the inhibition of tumour proliferation.

Sources for interstitial phototherapy

In interstitial phototherapy, one or more optical fibres are inserted into the target tissue to deliver *in situ* therapeutic light, for example, by their insertion into catheters. Most applications are in interstitial PDT (I-PDT): light sources are generally lasers, whose wavelength matches the absorption peak of the photosensitizing molecule;

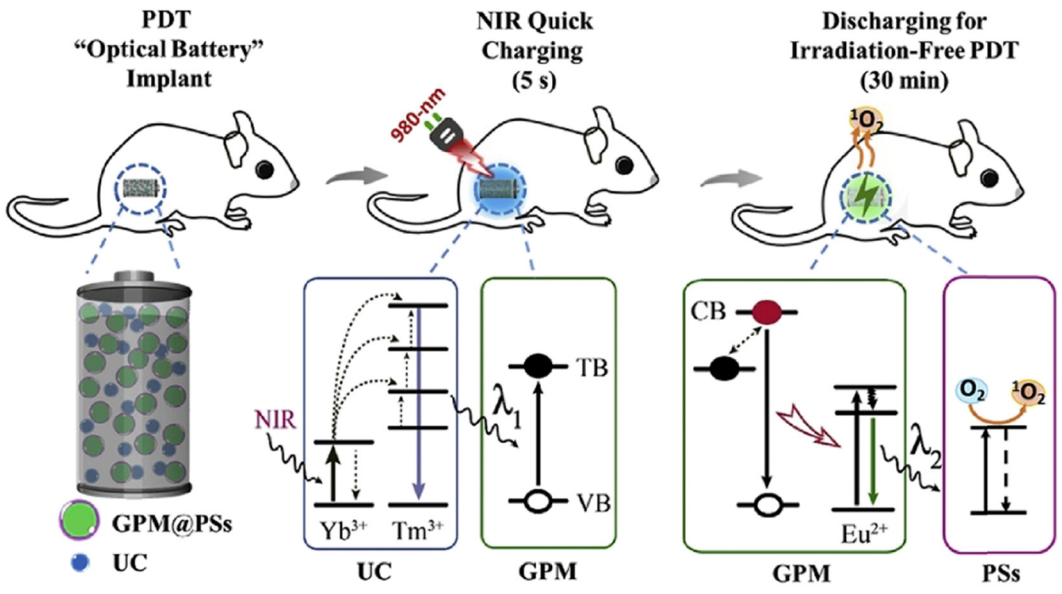

Figure 8: Schematic illustration of the "optical battery" implant for PDT. GPM: green persistent luminescence materials; PSs: photosensitizers; UC: upconversion materials; TB: trapping band; VB: valence band. Figure from ref. [65].

applications are mainly antitumoral, with different possible organs to address [66]. To completely exploit the therapeutic scheme of fibre-driven light delivery, innovation has focused on the design of various light-emission geometries (e.g. point emission from the fibre tip and cylindrical emission along the fibre). Together, treatment planning software and procedures have been developed for fibre positioning and dose release protocols both in space and in time, resembling the more established practices of treatment planning in radiotherapy. Intrinsically, I-PDT and the associated sources are more invasive than the therapeutic approach with wearable devices, though much less invasive than intraoperative phototherapy (see next paragraph). Besides, sources for I-PDT are adaptable to the specific organ and anatomical region [59,67–70] and are now being considered as an alternative (or adjuvant) to more established techniques such as surgery and radiation therapy.

Sources for intraoperative phototherapy

The most straightforward approach to delivering light in deep tissue is to take advantage of the presence of exposed areas during surgical intervention, allowing for direct light delivery. Similar to interstitial phototherapy, light is generally guided through optical fibres, possibly inserted into needles, catheters, balloons, or other devices. Generally, optical fibres are modified to emit diffuse light (Figure 9). This can be realized by adding roughness or scattering particles in the core-cladding borders. Diffuser balloons can also be employed and eventually filled with scattering liquid (typically a lipid suspension) to improve light delivery and uniformity to the tissue under treatment.

Dupont et al. [71] developed a new device for intraoperative PDT dedicated to glioblastoma treatment, consisting of a balloon coupled with a cylindrical diffuser fibre and mounted on a trocar. After tumour resection, the balloon is positioned in the surgical cavity and inflated with a diffusing solution to conform its shape to the anatomy of the operative cavity. The light source is set to provide a therapeutic fluence value at a 5 mm depth within surrounding tissues. The device allows homogeneous irradiation of the resection area, improving the treatment efficacy [72]. A novel mini-invasive approach in the glioblastoma multiforme treatment was proposed by Leroy et al. [73]. Cylindrical diffusing optical fibres are introduced inside the tumour, without large craniotomy, to illuminate the cancer cells, previously sensitized via a photosensitizer. Other recent works focused on the treatment of breast cancer [74,75]. In a different work, Chamberlain et al. [76] developed an intraoperative flexible optical fibre-based surface applicator able to administer controlled and homogeneous light irradiance during surgery within the thoracic cavity. The main drawback of intraoperative sources is that they do not allow chronic implantation, thus reducing the light delivery to a single dose.

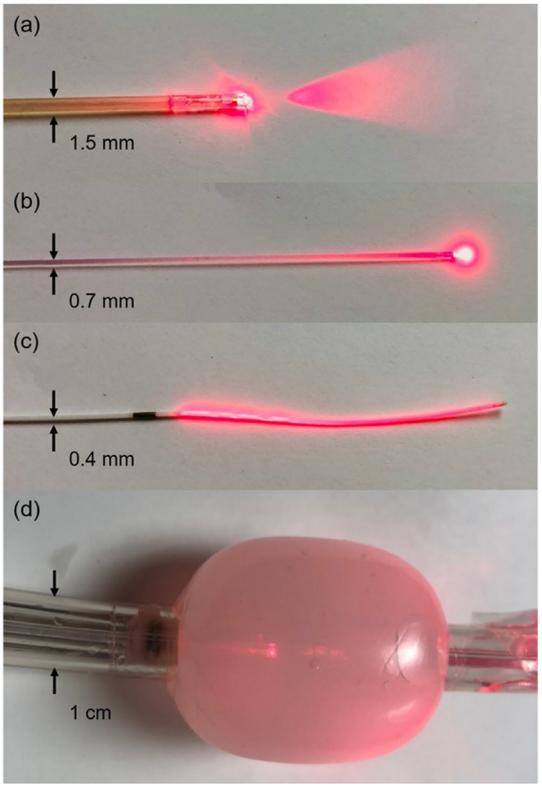

Figure 9: Fibres with (a) microlens, (b) spherical and (c) cylindrical diffusor, and (d) balloon applicator with integrated fibre surrounded by scattering medium. Image from ref. [42].

Implantable sources

A very innovative and interesting approach that can overcome the limitations discussed above is represented by implantable and wireless photonic devices, generally powered via external ultrasound or electromagnetic waves: their tiny dimensions allow direct implantation at the target size with minimally invasive procedures, such as incisional biopsy (Figure 10). Bansal et al. [77] reported miniaturized wireless powered photonic implants activated by an external radiofrequency source (1–1.5 GHz). The device consists of a helical coil and a micro-printed circuit board that also includes LEDs encapsulated in medical-grade silicone. When sufficient radiant power is sent to the device, part of its energy is extracted by the incident field via the coil and used to turn on the LEDs (660 and 400 nm), producing a total radiant power of 1.3 mW. The device can also communicate the effective light dose delivered to the surrounding tissue, thus providing a real-time wireless dosimetry system. The efficacy of this device has been tested *in vivo* for *in situ* photosensitizer activation through more than 3 cm thick tissue to suppress tumour activity in a murine cancer model. A similar approach has also been reported by Kim et al. [78] proposing an implantable micro source powered by ultrasound and enabling light delivery in deep-seated solid tumours (Figure 10). The device has red (655 nm) and blue (470 nm) LEDs and can produce up to 6.5 mW/cm^2 of optical power when powered with an acoustic wave at 720 kHz. *In vivo* tests in mice with 4T1-induced tumour (breast cancer) show light delivery capability at the therapeutic dose levels. Multiple implants can be powered simultaneously on the same tumour.

Ingestible light sources for the eradication of stomach infections

Ingestible medical devices have been developed, patented, and used in the clinical practice for several years, to provide advancement in the diagnosis and treatment of gastrointestinal tract-related conditions [79]. Most of them have a diagnostic purpose (sensing and/or sampling), and some release a payload (e.g. insulin) to perform therapy. One of the very few examples of ingestible devices for phototherapy is represented by a luminous pill for the control and eradication of *Helicobacter pylori* (*Hp*)

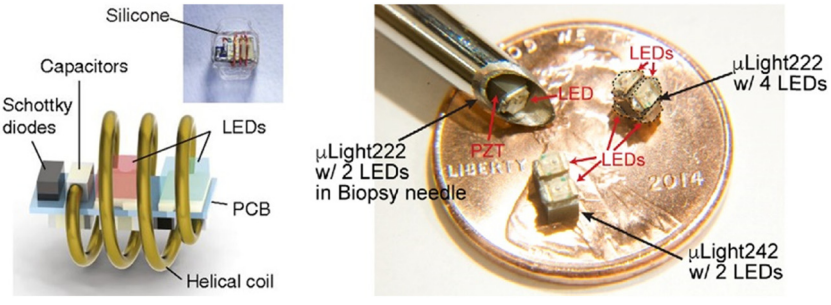

Figure 10: Examples of implantable wireless light sources powered by an external radiofrequency source (left) and by ultrasound emitter (right). Images adapted from refs [77] and [78], respectively.

infection in the stomach, whose elective therapy is based on antibiotics and associated drugs like pump inhibitors. Building on previous research on *Hp* photo-inactivation via endogenous porphyrin excitation [80–82] and subsequent clinical trials with modified gastroscopes [83,84], a new medical device was designed, patented, and prototyped in the form of a smooth cylinder-shaped capsule, provided with visible LEDs powered by a battery and driven by a programmable board [85–87] (Figure 11a and b). LED emission covers the biggest possible solid angle, being photokilling based on the passive capsule positioning inside the stomach cavity and its displacements associated with the physiological peristaltic movements. The light emission parameters have been defined following an *in vivo* action spectrum study for *Hp* photokilling (Figure 11c) obtained by semi-theoretical methods [88,89], together with safety studies on *in vitro* models [90] and more recently *in vivo* on minipigs (work under submission). Interestingly, absorption by the gastric mucosa tissue seems to have a crucial role in this case: due to *Hp* positioning on both the mucosa surface and in between the gastric plicae and rugae, the excitation light is preferentially absorbed by the surrounding tissue before reaching the bacterial target. This is compatible with green and red being the best-expected excitation wavelengths to optimize PDI [88]. The device is provided with a temperature and pH sensor; this last sensing the passage from the stomach to the intestine where phototherapy is avoided for safety reasons. In 2016, a similar device based on LED sources was designed and characterized, provided with a pH sensor and a wireless communication module, being anyway limited by blue-light emission only [91]. These devices are good examples of light delivery instead of drug delivery, especially considering the rise in antibiotic-resistance rates at a worldwide level. The similarity in the therapeutic approach with respect to antibiotics (both imply the use of "pills") makes these devices a very promising alternative also from the point of view of the patient's compliance, the final important passage between the concept of innovation and the release of the therapeutic principle, light in our case.

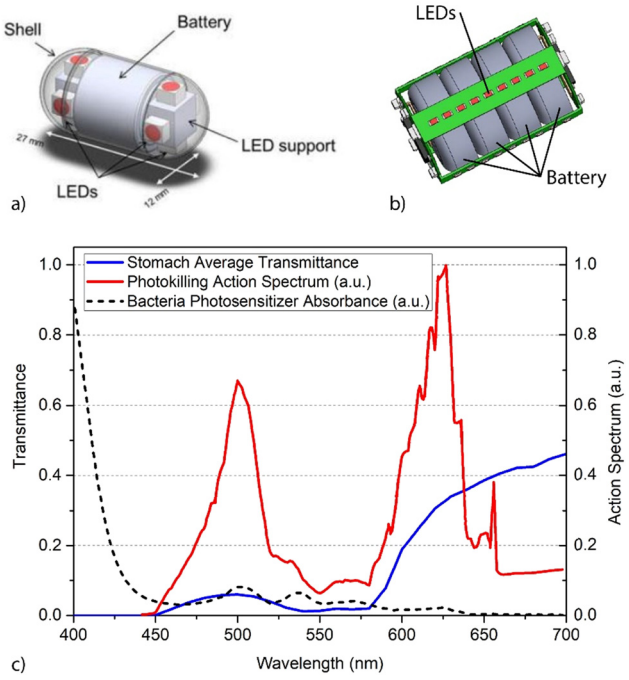

Figure 11: (a) First and (b) second prototype version of the ingestible light source for the eradication of stomach infections. In (c) the action spectrum for *in vivo* photokilling of *H. pylori* and the average stomach antrum wall transmittance spectrum. Figures (a) and (b) adapted from refs [85] and [87], respectively.

Inhalable light sources for controlling lung infections

Since the beginning, most of the research on lung phototherapy has been applied to cancer treatment [92]. Light delivery is accomplished thanks to modified fiberscopes, possibly integrating both illumination and irradiation fibres [93,94] and the synergy between different photoinduced effects, like in the case of combined photothermal and photodynamic therapies [95]. These approaches certainly contain innovative aspects, mainly from a technical point of view linked to the modification of existing diagnostic instrumentation to provide them with a therapeutic purpose.

Towards the definition of less invasive approaches, an inhalable light source based on phosphorescence has been recently proposed to perform PDI for the control of antibiotic-resistant and recalcitrant lung infections [96,97].

Through a bottom-up approach, the project encompasses the following steps (Figure 12): (i) synthesis of biocompatible and phosphorescent nanoparticles, (ii) their aerosolization and (iii) activation by external light excitation, (iv) luminous aerosol inhalation, and (v) therapeutic action via bacterial PDI. This therapeutic scheme represents a further step in an ideal path of light source "dematerialization" and towards minimal invasiveness, also considering the absence of externally administered photosensitizers. Therefore, the aerosol particles are at the same time the vehicle and the source of therapeutic photons into the various lung regions by way of their

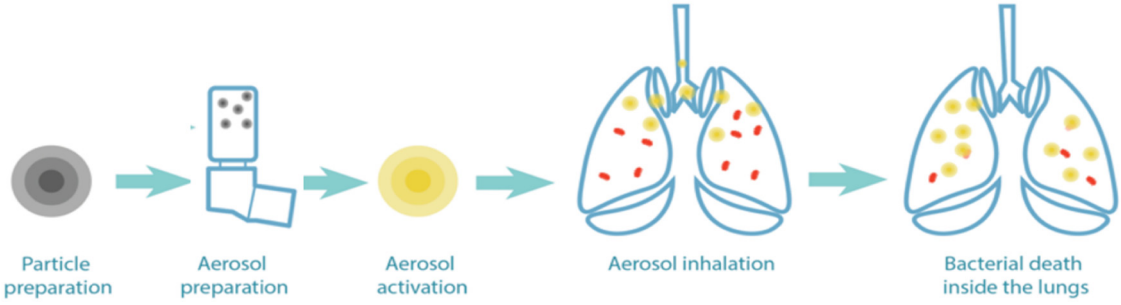

Figure 12: Light4Lungs: five-step concept.

phosphorescence properties. This does not exclude the possible and contemporary administration of exogenous photosensitizers, possibly incorporated in the aerosol particles themselves, to enhance the photokilling effect. The aerosol-mediated delivery of photons has a more "classical" (still innovative) counterpart in the aerosol-based delivery of drugs into the lungs, especially in the case of lung infections [98].

This approach starts from state-of-the-art technology for aerosolization, which must be modified to be compatible with aerosol excitation prior to its delivery. Therefore, innovation stems from both new technological solutions and the synthesis of new biocompatible light-emitting materials with a long afterglow. Correspondingly, innovative therapeutic protocols will be defined in the direction of a self-administration of the light.

Antiviral far UVC source

Light *per se* has long been used as a powerful antimicrobial. UV radiation kills viruses and bacteria by chemically altering the genetic material. The most effective wavelengths for inactivation correspond to DNA and RNA absorption peaks, located in the UVC range (100–280 nm). The most widespread technology to produce UVC radiation is based on mercury vapour lamps, emitting a significant component at 254 nm. This radiation is mutagenic and can induce skin cancers [99], cataracts, and corneal damage [100]. Therefore, although economical and efficient, these sources are not suitable for areas frequented by people, unless their use is restricted to night-time or purposely dedicated time. Innovation in this respect is especially desirable to extend the source compatibility for a "real time disinfection," applicable to a myriad of different contexts from working spaces to public transport, public/private offices, and cultural or recreational activities [101]. The key point here is represented by reaching a compromise between a low radiation penetration into human tissues (to minimize negative effects) and a good absorption by the pathogen of interest. Given the typical bacterium and virus sizes (~1 and 0.1 µm, respectively), the penetration of UVC radiation into their respective structures does not constitute a limit factor, paving the way to an effective biocidal action, which as usual depends on the light dose. These considerations bring our attention to the far UVC region. Between 170 and 240 nm, the only sources of a certain efficiency are excimer lamps and lasers (Figure 13), where excimer refers to a diatomic excited molecule generally composed of a noble gas and a halogen atom. As an alternative, UVC LEDs are still limited by low efficiency and poor emitted power especially in the far UVC region [102], making them unsuitable for clinical applications. Excimer lamps, and in particular those emitting at λ = 308 nm, have long been used in dermatology for targeted phototherapy [103]. Recent studies show that the antimicrobial efficacy of 222 nm radiation is high and comparable with 254 nm radiation. This has been demonstrated *in vitro* on both bacterial [104] and virus models [105], including

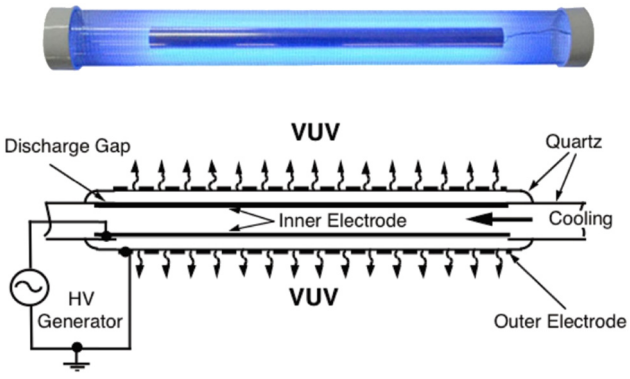

Figure 13: Picture of commercial UVC sources emitting at 222 nm (www.firstuvc.com). The sketch shows the internal components of a cylindrical excimer UVC source (adapted from ref. [111]).

coronavirus [106]. Antibacterial efficacy of 222 nm radiation has also been demonstrated in human patients' sacral and gluteal pressure ulcers. Its effectiveness also spans numerous bacterial species including methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* [107]. At the same time, the risks to human health associated with exposure to UVC radiation at λ = 222 nm seem to be much lower than those associated with UV radiation at longer wavelengths [108,109]. The reason for this lies in the very small penetration depth in tissues (a few μm at 222 nm). In the skin, far UVC radiation is absorbed by the superficial stratum corneum containing dead cells, with negligible relative presence in the underlying tissues (e.g. the dermis). Similarly, corneal damage is negligible or absent even at high UVC doses, compared to the damage induced by 254 nm radiation [110]. The net result is that the mutagenicity of far UVC seems to be substantially negligible, as is the ability to induce inflammatory reactions compared to UVC at longer wavelengths [108].

Conclusion

We have shown examples of innovative light sources for phototherapy, describing and justifying the reasons for their innovation content. Probably, the doubt remains about the "best" definition of source and of innovation: how is a therapeutic light source defined? Does it correspond merely to the light emitter itself or should it also comprise the whole device, including all the technical solutions to deliver light to the region or district of interest? Should we then refer to "innovative light-emitting devices and protocols" instead? This would probably be more suitable if the clinical application context is recalled. Talking about innovation: is it necessarily linked to new emitter solutions or, on the opposite side, to new solutions for using state-of-the-art emitters? For example, let us consider that the sun has come back again as an innovative source with the advent of daylight phototherapy in dermatology.

Among all possible novelties, non-invasiveness could be considered as the feature most research is aiming at (e.g. ingestible and inhalable sources, self-luminescent therapies, and wearable devices). Considering the results obtained up to now, one of the main goals of future work will be to avoid the loss of therapeutic effectiveness that comes at the price of non-invasiveness: wearable sources are limited by light penetration issues while un-tethered sources (inhalable and ingestible) are limited by the emitted radiant power. This is very much linked to the development of new and more effective solutions to store energy and efficiently exploit it. Fortunately, there are many different forms of energy to exploit.

Acknowledgments: The authors would like to thank Dr Maria Méndez (ICIQ, Tarragona) for useful discussions about nanoemitters and all the partners of the Light4Lungs consortium.

Funding information: This work was supported by the projects "Device endoscopico per fototerapia antibatterica intragastrica" and "Terapia fotodinamica contro il batterio *pseudomonas Savastanoi* agente della rogna dell'olivo" by Fondazione Cassa di Risparmio di Firenze. This research project is also funded by the Tuscany Region, through the "Suppression of Airborne Viral Epidemic Spread by Ultraviolet light barriers" (SAVES US) project and by the project "Light4Lungs" H2020-FETOPEN-2018-2020, grant agreement no. 863102.

Authors contributions: G.R., G.I., and F.F. wrote the original paper. All authors revised the manuscript.

Conflict of interest: F.F. and G.R. acknowledge being also Probiomedica srl. Other authors state no conflict of interest.

Data availability statement: The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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