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Phototherapy and Optical Waveguides for the Treatment of Infection

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Abstract

With rapid emergence of multi-drug resistant microbes, it is imperative to seek alternative means for infection control. Optical waveguides are an auspicious delivery method for precise administration of phototherapy. Studies have shown that phototherapy is promising in fighting against a myriad of infectious pathogens (i.e. viruses, bacteria, fungi, and protozoa) including biofilm-forming species and drug-resistant strains while evading treatment resistance. When administered via optical waveguides, phototherapy can treat both superficial and deep-tissue infections while minimizing off-site effects that afflict conventional phototherapy and pharmacotherapy. Despite great therapeutic potential, exact mechanisms, materials, and fabrication designs to optimize this promising treatment option are underexplored. This review outlines principles and applications of phototherapy and optical waveguides for infection control. Research advances, challenges, and outlook regarding this delivery system are rigorously discussed in a hope to inspire future developments of optical waveguide-mediated phototherapy for the management of infection and beyond.

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Declaration of Competing Interest

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1. Introduction

Infection refers to the process in which pathogens colonize host tissues producing a subsequent host response to respective pathogens or its toxins. Pathogens that cause infectious disease include bacteria, fungi, protozoa, helminths, and viruses among others. However, many are commonplace in the environment, and even function symbiotically with host species. For example, many symbiotic bacteria and fungi are present in gastrointestinal tract (GI), mucous membranes, and on the skin in mammals. The human body has multiple lines of physical and chemical defenses against pathogenic microbes under normal circumstances. However, if these barriers are compromised due to trauma, burns, immunosuppression, chronic illness or other comorbidities, infection can manifest in significant patient morbidity or death. Moreover, due to improper use of drug therapies, antimicrobial and antiviral treatment resistance is emerging globally with the onset of multi-drug resistant pathogens that are refractory to present pharmaceutical treatments[1]. According to the Centers for Disease control and Prevention (CDC), 2.8 million people are affected by resistant infections with an annual death toll of approximately 35,000 in the United States[2]. Furthermore, it is difficult for current systemic antimicrobials to sufficiently penetrate biofilms, a protective extracellular polymeric matrix produced by particular bacterial and fungal species, which demands high doses of medications that increase the risk of adverse effects without the promise of sufficient efficacy[3–7]. Despite government incentives, such as the Generating Antibiotic Incentives Act (GAIN), to develop novel pharmaceutical agents (i.e. antibacterial vaccines, phage therapy, immunostimulants, adjuvants, probiotics, and others), medication development is a slow and costly process relative to the emergence of resistant microbes. Further, the development of novel pharmaceutical agents still leaves the risk of resistance development to these new therapies[1, 8].

There is potential for phototherapy to be considered as an alternative or adjunct to conventional pharmaceutical therapies for infection control attributed to the low treatment resistance (with exceptions seen in photothermal and UVC therapies), and a broad spectrum of antimicrobial and antiviral activities[9–25]. Implementation of this alternative therapy into routine clinical practice can reduce the use of drug therapies and may be leveraged against existing drug-resistant strains of pathogens[9]. Most phototherapies have minimal invasiveness, and negligible systemic side effects, unlike their pharmaceutical counterparts[7, 26, 27]. Phototherapy comprises any therapeutic approach involving the use of light[9, 28–31]. Types of phototherapy can be classified according to the type of incident light and therapeutic mechanism. Categories include photodynamic, laser, photothermal, and other light-based (i.e. ultraviolet (UV) light, blue light) therapies. By illuminating an infected region with the appropriate wavelength, dose, duration, and frequency of light with or without exogenous agents (i.e. substrate, photosensitizer, or medium to propagate light), pathogens at the source of infection can be inactivated or irradicated. Amongst the widespread advantages compared to traditional therapies, there remain shortcomings of phototherapy in infection treatment, such as limited penetration depth, imperfect selectivity for pathogenic cells, lack of flexible and precise delivery, and safety issues (e.g. inflammation, healthy tissue damage, carcinogenesis) that warrant further research

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to reach the full therapeutic potential of phototherapy for infection treatment. Delivering phototherapy via optical waveguides is an auspicious approach to overcome some of the shortcomings of phototherapy by directing the propagation of light with minimal losses and less off-target irradiation than that of phototherapy alone to address local infections even to deep tissues.

Optical waveguides are indispensable to modern living being an integral component of telecommunications, sensors, and photonic integrated circuits to name a few applications. Optical waveguide-mediated phototherapy is a recently revived area of research being investigated for cancer ablation, biosensing, endoscopy, surgical laser delivery, and infection treatment[17, 32–36]. The latter application will be examined in this review. Optical waveguides are constructs with different geometries composed of dielectric materials that confine light propagation to a particular destination due to differences in the refractive indices of constituent materials[37–40]. Conventional optical waveguides are made of non-compliant and rigid materials (i.e. glasses and plastics), that are destructive to most body tissues[37–44]. Curvlite Sales developed an optical waveguide comprised of polymethyl methacrylate (PMMA), a polymer widely used for dental illumination in 1939. This and the emergence of interdisciplinary research fields, such as biomedical engineering and materials science and engineering, have since inspired the development of a plethora of transparent, biocompatible polymers intended for optical waveguides in medicine[45]. Increasingly, advanced, multifunctional, and/or stimuli-responsive optical waveguides possessing suitable mechanical and optical properties are being developed to perform in clinical environments[40, 46, 47]. The delivery of phototherapy with emerging optical waveguide technology has the potential to serve a critical role in local infection treatment, especially for drug-resistant microbes and viruses, deep tissue infections and biofilm-forming pathogens while eschewing off-site effects that are often inevitable in photo- and pharmacotherapies (Fig. 1). While other reviews eloquently focus on optical waveguide materials or medical applications, various types of phototherapies for infection and biomedical applications at large, as well as elucidation of components of such therapies (i.e. photosensitizers (PS), photothermal agents (PTAs)), this review uniquely compiles the basic principles, applications, and combinatory use of phototherapy and optical waveguide techniques specifically towards infection control. Pertinent research advances, current challenges, and future directions are highlighted in this work to shed light on opportunities for innovation and optimization of this promising therapeutic strategy to tackle the shortcomings of conventional treatments for infectious disease.

2. Phototherapy for infection treatment

The birth of phototherapy began with Niels Finsen, who was awarded the Nobel Prize for successfully treating smallpox and cutaneous tuberculosis using red and UV light in 1903[48, 49]. Phototherapies are effective at treating pathogenic organisms through various mechanisms all with the commonality of administering some form of light to a colonized site. This review categorizes the types of phototherapies according to pathogen inactivation mechanisms. The classifications reviewed herein include photodynamic therapy (PDT), photothermal therapy (PTT) and direct light-based phototherapies. The above classification was based on the pathogen inactivation mechanisms rather than the wavelength or the

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form of the light source. For example, when the laser was used to excite photosensitizers or photothermal agents to generate ROS or heat, the phototherapy should be categorized as PDT or PTT, respectively. When the laser was used directly to change the membrane potential of the pathogen, the phototherapy should be categorized as direct laser therapy. Similarly, if the visible light was used to generate ROS, the phototherapy should be categorized as PDT no matter which wavelength was used.

2.1 Photodynamic therapy

Among the types of phototherapies, photodynamic therapy is the most commonly studied technique. Photodynamic therapy (PDT) or photodynamic inactivation (PDI) is a means of phototherapy combining light, a substrate, and a photosensitizer to generate free radicals and reactive oxygen species (ROS) to eradicate undesired cells[50, 51].

2.1.1 Mechanism and principles—The underlying principles of PDT can be best illustrated by a Jablonski diagram (Fig 2a). This diagram demonstrates that after a quantum event, an electron in the singlet ground state (S_0) absorbs a photon exciting it to a higher energy level (i.e. the singlet excited state (S_n)) with the same spin. Subsequently, the excited electron may return to the ground state from S_1 to S_0 by means of releasing a photon (fluorescence; lifetime ~10^{-8} s) or vibrational energy dissipated as heat by a process referred to as internal conversion (IC). The process when the excited electron changes spin state and enters the lowest excited triplet state (T_1) is known as intersystem crossing (ISC). Afterwards, the electron relaxes to the S_0 state in the form of photon release (phosphorescence, lifetime above 10^{-6} s) or as heat through IC. Based on quantum mechanics principles, the radiative decay process from T_1 to S_0 is forbidden. Hence, the decay time from T_1 to S_0 relative to S_1 to S_0 is longer[52]. The longer lifetime of triplet excitons results in the increased opportunity to transfer electrons (type I reaction) or energy (type II reaction) to target molecules rather than decay through internal conversion by heat. These processes are referred to as photosensitization and are necessary for PDT activity in infection treatment. The molecule which absorbs photons is known as the photosensitizer (PS), while the target molecule of photosensitization is referred to as the acceptor or substrate.

Following a type I reaction, two radicals or radical ions (i.e. $O_2^{\bullet -}$ and $^{\bullet}OH$) and/or H_2O_2 are generated. In contrast, type II reactions result in singlet oxygen ($^1O_2$) generation following energy transfer to ground state molecular oxygen ($^3O_2$)[51, 53]. According to current evidence, both type I and II PDT result in the damage of most biomacromolecules including proteins, lipids and nucleic acids to kill cells and has roles in inflammatory processes[54, 55]. The potential differences in pathogen control between applying type I and type II PDT has yet to be elucidated. It should be noted, however, that type I and type II photosensitization generally occur concurrently in PDT where the ratio of type I to type II reactions is dependent on the PS, PS concentration, substrates, and environment[56]. The differences between the effects of type I and II reactions in addition to the downstream effects of damage to biomacromolecules inflicted by PDT can be a focus of future research. Such studies may deliver a more profound understanding of the killing mechanisms of type

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I and II reactions to direct novel designs of PSs and inform researchers how to protect host cells while selecting for pathogenic cells.

There is some inherent selectivity for pathogenic cells by PDT, which is believed to be attributed to: 1) the smaller cell volume and larger specific surface area of microbial cells and viral particles compared to that of mammalian cells, which results in a more probable binding and uptake of PSs by pathogenic cells; 2) the limited diffusion distances of ROSs (e.g. that of $^1O_2$ is 100-200 nm) make it less probable for ROS to penetrate and damage enough cellular structures in larger host cells than that of the small pathogenic cells; 3) the higher rate of division and metabolic processes of pathogenic cells compared to that of host cells leads to increased sensitivity to free radicals and ROS[51, 57]. Increased selectivity for pathogenic cells may be facilitated by local application of PSs, as opposed to systemic administration, as well as through conjugating targeting moieties to PSs (e.g. cationic groups)[51].

2.1.2 PDT components and materials—The three necessary components for PDT include incident light, a photosensitizer, and a substrate. Since PDT has a broad working wavelength range, various light sources can be used, such as light emitting diodes (LEDs) and lasers. Ultrafast laser is a promising light source in PDT due to high spatial accuracy, the minimal potential for non-specific tissue damage and enhanced penetration depth[58]. As the source of excitation, light should be of the appropriate energy to bring PSs to the excited state. Near infrared (NIR) light can penetrate deeper into tissues than shorter wavelength light. Hence, NIR-activated PSs are more desirable for infection treatment. Some PSs have working wavelengths in the NIR region; however, the working wavelength of most current PSs is within the UV-visible region. For example, the absorption of riboflavin falls into UV to blue light range and blue light is commonly used for riboflavin activation in practical PDT applications[59–61]. Methylene blue (MB), toluidine blue O (TBO) and protoporphyrin IX (i.e. PPIX, active form of the prodrug, 5-aminolevulinic acid (5-ALA)) all work in the red light range in practical PDT applications[59, 62–65]. Similarly, most aggregation-induced emission luminogens that can function as PSs typically work in the visible region[66–68]. There are few reported PSs that can respond to NIR, such as indocyanine green (ICG)[59, 69]. More photosensitizers used in clinical trials and antimicrobial applications can be found in the following reviews[10, 17]. A suitable triplet state energy of the PS is also crucial for ROS generation in PDT. Photoluminescent materials with efficient ISC, high quantum yield of triplet excitons, and relatively long triplet state lifetime constitute ideal properties for PSs for PDT applications to achieve sufficient free radicals and ROS generation. If the lowest triplet state energy level (T_1) of the PS is lower than the energy level of excited state of molecular oxygen ($O_2(b^1\Sigma_g^+)$ and $O_2(a^1\Delta_g)$), the energy/electron transfer process is unable to occur. The rate constant of ISC (k_{ISC}) is dependent on the spin orbital coupling (SOC) constants (ξ) as well as the energy gap between the singlet and triplet states (ΔE_{ST}) according to perturbation theory and Fermi's golden rule[70, 71]. Materials with large ξ, having a greater ability to alter the electronic spin direction, and low ΔE_{ST} will increase k_{ISC}. To achieve a large ξ, heavy atoms (i.e. atoms with atomic number (Z) greater than 30 and halogens except for fluorine) are used to exploit the heavy atom effect. Therefore, it is common to covalently conjugate halogen atoms to PS molecules to enhance ROS

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quantum yield in PDT materials[72]. Ruthenium (Ru), platinum (Pt), and iridium (Ir) may also be used. However, these elements are not only costly, but they are also undesirable for biomedical applications due to inherent toxicity. Another way to increase ROS quantum yield is to reduce the ΔE_{ST}. This is commonly done by incorporating a donor-acceptor (D-A) structure with a twisted conformation[73, 74]. However, this design approach is not desirable for PDT applications because the twisted conformation results in a reduced extinction coefficient and hypsochromic shift (i.e. blue shift) compared to non-twisted structures[75]. Substrates that are conducive to effective PDT should possess an appropriate redox potential and energy level to increase the proclivity to accept energy or electrons from PSs. It is also critical that substrates are abundant physiological environments. Main substrates include molecular oxygen and water.

There are several types of materials studied for PDT applications, such as organic-metal complexes and inorganic semiconducting materials[76]. A comprehensive review of PSs can be found in the review by Lan et al.[77] When metal oxides and other inorganic materials are excited by light with greater photoenergy than the band gap of the material, valence electrons can travel across the band gap to the conductive band resulting in a charge separated state, which facilitates electron transfer reactions (i.e. type I photosensitization) (Fig. 2b)[78]. Several metal oxides[79–87] and carbon nanomaterials[86, 88–97] were reported to have promise as PSs for PDT. However, metal oxides mainly absorb in the UV range limiting their penetration depth[56]. As a result, combining upconversion materials, of which can convert lower-energy NIR light to higher-energy UV emission, with metal oxide nanomaterials[98–106] and applying optical waveguides can be two feasible approaches to overcome this issue. Some other PDT related works are also listed here including novel developments involving composite organic and inorganic nanomaterials and metal peroxides[107–117].

For most organic materials, following photoexcitation electrons undergo rapid vibrational relaxation to the S_1 and only a minority of electrons will transit to T_1 through ISC. However, owing to biocompatibility, tunability, processability and low cost, organic materials are PSs popular for biomedical applications. Efforts to enhance ISC processes in organic materials have occurred since the 1970s when the first generation of organic PSs were developed, which included hematoporphyrin derivatives. The first-generation PSs suffered from poor selectivity and low extinction coefficients within their therapeutic window. The second-generation PSs emerged in the late 1980s. Representative second-generation PSs include tetrapyrrolic macrocycles and derivatives, transition metal coordination complexes, and cationic compounds, such as phenothiazines, xanthenes and cyanines. With the development of nanotechnology, the design of the third generation of PSs mainly focusing on improving delivery and targeting ability of PSs by nanocarriers[56]. For example, Zhang *et al.* developed a nanoassembly of Förster resonance energy transfer (FRET) photosensitizer pairs using FDA approved chlorin e6 (Ce6) as the donor component and 1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide (Dir) as the acceptor[118]. For infection control, there has been several attempts to use conventional organic PSs, such as ICG[119, 120] and polymer-based PSs[121] alone or in combination with other therapeutic components to form synergistic PDT nanosystems. Conventional organic PSs usually contain highly conjugated chromophores, which tend to self-assemble in the aqueous

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environments leading to photoluminescence quenching (i.e. aggregation-caused quenching (ACQ)) typically destroying the PDT performance. Opposite to ACQ, aggregation-induced emission (AIE) was identified by Benzhong Tang in 2001[122], which is attractive for PDT applications. There are many reports studying AIE-based materials and platforms in PDT[68, 123–149].

Molecular oxygen serves as an excellent substrate due to its triplet ground state ($O_2(X^3\Sigma_g^-)$), which is conducive to accepting energy of triplet excitons that are the products of ISC[57, 150, 151]. Fortunately, molecular oxygen is relatively stable, inert, and abundant in the biological environment with an ability to travel far distances and permeate cell membranes and is a primary substrate of type I reactions. Water (H_2O) is common substrate for type II reactions[56, 152–155].

2.1.3 Applications of photodynamic therapy for infection treatment—Many studies have demonstrated remarkable success with PDT against a wide array of pathogens including bacteria, fungi, viruses, and protozoa. Moreover, PDT is effective in biofilm producing organisms, which are difficult to treated by conventional pharmaceutical therapies and often require high doses of medication[156–167]. PDT treatment has been employed for several clinically relevant infections, such as diabetic ulcers, osteomyelitis, middle ear infection, acne, viral lesions, burns and wounds, and periodontitis in addition to being evaluated blood sterilization as detailed in other review works[9, 10, 12, 168–171].

PDT has been most often studied in bacterial and fungal models. For infections caused by bacteria, PDT has demonstrated to be effective against Gram-positive species like *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), as well as, Gram-negative species like *Acinetobacter baumannii, Pseudomonas Aeroginosa*, and drug-resistant strains of Gram-negative bacteria[9, 172–216]. Lombard and colleagues have demonstrated efficacy to treat brain abscesses by topically applying hematoporphyrin intraoperatively and irradiating the infected site for five minutes[217]. Acne vulgaris, caused by the colonization of *Cutibacterium acnes* (formerly *Propionibacterium acnes*) results in skin lesions typically found on the face, back, and upper arms and has been shown to be sensitive to PDT therapy using different PSs and wavelengths of light. Examples of PDT regimens for acne vulgaris include methyl aminoevulinate (MAL) with blue light, 5-aminolevulanic acid (ALA) with 550-570 nm light, and indocyanine green (ICG) activated by NIR irradiation[218–222]. Colonization of the skin by *Corynebacterium minutissimum* in superficial skin layers and folds leads to an infection known as erythrasma and has been treated with red light PDT[223–225]. More recent publications are listed here[226–243].

Among fungal species, *Candida* is one of the most prevalent pathogenic fungi, which has attracted many *in vitro* and *in vivo* studies[63, 244–256]. Cutaneous infection commonly found in skin folds caused by *Candida albicans* and *Trychophyton* species has been treated with red light and ALA PDT. Other studies have also demonstrated PDT activity against *Trichophyton rubrum*[257, 258], *Aspergillus fumigatus*[259, 260], *Metarhizium anisopliae* and *Aspergillus nidulans*[261]. More recent antifungal PDT works are provided in the following references:[262–281].

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For viral infections, study results have indicated that compared to non-enveloped viruses, enveloped viruses are more sensitive to PDT[282–287]. The difference in sensitivity may be due to increased accessibility of the phospholipid membrane, which is critical for the pathogenicity of enveloped viruses, by ROS. *Herpes simplex* virus (HSV), a highly contagious virus leading to lesions of the lips and genitals, was popularly treated with PDT in the late 20th century until it as found that it lacked therapeutic benefit while having adverse effects and potentially increasing risk of cancer. Human papilloma virus (HPV) infection manifests as genital warts and increases risk for cervical cancer. HPV has been treated with both been treated with PDT using a 630 nm laser with polyhematoporphyrin as well as with ALA- and MAL-PDT. ALA-PDT with activation from a helium-neon laser showed significantly less recurrence and comparable efficacy when compared to CO_2 laser therapy after two treatments[288]. However, other randomized controlled trial results have demonstrated no difference in recurrence between the two treatment types[289]. Other studies using ALA and red light have similarly shown high response rates with low recurrence. Vesicular stomatitis virus (VSV), a disease that plagues many livestock animals, caused by *Rhabdoviridae* and Semliki forest virus transmitted by mosquitoes in Africa caused by *Togaviridae* infection are enveloped viruses sensitive to PDT with buckminsterfullerene (C_{60})[283, 290].

The coronavirus disease (COVID-19) pandemic caused by the SARS-CoV-2 virus remains a serious threat to public health. Various therapeutic strategies, such as pharmacotherapeutic therapies have been investigated[291, 292]. PDT is considering to be a promising therapeutic approach to treat SARS-CoV-2 infection[293–314]. For example, Kipshidze *et al.* first proposed using PDT and sonodynamic therapy (SDT) to treat COVID-19 by injecting porphyrin-based photosensitizers either systemically or locally into the lungs through the pulmonary artery using micro-catheters and in the absence of specialized photonics or in resource-limited settings, some PSs may be activated using transthoracic continuous wave ultrasound (SDT)[315, 316]. Weber *et al.* reported a successful reduction of SARS-CoV-2 viral load in 20 COVID-19 positive patients by PDT and verified by qPCR[317]. Besides PDT, several other biophotonic technologies and phototherapies were proposed or conducted to diagnose or treat COVID-19 or help biomodulation and rehabilitation during and after COVID-19[318–330].

Current antimicrobials are often ineffective against parasitic and protozoa infections that cause diseases like granulomatous amoebic encephalitis (GAE), amoebic keratitis, leishmaniasis, malaria, trypanosomiasis, and giardiasis due to rapidly emerging resistance[17, 331–334]. Consequently, several studies have been conducted to show activity against these refractory microbes using PDT. Sand flies from the *Phlebotominae* subfamily are a vector for the protozoan parasites in the genus *Leishmania* that can lead to a disease known as leishmaniasis that burdens people in developing nations. Clinical studies showed topical PDT is safe and effective in the treatment of cutaneous leishmaniasis boils. Some results have demonstrated significantly better efficacy compared to treatment with paromomycin and methylbenzethonium chloride. Further, PDT has been shown to be effective against protozoa that were refractory to other therapies[9, 332, 335–339]. There are several studies on the efficacy of PDT for microbial killing *in vitro* and *in vivo*[332, 340–345]. Other notable results of PDT to treat protozoa and parasitic organisms

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are as follows: Kassab *et al.* reported a complete inhibition of viability of *Acanthamoeba palestinensis*[346]; Chen *et al.* demonstrated that PDT using hypocrellins B (HB) induced complete arrest of the growth stage of protozoa and cysts in a dose-dependent manner[347]; investigation from Mito *et al.* showed that MB-mediated PDT reduced the respiratory activity of *Acanthamoeba castellanii* trophozoites (i.e. growing state of protozoa) in an MB-concentration dependent manner[348]. For *Plasmodium* spp., two studies demonstrated that PDT treatment can induce effective inactivation and can be used as an alternative approach to antimicrobials to control the infection[349, 350]. Other evidence showed that PDT is also capable of eliminating *Trypanosoma cruzi*, a protozoan parasite common to Latin America causing Chagas disease[351–356]. More recent publications are also listed here[357–373].

Another therapeutic approach to prevent the spread of infectious diseases is through treatment of pathogen vectors (i.e. insects and pests). PDT has been reported to inactivate pest populations of *Anopheles*, which transmits malaria, and *Aedes*, which mainly spreads diseases like dengue fever, yellow fever, West Nile virus, eastern equine encephalitis, and Zika virus[374–379]. More recent and related publications on PDT for mosquito control are listed here[380–390]. This preventative approach is a promising technique to reduce disease transmission.

Since therapeutic resistance to conventional antimicrobials is a leading global concern, some groups have investigated the potential for pathogens to develop resistance to PDT. To date, evidence does not demonstrate induced resistance of pathogens to PDT therapy. This is likely due to the fact that ROS have various structural and metabolic targets that harm pathogens, rather than single target like conventional antibiotics, making it more difficult to develop a viable resistance mechanism[17, 18]. Lauro *et al.* tested whether the photosensitizing action of porphycenes leads to the selection of photoresistant cells or a change in the spectrum of sensitivity to the action of different antibiotics and no appreciable resistance and no difference in sensitivity to antibacterial drugs were found[11]. Tavares *et al.* reported that PDT treatment using Tri-Py^{+}-Me-PF as a photosensitizer presented a promising approach to efficiently destroy *Vibrio fischeri* and recombinant *Escherichia coli* after a single treatment. After treatment, the microorganisms did not recover their viability and after ten generations of partially photosensitized cells neither of the bacterial species developed resistance to PDT[19]. Giuliani *et al.* also demonstrated that 20 consecutive antimicrobial PDT with RLP068/Cl did not result in any resistant mutants[20].

2.1.4 Challenges for PDT materials—Although PDT is a promising therapy option for infection treatment, it is still a method that can be improved. For example, PSs that absorb long wavelengths of light often necessitate large conjugated systems, which lead to strong π-π interactions and aggregation, causing a reduction in ROS quantum yield. Additionally, current PSs with a large two-photon absorption cross section (δ) that are desirable for NIR excitation and resulting increased penetration depth possess high intramolecular charge transfer (ICT)[391–393]. However, ICT usually facilitates non-radiative decay of an excited state, which strongly competes with energy transfer from PSs to molecular oxygen, and hence harms the production of ROS[394]. Furthermore, a PS that exhibits high ICT possesses a high propensity for intermolecular charge transfer,

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which also promotes non-radiative decay diminishing its therapeutic activity[395–398]. Moreover, large conjugated systems also increase hydrophobicity and therefore, reduce water solubility of photosensitizers limiting biological applications. Currently, poor water solubility can be improved using nanocarriers[75, 399–407]. Although AIE can enhance the ROS quantum yield in the aggregated state, the current PDT platform still suffers from poor water solubility, complicated composition, poor reproducibility, unstable, harsh and high-cost synthesis conditions. Another challenge for PDT is patient tolerability to therapy. Due to incomplete sensitivity for pathogens, ROS production and chemicals used for PSs may lead to patient discomfort or harm. There have been reports of tissue damage *in vivo* and minor burning at the site of treatment[9]. Hence, increasing selectivity for bacteria over host cells is another area worth attention to minimize patient harm and optimize efficacy. This calls for a deeper investigation into underlying mechanisms to instruct ideal irradiation regimens and PS designs.

2.2 Photothermal therapy

Photothermal therapy (PTT) is comprised of: photothermal agents (PTAs) and incident light. The light sources of PTT are the same as those of PDT. However, unlike photodynamic therapy, PTT is not dependent on oxygen or other substrates for efficacy. Instead, incident light interacts with PTAs to elevate the temperature of infected sites and inactivate pathogens[408]. Hence, materials that can efficiently convert light to heat energy (vibrational dissipation through ISC) are appealing candidates for PTT. Photothermal conversion efficiency (ηPT) can be calculated by equation (1):[409–411]

$$\eta_{PT} = \frac{hA\Delta T_{max}}{I} \quad (1)$$

where h is the heat transfer coefficient, A is the surface area of the system, ΔT_{max} is the temperature difference between the maximum steady-state temperature and ambient temperature, and I is the power of the incident light. A method to calculate heat transfer of metallic nanomaterials has also been developed and requires measurement of the extinction cross sections of the samples[23, 412–415].

2.2.1 Classification and mechanisms of PTT—PTT treatment is divided into three subtypes depending on the thermal therapeutic range as follows: diathermia (<41 °C); hyperthermia (41-46 °C); and thermal ablation (>46 °C)[23, 416–420]. Diathermia is a mild treatment used for radiation and chemotherapy that sensitizes cells through increasing blood flow[23, 416]. Hyperthermia can induce protein denaturation and aggregation, loss of cell membrane integrity, and DNA cross-linking resulting in cellular dysfunction and eventual inactivation[23, 417, 418, 421]. Studies have shown that treatment with hyperthermia PTT can sensitize pathogenic cells towards heat[419], antibiotics[422] and other therapies[420]. In thermal ablation, stress caused by heat results in coagulative necrosis and irreversible damage of cells within a few minutes. Temperatures exceeding 60 °C leads to rapid necrosis of cells will occur owing to protein denaturation and enzyme inactivation[23, 416, 423].

2.2.2 Materials used in PTT—To date, several PTA candidates have been reported to achieve thermal ablation temperatures. Inorganic materials include carbon-

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based nanomaterials[97, 424–426], metallic nanomaterials[427–431], phosphorus-based nanomaterials[107, 110, 115, 116, 417, 432–434], metal-organic frameworks (MOFs) [114], manganese dioxide[115, 435], metal sulfides[116, 408, 436], metal peroxides[108], organic dyes[117, 437, 438], and conjugated polymers[439–441]. Major types of organic PTAs include cyanine- [112, 442–458], diketopyrrolopyrrole-[459–462], croconaine-[463–466], porphyrin-[467–470], polymer-based agents[471–481] among others[109, 482–485]. Additionally, AIE-based materials have emerged as a novel family of PTAs[148, 149, 486–496]. Many organic PSs can be viable PTAs since they can be tailored to dissipate absorbed light through internal conversion and/or intersystem crossing generating heat with or without ROS generation. The heat generation mechanisms of inorganic materials are more complicated and diverse that that of organic ones. There is a recent review by Zheng *et al.* detailing the primary photothermal mechanisms of inorganic materials: 1. the localized plasmon surface resonance (LSPR) effect present mainly in metals and semiconductors, metal oxides, and quantum dots; 2. relaxation of electron-hole pairs in low electron density semiconductors; and 3. ladder-like energy level of rare earth ions[23].

2.2.3 Applications of PTT for infection control—There have been plenty of successful *in vitro* and *in vivo* studies testing vast antimicrobial applications of PTT. Chen *et al.* and Xu *et al.* highlighted recent advances of nanomaterial-based PTT and its potential in antibacterial treatment[497, 498]. Fan *et al.* reported a metal-organic-framework (MOF)-derived 2D carbon nanosheet platform with PTT capability for localized bacterial eradication. This work achieved nearly 100% bactericidal efficiency at low concentrations while providing rapid and safe skin wound disinfection without damaging skin tissues or yielding accumulative toxicity[499]. Liu *et al.* developed humic acid (HuA) encapsulated zeolitic imidazole framework-8 (HuA-ZIF-8) nanocomposites. Synergistic antimicrobial action occurred through concomitant photothermal activity and zinc (Zn^{2+}) release demonstrating excellent bactericidal efficiency against *S. aureus* and *E. coli* (i.e. 99.59% and 99.37%, respectively) upon 20 min of NIR irradiation[500]. Wang *et al.* proposed a synthetic, intelligent hydrogel for *S. aureus* and biofilm detection and treatment. The system worked by changing in color in response to pH change caused by bacteria colonization followed by treatment by achieving local hyperthermia under irradiation with a NIR laser (808 nm) that was able to penetrate biofilms[501]. Qing *et al.* described a smart nanostructure, Thermo-Responsive-Inspired Drug-Delivery Nano-Transporter or TRIDENT. This system was capable of fluorescence monitoring and synergistic killing of bacteria through using the photothermal effect to facilitates increased permeation of imipenem, a broad-spectrum antibiotic, into cells. The TRIDENT system showed desirable *in vitro* and *in vivo* MRSA eradication even at low doses[502]. Yan *et al.* reported a pH switchable nanoplatform, which was fabricated by grafting polyaniline (PANI) and glycol chitosan (GCS) onto the surface of persistent luminescence nanoparticles (PLNPs). Through persistent luminescence imaging, PTT selectively destroyed pathogenic cells due to the higher affinity of PLNP-PANI-GCS for bacterial cells as well as provide a stronger photothermal effect in acidic environments fostered by bacteria colonization. *In vivo* imaging-guided PTT to bacterial infection abscess showed effective treatment[503]. Liu *et al.* developed an enzyme-responsive delivery antibacterial system, AA-Ru-HA-MoS_2. This system used mesoporous ruthenium nanoparticles (Ru NPs) as nanocarriers and

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loading the prodrug of ascorbic acid (AA), an antioxidant encapsulated by hyaluronic acid (HA) to combat resistant bacterial infections by combining chemical and photothermal therapies[504]. Some other representative works may also be found in the following references[119–121, 426, 505–522]. For more information regarding disinfection of surfaces using PTT, the reader is encouraged to consult the review by Zou *et al.*[426].

2.3 Direct light-based therapies

Certain forms of incident light and wavelengths can damage pathogenic cells without the need for exogenous compounds. These direct light illuminations provide a simple and noninvasive means to control infection. The following sections comprise overview and evidence of direct laser therapy as well as direct UV and direct blue light illumination therapies for pathogenic inactivation.

2.3.1 Direct laser therapy—

"Laser" is an acronym for "light amplification by stimulated emission of radiation". Although laser light can be used in PDT and PTT to activate PSs or generate heat, respectively, there are laser therapies that possess different inactivation mechanisms against pathogens. Ultrafast laser therapy and dual-wavelength laser therapy are two direct laser therapies that will be discussed in this section.

Ultrafast (ultrashort) lasers administer short pulses of light to achieve peak power that can reach up to gigawatts (GW) in magnitude, which is sufficient to achieve two-photon absorption[17, 523]. For infection control pulse durations are typically on the order of femtoseconds (10^{-13}). Femtosecond laser therapy has been reported to be effective against enveloped and non-enveloped viruses[524–532], Gram-positive and Gram-negative bacteria[529], as well as fungi[533]. Proposed mechanisms of action are specific to the type of pathogen. In viruses, hydrogen bonds, hydrophobic interactions, and some covalent bonds (i.e. disulfide bonds) can be disrupted by the mechanical agitation under femtosecond laser illumination[529, 534]. Meanwhile, bacterial and fungal DNA may be damaged through two-photon absorption of visible femtosecond lasers[529]. There is evidence that supercoiled DNA in bacteria are relaxed by femtosecond lasers inducing cell death[535]. These unique mechanisms confer selective killing of targeted pathogens while leaving healthy cells unharmed[535].

For dual-wavelength laser therapy, two different wavelengths usually in the red to NIR range of laser are applied simultaneously. There are few investigations to date studying mechanisms, safety, and efficacy of this therapy[536]. Evidence suggests the efficacy of dual-wavelength laser therapy is attributed to a decrease of the transmembrane potential of respective pathogens and an increase in ROS generation resulting from optically-mediated mechanotransduction of cellular redox pathways[537]. However, it is noted that currently available studies demonstrate successful inactivation of various pathogens, such as *S. aureus*, MRSA, *E. coli, C. albicans*, *T. rubrum*, as well as *Pantoea agglomerans* in pressure ulcer model[536–538]. Remarkably, Krespi *et al.* reported that 870/930 nm laser treatment can re-sensitize erythromycin-resistant bacteria. The authors postulated the change in the cellular redox state due to the light therapy suppressed the activity of drug efflux pumps, a common mechanism of antimicrobial resistance[538].

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2.3.2 Direct UV therapy—UV light can be divided into three spectral regions: UVA (315-400 nm), UVB (280-315 nm), UVC (100-280 nm)[539, 540]. Among them, UVC is the most effective and commonly used wavelength range for disinfection attributed to formation pyrimidine dimers after absorption by nucleic acid strands. Moreover, UVC light may also damage proteins in aromatic amino acid residues, which have maximum absorption in the UVC region. Specifically, phenylalanine has an absorption maximum at 260 nm, tyrosine at 275 nm, and that of tryptophan is near the UVC region at 295 nm[52, 539, 541].

There are several *in vitro* and *in vivo* studies demonstrated the efficacy of UVC therapy against bacterial and fungal infections as well as in species that produce biofilms[542–547]. Clinical investigations have also been completed by Freytes *et al.*, Nussbaum *et al.* and Thai *et al.* to treat ulcers caused by MRSA[548–550]; Thai *et al.* also confirmed that UVC can kill other bacteria, such as *P. aeruginosa*, *S. aureus* and MRSA present in the superficial layers of chronic wounds[551]; Shimomura *et al.* demonstrated that UVC has potential to eliminate multiple species of bacteria and be used in prophylaxis of catheter related infections[552]; Boker *et al.* successfully treated onychomycosis, a fungal infection of finger and toe nails, using UVC irradiation[553]. It should be noted that induced resistance has been reported to direct UV therapy[22]. Several publications on direct UV therapy to treat COVID-19 are listed here[554–562].

Although there are several studies which indicate that short-term, UVC therapy at appropriate fluences does not induce significant damage to human cells and tissues[544, 563–567], the safety concerns of UVC therapy need to be taken into consideration prior to use in real-world applications. Since UVC can cause damage to DNA and protein, prolonged and repeated exposure to UV light can harm host cells leading to sequelae like skin cancer and burns[568, 569]. UVC can also lead to ophthalmological problems, such as photokeratitis (i.e. snow blindless or welder's flash), cataracts, and chronic retinopathy, limiting the applications of UVC therapy in eye infections[570–573]. Inflammation may also be induced by UVC irradiation (i.e. sun burn)[574–576]. Treatment regimens that are effective with minimal exposure and direct delivery of UVC light to an infected area can mitigate damage to healthy tissue. Although delivery of UVC light using optical waveguides is a current challenge, precise delivery of therapeutic light could be a plausible solution to these safety concerns.

2.3.3 Direct blue light therapy—Blue light is typically defined as wavelengths between 400 to 500 nm having less energy than ultraviolet light[17]. Wavelengths falling in this blue light range can be further subclassified as violet, blue and cyan. Therapy predicated on blue light has drawn increasing attention due to its higher safety profile compared to UV light with relatively less photodegradation of the molecules it irradiates. As opposed to PDT, an exogenous photosensitizer is not necessary in blue light therapy due to endogenous photosensitizers (e.g. porphyrins and flavins) and blue light receptors present in microbes. Although, the mechanism of blue light therapy is not fully elucidated yet, current evidence indicates blue light therapy works similarly to PDT in which free radicals and ROS are generated after photosensitizer excitation causing subsequent damage to macromolecules[27, 577–580].

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Blue light has broad-spectrum activity against both Gram-positive and Gram-negative bacteria as well as fungi *in vitro* and *in vivo.* Wavelengths between 402-420 nm have been reported to be the most effective range to inactivate bacteria. Wavelengths between 455 nm-470 nm have shown activity against *S. aureus*[578, 581–593]. Recently, Lu *et al.* reported a combination therapy of blue light and the photochemical, carvacrol, had synergistic effects to cure acute and chronic biofilm-associated *A. baumannii* as well as MRSA infections in third-degree burn wounds of mice. Furthermore, survival was higher in the light treatment groups *P. aeruginosa* skin wound infections of mice. Excellent pathogen targeting was exhibited due to the abundance of porphyrin-like molecules in bacteria[21]. Consistent with other studies, the authors did not find evidence of induced resistance after up to 20 cycles of treatment[19–21].

2.4 Light source, penetration depth and irradiation mode

Optical penetration depth (δ) is the distance at which the light intensity reduces to $\frac{1}{e}$ of the initial light intensity[594]. Multiple factors, such as wavelength, light source, and tissue physiology can affect penetration depth of light in living tissues[595]. Endogenous fluorophores, especially hemoglobin and melanin, have a strong absorption below 600-700 nm[594–596]. Therefore, NIR light (700–2,500 nm) can penetrate biological tissues more efficiently than visible light because these tissues scatter and absorb less light at longer wavelengths[594–597]. At wavelengths longer than 950 nm, however, the absorption of water and lipids increases drastically, which would adversely affect light transmission in tissue[596, 598–603]. Therefore, the region from about 600 to 1300 nm is often called the optical window of tissue[595, 597, 604–606]. However, NIR light longer than 850 nm was found to be less effective in activating PSs in practical PDT because of the relatively fast non-radiative transition resulting from the narrow energy gap and the insufficient triplet energy level[595, 604, 607, 608]. Thus, current desirable PSs should possess strong absorption at the wavelength ranging from 600 to 850 nm. There are experimental reports of penetration depths of various lights in different tissues. Ogawa and Kobuke stated based on two publications that generally, the penetration depth ranges between 0.5 and 1.5 mm at the wavelength from 480 to 600 nm and gradually improves to 4–5 mm with increasing wavelength[606]. Kim and Darafsheh reported $\delta < 0.5$ mm at 400–430 nm, 1 mm at 500 nm, 2–3 mm at 630 nm, and 5–6 mm at 700–800 nm in most tissues[594]. Stolik *et al.* reported how δ changes upon varying wavelengths of red and NIR light in human *ex vivo* tissues[609]. Clement *et al.* and Ash *et al.* reported that red light penetrates 4–6 mm beneath the surface of the skin, blue light penetrates around 1 mm, and ultraviolet light hardly penetrates human tissue[610]. Such limited penetration depth of phototherapies largely hinders their wide applications in deep tissue.

As for the light source, take PDT as an example, no single light source is ideal for all PDT applications, even with the same PS[604]. PS absorption spectrum, location and size of lesions, and tissue characteristics should be considered when the light source of PDT was chosen[604]. Both lasers and incandescent light sources have been used for PDT and show similar efficacies[611]. Compared to the pumped dye lasers, diode lasers are smaller, more cost-effective, have facile installation, a longer operational lifetime, and are capable of automated dosing[604]. Light-emitting diode (LED) is an alternative light source with

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relatively narrow spectral bandwidths and high fluence rates[612, 613]. Complex dosimetry, such as total light dose, light exposure time and light delivery mode (single, fractionated and metronomic light delivery) can affect the clinical efficacy of PDT[495] and the light fluence rate also affects PDT response[614]. Integrated systems that measure the light distribution and fluence rate interstitially or at the irradiated tissue surface can inform how to adjust the light output for effective treatment. Examples of uses of various light sources for PDT treatment include, the use of lasers can be coupled into fibers with diffusing tips to reach the lesions in the urinary bladder and the digestive tract[604, 615]. Inflatable balloons can be fit into organs with strongly scattering material on the inside to evenly disperse light are also commercially available[604, 615]. Furthermore, implanting a light source in solid organs under image guidance is feasible[604]. The proper combination of PSs, light sources, and treatment parameters is crucial for an optimal PDT efficacy[616, 617].

The most commonly applied irradiation mode in phototherapy is single light delivery. The light dose can also be administered in a fractionated manner, which means there is a dosing interval (seconds to hours) between two illumination doses[618]. In phototherapies with exogeneous compounds, such as PDT and PTT, the exogenous agents may also be administered in a fragmented manner[618]. The metronomic mode refers to low doses of exogeneous agents administered concomitantly with light over several hours[618, 619]. Several publications have reported fractionated PDT mediated pathogen inactivation and explored the antimicrobial efficacy difference between fractionated and single light delivery PDT. For example, Misba and Khan observed a 6–6.5 $\log_{10}$ reduction of planktonic and 3.6–4.2 $\log_{10}$ reduction in biofilm after irradiation with fractionated light compared to continuous light administration[620]. Sampaio *et al.* demonstrated that MB-mediated PDT was efficient to achieve total microbial load reduction in both fractionated and continuous modes, but in fractionated mode it was possible to use a lower light dose[621]. The metronomic mode has been tested in a preclinical brain tumor model with PDT[619] but not for antimicrobial applications to date. Both *in vitro* and *in vivo* results from the preclinical brain tumor model showed enhanced induction of apoptosis of cancer cells compared to acute, high-dose PDT (aPDT) and it worth to study the feasibility and efficacy of metronomic mode in antimicrobial phototherapy.

3. Current challenges and considerations in phototherapy

Amidst the multitude of therapeutic mechanisms and promise of phototherapy for infection control, there remains inherent limitations and considerations that can be found in Table 1. Main drawbacks common to each of the phototherapies include limited penetration depth, limited working wavelength ranges, incomplete selectivity for pathogenic cells, and off-site effects. Illumination treatment should be simple, fast and effective to facilitate patient adherence and practicality in the clinical setting.

Many of the drawbacks of PTT mirror that of PDT. PDT and PTT are both non-selective techniques that may target not only pathogenic microbes, but also microbes that are symbiotic with the host. By guiding light to the exact infected site, which is feasible with optical waveguides, collateral symbiotic flora and healthy tissue damage can be minimized. There are some reports on active-targeting nanoparticle systems or platforms

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with conjugated binding components so that PSs and PTAs actively bind to the target cells and can be only activated by specific wavelength of light illumination, which makes PDT and PTT safer and more accurate[622]. Additionally, PSs and PTAs may have inherent chemical toxicity or poor biocompatibility, which can lead to local irritation or damage[23, 77, 408, 426, 437, 497, 623, 624]. Moreover, patients exposed to sunlight or other strong light sources after receiving PDT or PTT treatment may potentially acquire over exposure and activation of PSs or PTAs[623, 624]. In terms of resistance, some studies have reported induced microbial resistance to PTT treatment within the hyperthermia temperature range via high expression of heat shock protein, a molecular chaperone that repairs thermal damage to cells[23–25]. Therefore, when designing materials, it is important to consider the resultant treatment temperature, the possibility of induced resistance in response to PTT treatment, and to consider measures to combat the possibility of induced resistance and minimize thermal damage to host tissue.

Regardless of wavelength, power, and source of light is used, light will inevitably be attenuated due to absorption by and scattering within tissues. The epidermal, dermal, and hypodermal layers of human skin have respective thicknesses of roughly 0.1 mm, 1.5-2 mm and 7-20 mm[625–627]. Light must be able to penetrate at least this much for superficial infections and more for infections beneath the skin. However, the penetration depth of 480 to 600 nm light generally ranges between 0.5 to 1.5 mm, and even longer wavelengths of light that have a higher penetration depth can only travel a couple millimeters into mammalian tissues[595, 604, 606, 628–630]. Multi-photon excitation techniques can help increase penetration depth, but still fall short of biomedical and clinical demands[606, 631–633]. Moreover, multi-photon excitation techniques necessitate extensive training, large instrumentation and delicate handling for proper operation making implementation into the clinical environment difficult.

Access to difficult-to-reach areas of the body may also be limited without the guidance of therapeutic light. In efforts to overcome limited penetration depth and off-site effects of phototherapies, optical waveguide technology can be used to precisely deliver phototherapy to the infection site[210, 578, 634–636]. The different types of phototherapies for infection treatment are illustrated in Fig. 3.

4. Optical waveguides

4.1 Basic principles and material requirements

As the name indicates, optical waveguides direct the propagation of particular wavelengths of light to a desired destination. The geometries of optical waveguides vary including fibers, films, strips, slabs, and microneedles[37–44]. Step-index optical fibers, which possess discrete differences in the refractive indices at the interface of constituent materials are the most prevalent of the optical waveguide design used in biomedical applications and infection control due to high mechanical flexibility and ability to guide light over long and variable distances without significant losses. Therefore, the following section will focus on the basic principles and applications of step-index optical fibers in conjunction with phototherapies to treat infection.

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The refractive index (***n***) describes how fast light travels through a material relative to the speed of light in vacuum and is a material-specific property:

$$\boldsymbol{n} = \frac{c}{v} \tag{2}$$

Here, ***n*** is refractive index (RI), c is the speed of light in vacuum (3.0×10^8 m/s), and v refers to the speed of light through a certain medium. Snell's Law describes the behavior of incident and refracted light at an interface by the given equation (3):

$$\boldsymbol{n}_1\sin\theta_1 = \boldsymbol{n}_2\sin\theta_2 \tag{3}$$

Where $\boldsymbol{n}_1$ and $\boldsymbol{n}_2$ are the RIs of medium 1 and 2, respectively, θ_1 is the angle between incidence and the normal and θ_2 is the angle between refraction and the normal. If $\boldsymbol{n}_1 > \boldsymbol{n}_2$, then $\sin\theta_1 < \sin\theta_2$ and $\theta_1 < \theta_2$. As θ_1 increases, θ_2 will follow. Refraction will disappear once θ_2 reaches 90° and the incident light will only be reflected. The corresponding angle for θ_1 is known as the critical angle (θ_c) and this phenomenon is described by total internal reflection (TIR) (Fig. 4). The core principle of optical waveguides is TIR (apart from photonic crystal fibers (PCFs) and holey fibers (HFs) which are predicated on the photonic bandgap effect). To achieve TIR, the RI of the inner layer of the waveguide must exceed that of the outer cladding layer or medium (i.e. air)[37–39, 41–44]. The most common approach to meet the RI requirements conducive to TIR is to fabricate a concentric cylinder structure with two layers. The inner layer is where incident light traverses and is referred to as the core, while the outer layer is referred to as the cladding (Fig. 4). There are non-cladding types of optical waveguides that treat the external environment as the outer layer to the core. However, waveguide designs without cladding come at the cost of increased risk for optical loss and sensitivity to the surrounding environment compared to cladded optical waveguide designs[45, 639, 640].

4.2 Materials for optical waveguides used in biomedical applications

A viable optical waveguide should have the ability to transmit light over variable distances with low optical loss over a broad range of therapeutic wavelengths. The refractive index of the core material should always be larger than that of cladding material over the working wavelength range to keep light attenuation low. Core materials should also minimally absorb the incident light to prevent losses during propagation and it is additionally desirable for materials to have optical clarity[641–648].

Conventional optical waveguide materials include glass, plastic, crystal, semiconductors, ceramics, and metals[45, 649–651]. However, these materials suffer from poor biocompatibility, non-degradability, poor tunability of properties, and noncompliance with mechanics of most body tissues. Taken together, conventional optical waveguide materials are poor candidates for waveguides in the clinical setting[45]. Since of the first biomedically compatible waveguides composed of PMMA was developed for dental illumination in 1939 many researchers have been developing optical waveguide materials and designing optical waveguides to achieve improved biocompatibility, degradability, chemical functionality,

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and desirable mechanical properties, and tunability of each with sufficient light-guiding performance relative to conventional waveguides for biomedical use[45, 652–657].

Several developed optical waveguides composed of various biocompatible materials that may be used to deliver phototherapy can be found in Fig. 5. Biomaterial candidates can be categorized according to their origin (i.e. natural or synthetic) and properties (i.e. mechanical, degradability, hydrophilicity, etc.). Natural materials, such as agar[658], gelatin and agarose[659], silk and silk proteins[639, 660, 661], have been processed to perform as biocompatible optical materials. Even mammalian and bacterial cells have been used to fabricate as optical waveguide biomaterials. Muller cells were found to serve as optical fibers helping image projection through retinal tissue with less image distortion and light scattering loss[662, 663], and *E.coli* was reported to also form functional optical waveguides[664, 665]. Synthetic materials have reduced batch-to-batch variability and less inherent antigenicity compared to that of natural materials[666–668]. Furthermore, synthetic biopolymers have the benefits of tunable properties that can be done through adjusting composition (i.e. ratios of constituent monomers or polymer(s), compositing, chemical conjugation, etc.), polymer concentration, molecular weight, functional groups, and degree of crosslinking. Hydrogels (i.e. superabsorbent polymers that absorb as much as 90% of their weight in water), elastomers, and biodegradable or nonbiodegradable polymers may all be synthetic or natural in origin[669]. Polydimethylsiloxane (PDMS), for example, is a synthetic elastomer that is bioinert and non-toxic, but is not biodegradable. Although not used in clinical setting yet, a biodegradable optical waveguide may be beneficial as it evades the need for a secondary surgery for removal and the associated risks. Among biodegradable polymers for optical waveguides, polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic) acid (PLGA), and silk fibroin are some of the most used and successfully developed materials in tissue engineering[639, 670–674]. More recently, citrate-based polymers, a new class of synthetic biodegradable polymers exhibit great potential for optical waveguide applications. Citric acid, a Krebs cycle intermediate, is the core chemical used in the citrate-based polymer syntheses, through which various biodegradable elastomeric polymers can be synthesized by reacting citric acid with different diols and/or amino acids via a facile polycondensation reaction. Differing from the natural polymers as silk or the aforementioned traditional synthetic degradable polymers that usually have limited tunability, citrate-based polymers are advantageous due to their ultrafine tuning refractive index ($\sim 10^3$), mechanical strengths (from tens of Pascal to mega Pascal), degradation rates (from a few days to over a year), antibacterial and anti-inflammatory effects in addition to excellent biocompatibility[666, 675–695]. Furthermore, due to the abundant carboxyl and hydroxyl groups in the polymers, citrate-based polymers are easily functionalized for drug tagging, imaging, sensing, or to bear desirable properties, such as electrical conductivity and luminescent properties. Therefore, citrate-based polymers are an ideal class of biodegradable polymer platform for the design of multifunctional devices promising for versatile biomedical applications such as tissue engineering (blood vessel, bone, nerve, skin etc.), wound healing, theranostic cancer nanomedicine, and biosensing[666, 675–702]. Among the citrate polymers, poly(octamethylene citrate) (POC) synthesized by reacting citric acid and 1,8-octanediol has been used to develop a number of FDA-cleared biodegradable interference screws and suture anchors such as Citrelock™,

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Citrefix™, and Citrespline™ for various orthopedic indications including knee, foot and ankle, shoulder, elbow, and wrist applications[667, 668]. To tune the refractive index of POC, another citrate polymer, poly(octamethylene maleate citrate) (POMC) was synthesized by partially replacing citric acid with maleic anhydride in synthesis. Although there is only a minor difference in the chemical structure between POC and POMC, POMC possesses a higher refractive index over a broad range of wavelengths from 300 nm to 1000 nm with an index difference of ~0.003, similar to that between the cladding and the core of silica optical fibers. Both POC and POMC have relatively low absorption (<0.13 dB/cm) at visible and near-infrared wavelengths. A flexible step-index optical waveguide was fabricated using POC as the cladding while POMC as the core that is promising for organ scale light delivery and collection[653].

One of the future trends will be to develop novel optical biomaterials with multi-functionality and stimuli-responsive properties to facilitate more practical and versatile clinical applications in which they can be used. For more extensive reviews on biomaterials used for optical waveguides and biophotonic applications, the reader is invited to peruse the following publications: [45, 703, 704].

4.3 Existing works on phototherapies delivered via optical waveguides to treat infection

Use of optical waveguides with phototherapy permits more freedom to vary multiple treatment factors than phototherapy alone. For example, total energy delivery, rate of energy delivery, penetration depth, and location can be tuned with optical waveguides[618]. Besides, implantable optical waveguides, integrated with sensing and/or imaging modules enables easier and more accurate post-treatment and real-time assessment. The use of optical waveguides for biomedical applications has established and investigational uses in skin imaging, scar analysis, biosensing, cancer ablation, and deep tissue photomedicine (Fig. 5)[655–657]. However, attempts to combine the optical waveguide and phototherapy for treatment of infections at present is underexplored and results implicating efficacy are mixed leaving a large unmet need for research to optimize this therapy alternative. By using optical waveguides to deliver phototherapy for infection treatment, minimally attenuated light is guided through the center of the waveguide to the target area to circumvent the physical barriers with minimum power loss and necessary penetration depth. Optical waveguides can precisely deliver phototherapy to deep tissue infections (i.e. respiratory, gastrointestinal tract) and to photosensitive regions that off-site exposure would be otherwise harmful (i.e. eye area, use of high energy light) (Fig. 6). The use optical waveguides to deliver shorter wavelengths for already available PSs and PTAs activated by UV to visible wavelengths of light could expand the optical range of PDT and PTT in treating various infections not achievable previously by PDT or PTT alone[7]. Moreover, optical waveguides that deliver phototherapy may be designed to possess multifunctionality and/or stimuli-responsive activity is an emerging area of research that provides additional therapeutic utility to standard phototherapy treatment. For example, many current research works are focused on the designs and applications of optical waveguide for pathogen sensing[634, 705–709]. The Seok Hyun Yun group demonstrated for the first time efficacy of a cell-containing optical waveguide composed of a polyethylene glycol (PEG)-based hydrogel to achieve *in vivo* cell-based sensing and therapy[710].

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Representative examples delivering phototherapy by optical waveguides are detailed here and can be found in Table 2. Bisland *et al.* proposed PDT as an alternative treatment to antibiotics for osteomyelitis using a bioluminescent strain of biofilm-producing *S. aureus* grown on kirschner wires (K-wires). The *S. aureus*-coated K-wires were exposed to methylene blue (MB) or 5-aminolevulinic acid (ALA)-mediated PDT either *in vitro* or following implantation into the tibial medullary cavity of SD rats. *S. aureus* infections were subject to PDT for 10 days post inoculation. 300 mg kg^{-1} of ALA was administrated intraperitoneally followed by percutaneous light illumination (635 ± 10 nm; 75 J cm^{-2}) 4 hours later via an optical fiber placed onto the tibia. This treatment resulted in significant inhibition of bacterial growth[711]. For treatment of dental infections, PSs can be deposited into dental pockets followed by direct irradiation with light noninvasively via optical fibers. This procedure can be usually completed in a few minutes giving optical waveguide PDT therapy a significant advantage over treatment with antiseptics and antibiotics that have difficulty reaching sufficient concentrations in the infected dental area, longer treatment times, and systemic side effects[27, 712]. Kömerik *et al.* reported effective inactivation of *Porphyromonas gingivalis* by applying up to 48 J of a 630 nm laser light via an optical fiber in the presence of toluidine blue[210]. Lee *et al.* used a phenothiazinium-based PS and delivered low-intensity red laser light via an optical fiber with a diffuser to access the root canal lumen to treat Gram-positive bacteria without damaging the host tissues[636]. Soukos *et al.* performed antimicrobial PDT with *E. faecalis* using methylene blue (25 μg/mL) for 5 min followed by exposure to 30 J/cm^2 of 665nm light delivered by an optical fiber with multiple cylindrical diffusers that uniformly distributed light over 360° to achieve a 53% killing rate, which was then increased to 97% after increasing the power to 222 J/cm^2[713].

Furthermore, optical waveguide-mediated delivery of phototherapy may be a potential treatment option for *Helicobacter pylori* infection in the stomach, but still demands further research to optimize treatment conditions for sustained eradication. Lembo *et al.* were the first ones to report in patients infected with *H. pylori*, the whole stomach can be safely illuminated with violet light. In this study, a novel light source consisting of laser diodes connected to diffusing fibers to deliver 408 nm light to yield a significant antibacterial effect[716]. Moreover, Ganz *et al.* delivered violet light (405 nm, 40 J/cm^2) to 1 cm diameter spot-size in the gastric antrum via an optical fiber to achieve inactivation of *H. pylori*[585]. Kipshidze *et al.* recently proposed to direct energy delivery through an endoluminal microcatheter with an illuminating balloon containing a diffusing fiber-optic array at its distal tip capable antiviral, antibacterial, anti-inflammatory, and vasculoprotective properties of the blue and red wavelengths of light[311]. Khan *et al.* developed an optical fiber-based photonic crystal fiber sensor for THz sensing of COVID-19 disinfecting products[323]. Stawiki proposed to treat COVID-19 by using diffusive optical fibers to deliver UVC light with repeated short-term tracheobronchial illumination[561]. Shan *et al.* developed the aforementioned biodegradable, citrate-based step-index optical fibers with low optical loss of 0.4 dB/cm. A proof of concept study using a 20 mW 532 nm laser in Sprague-Dawley (SD) rats was conducted to demonstrate a strong potential for active optical waveguide mediated-phototherapy for infection treatment[653].

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4.4 Challenges and considerations in phototherapy delivered by optical waveguides for infection treatment

Although combining optical waveguide techniques with phototherapy shows promising efficacy for infectious diseases, there are some drawbacks to their unique advantages. Firstly, optical waveguides deliver the light locally meaning an invasive approach and incisions to the site of deep tissue infections that are not easily accessible are typically necessary[639, 656, 661]. To minimize invasiveness, microneedles have been used to penetrate skin to guide light into tissues[655, 717]. However, the penetration depth was still limited. For deep tissue light delivery, traditional non-biodegradable optical waveguides need to be removed from the body after treatment. By replacing the traditional optical waveguides with biodegradable counterparts, the removal step may be evaded. The biocompatibility of optical waveguides, its respective degradation products if degradable, and PSs and PTAs used should all be considered to minimize the risk of adverse host responses. Regarding the optical waveguide material design, it is imperative to be mindful of the desired operational wavelengths, area of treatment, and tissue mechanics for the design and fabrication of effective optical waveguides.

5. Outlook and perspectives

Since antibiotic resistance is becoming increasingly serious with the emergence of “super bugs” refractory to conventional therapies, the development of alternatives or combinational therapies is critical to combat infectious diseases. Namely, phototherapy appears to be a promising approach for the local infection treatment and prophylaxis due to its broad-spectrum antimicrobial and antiviral activities, low invasiveness, minimal systemic side effects, and no evidence of inducing treatment resistance (except direct UV therapy and PTT). Phototherapies reviewed in this paper include photodynamic (PDT), photothermal (PTT), direct laser, direct UV and direct blue light therapies. These modes of therapies have been combined with optical waveguide technologies to target a variety of pathogens through multiple mechanisms with access to deep or normally inaccessible infections and overcome the off-site effects that are experienced by phototherapies alone. It is likely that the biodegradable optical waveguides may also be loaded with drugs as a drug delivery platform. After the phototherapy treatment, as the optical waveguide degrades, the drugs may be released in a designed manner, either enhancing the therapeutic efficacy or facilitating the healing process. Moreover, the combination of optical waveguides with PDT and PTT should enable the use of PSs and PTAs that are responsive to lights at UV regions for deep tissue treatments. PSs and PTAs that are only UV-light responsive are usually smaller and less conjugated than their NIR-responsive counterparts resulting in better solubility, processability, biocompatibility and stability.

Another area at the forefront of research is stimuli-responsive and multi-functional optical waveguide-mediated phototherapies for more precise targeting and treatment. Phototherapy can be combined with drug delivery options as well as with other nonpharmacologic treatment modalities, such as sonodynamic therapy. Phototherapy combined with sensing and diagnostic techniques can potentially be developed into point-of-care theranostics that enable feedback-informed treatment through monitoring the treatment progression in real-

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time. The development of biodegradable optical waveguide materials with tunable refractive indexes, biomimetic mechanics, flexibility and multifunctional or self-cleaning potential is a promising direction for the design of new optical waveguide-mediated phototherapies.

Furthermore, an underexplored phenomenon in the field of optical materials that is gaining increasing attention is organic ultralong room temperature phosphorescence (URTP)[718–722]. Thus far, materials with URTP capabilities have been studied for applications, such as anticounterfeiting, data encryption and bioimaging investigations[722–728]. However, the biomedical applications of URTP materials haven not been extensively studied other than some bioimaging applications. The ultralong triplet lifetime of URTP materials confers higher probability of energy/electron transfer compared to the traditional PSs making them appealing for PDT. Some possible reasons that URTP materials have not been exploited for PDT applications include: 1. The absorption maximum of the current URTP materials is always in the UV range with few reports in the violet range thus it is not suitable for deep tissue treatment by itself; 2. Crystallization is the most common and effective approach to achieve URTP. Unfortunately, crystals that have compact structure prevents the diffusion of the quencher (e.g. molecular oxygen), which attenuates energy/electron transfer to substrates resulting in poor ROS generation efficiency. There should be a niche area for the use of URTP materials if combined with optical waveguides. Optical waveguides may allow the delivery of shorter wavelengths that activate URTP materials in deep tissues for phototherapies . With such long lifetimes and high triplet quantum yield, PDT in conjunction with URTP materials loaded in the optical waveguides has great potential to further improve the efficacy of phototherapy for infection control.

The use of phototherapies in combination with optical waveguides overcome many of the challenges and shortcomings of the conventional pharmaceutical and phototherapies. Optical waveguide-mediated phototherapies have gained significant attention as a powerful therapeutic approach or alternative to the current antimicrobial and antiviral therapies and holds great promise for the management of the infection-related diseases and beyond.

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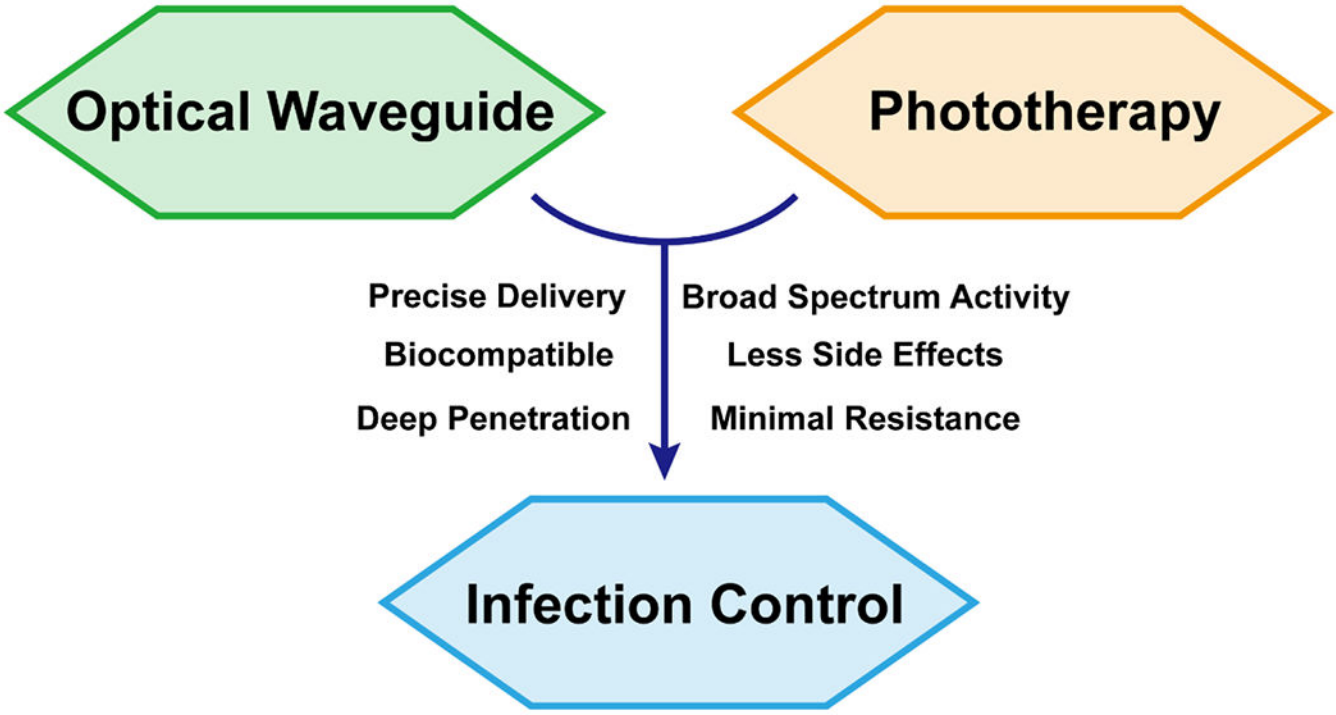

Fig. 1.

The integration of phototherapy and optical waveguide technology is an innovative and promising approach to combat pathogens and tackle the rapidly emerging threat of multi-drug resistant microbes and viruses. Optical waveguides of which are ideally biodegradable, biocompatible, and mechanically compliant with the working environment can direct incident light to the immediate site of infection minimizing off-site effects and systemic side effects that are often inevitable with traditional phototherapy and pharmaceutical therapy, respectively. The use of optical waveguides for treatment of infection harnesses the benefits of phototherapy, meanwhile overcoming the barrier of limited penetration depth expanding the use of phototherapy to deep tissue infections. Through the multiple mechanisms of action that phototherapy provides and the precise delivery by optical waveguides, there is great potential to fulfill the requirements of infection control caused by a variety of pathogens including those refractories to conventional therapies while reducing the need for drug treatment.

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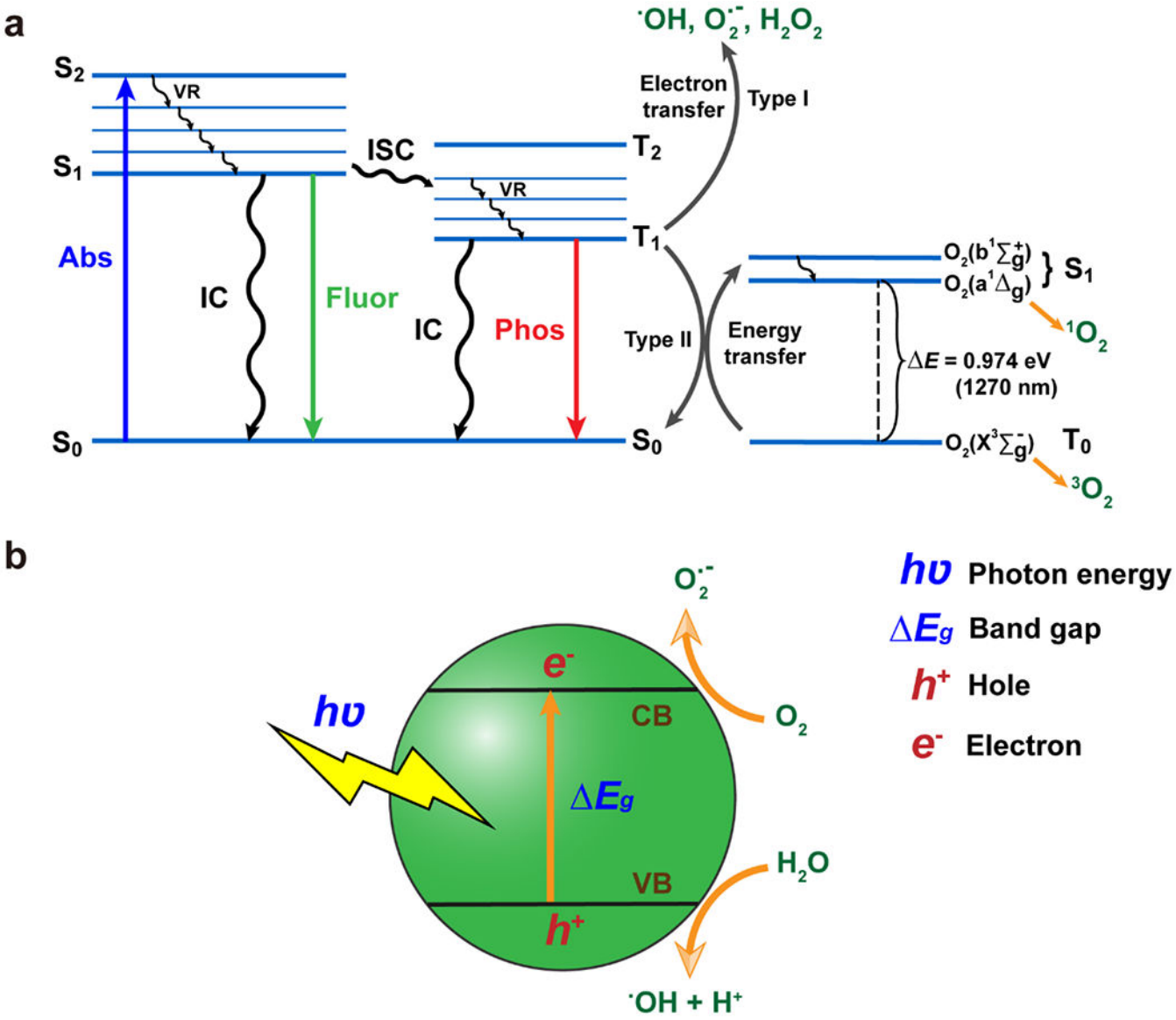

Fig. 2.

Underlying principles of PDT and PTT. (a)The Jablonski diagram demonstrates the general mechanism of reactive oxygen species and free radical generation in PDT and PTT upon photon absorption (abs) by a photosensitizer or photothermal agent, respectively. Following photon absorption, electrons are promoted from the ground state (S_0) to an excited state (S_n; n≠0) then relax by emitting energy as heat (VR, IC) or light (fluorescence or phosphorescence). Type I reactions result in the generation of free radicals ($O_2^{\bullet-}$, $^{\bullet}OH$) and H_2O_2. Type II reactions result in singlet oxygen generation ($^1O_2$). (b) Schematic of free radical generation in metal oxide nanomaterials. Valence electrons are excited from the valence band (VB) to the conductive band (CB) when exposed to light that exceeds the energy of the bandgap. The resulting charge separated state is conducive to energy transfer (type II) reactions producing free radical species, which degrade microbial and viral macromolecules.

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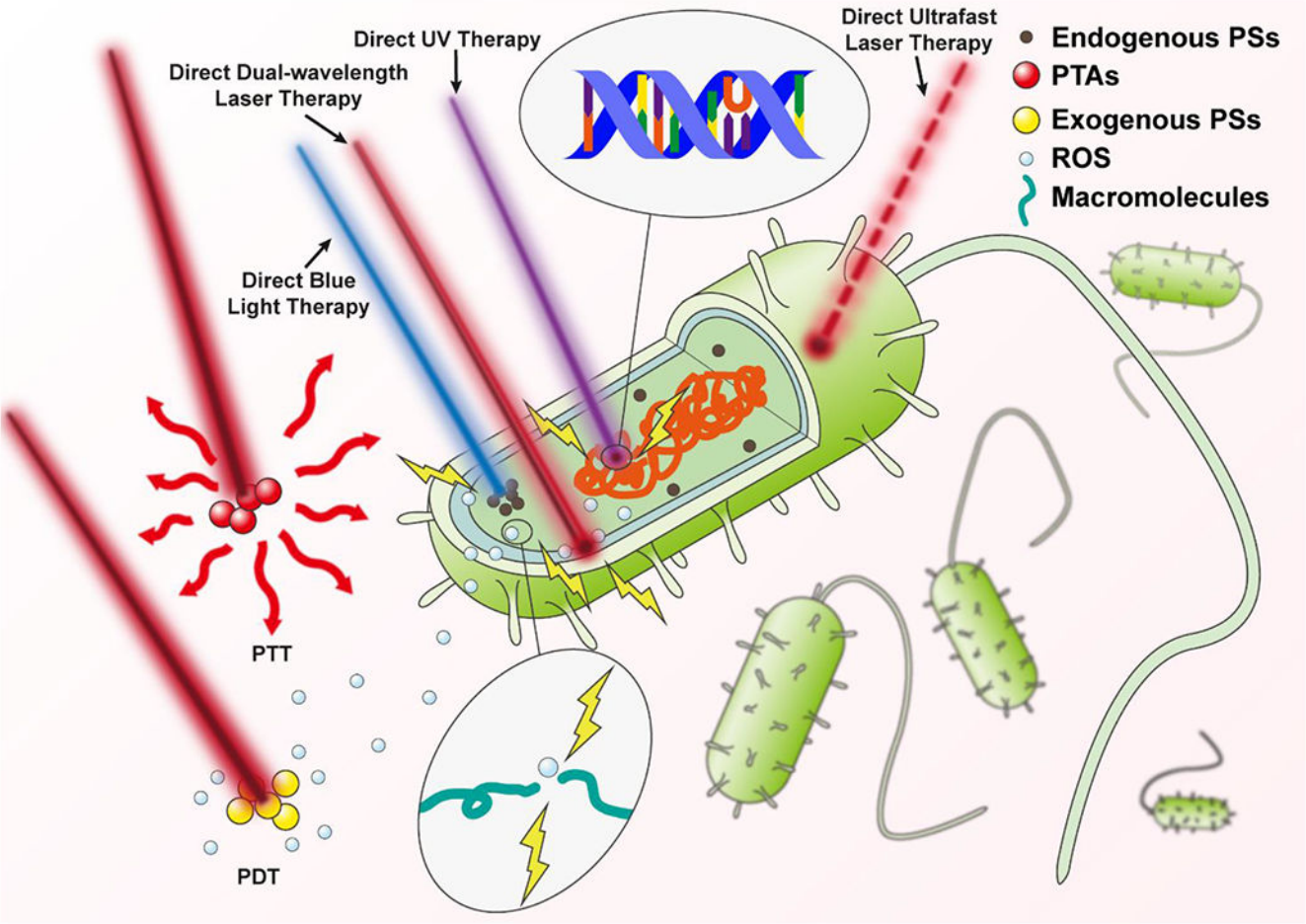

Fig. 3.

Schematic illustration of different types of phototherapies for infection treatment. From left to right: Photodynamic therapy (PDT) activates exogenous photosensitizers (PSs), which interact with substrates to produce reactive oxygen species (ROS) that damage biomacromolecules[54, 55] (the colors used in the picture do not directly reflect the actual wavelengths); Photothermal therapy (PTT) relies on the illumination of photothermal agents (PTAs) to generate heat for pathogen inactivation[408] (the colors used in the picture do not directly reflect the actual wavelengths); Direct blue light therapy is believed to activate endogenous PSs to yield similar effects to that of PDT[27]; Direct dual-wavelength laser therapy may reduce membrane potential, activate endogenous PSs, and alter cellular respiration[536]; Direct ultraviolet (UV) therapy induces dimerization of thymine nucleotides preventing DNA replication and translation[539]; Direct ultrashort laser therapy delivers rapid-pulses of light providing microbe specific damage[534, 535].

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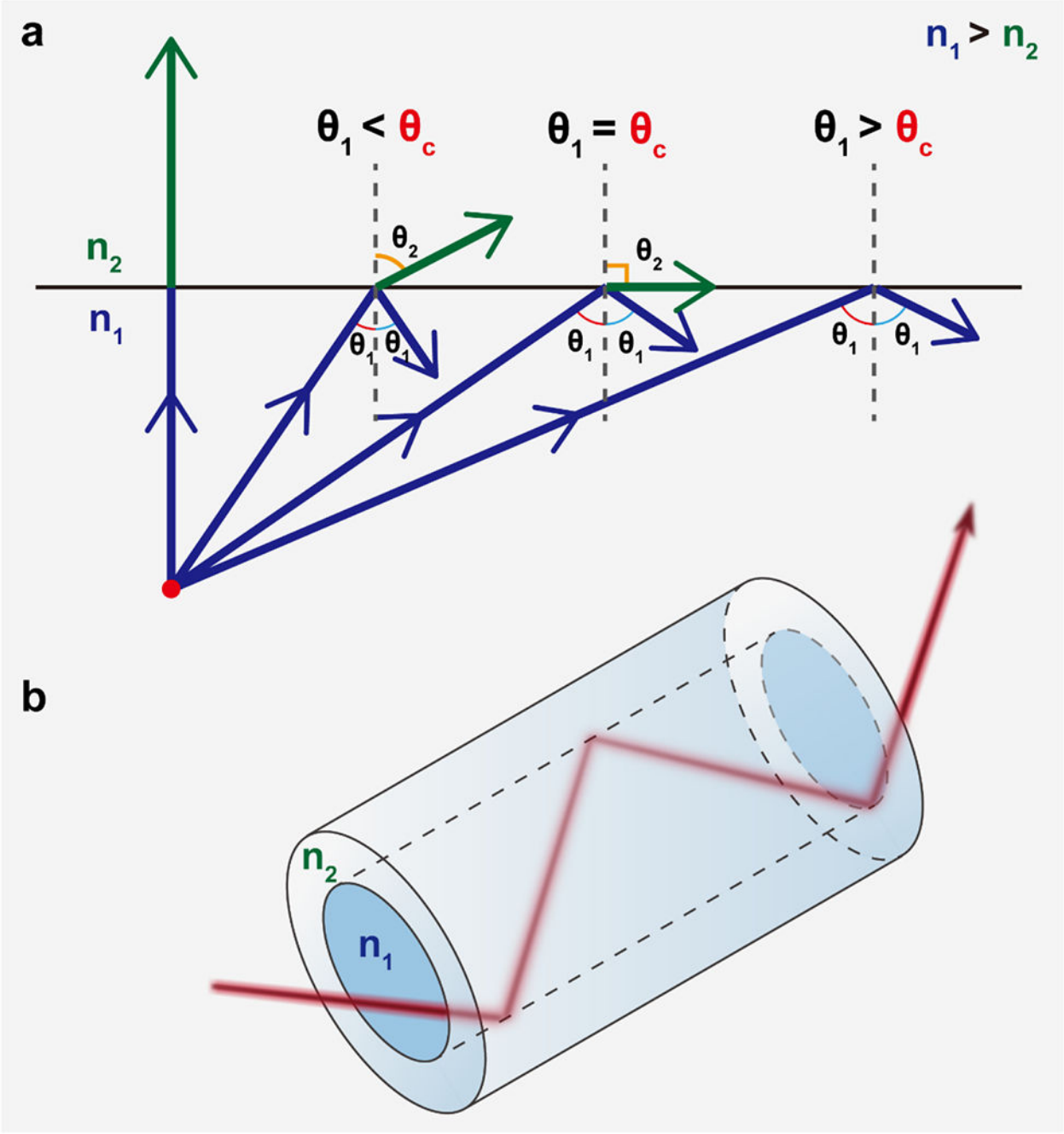

Fig. 4.

Schematic illustration of the (a) dependence on incident light angle and refractive index to achieve total internal reflection and (b) light propagation through a step-index optical fiber via total internal reflection resulting in minimal energy loss over the length of the fiber. θ_1: incident angle; θ_2: transmitted angle; θ_c: critical angle; $\boldsymbol{n}_1$ and $\boldsymbol{n}_2$: refractive indices of media 1 and 2, respectively.

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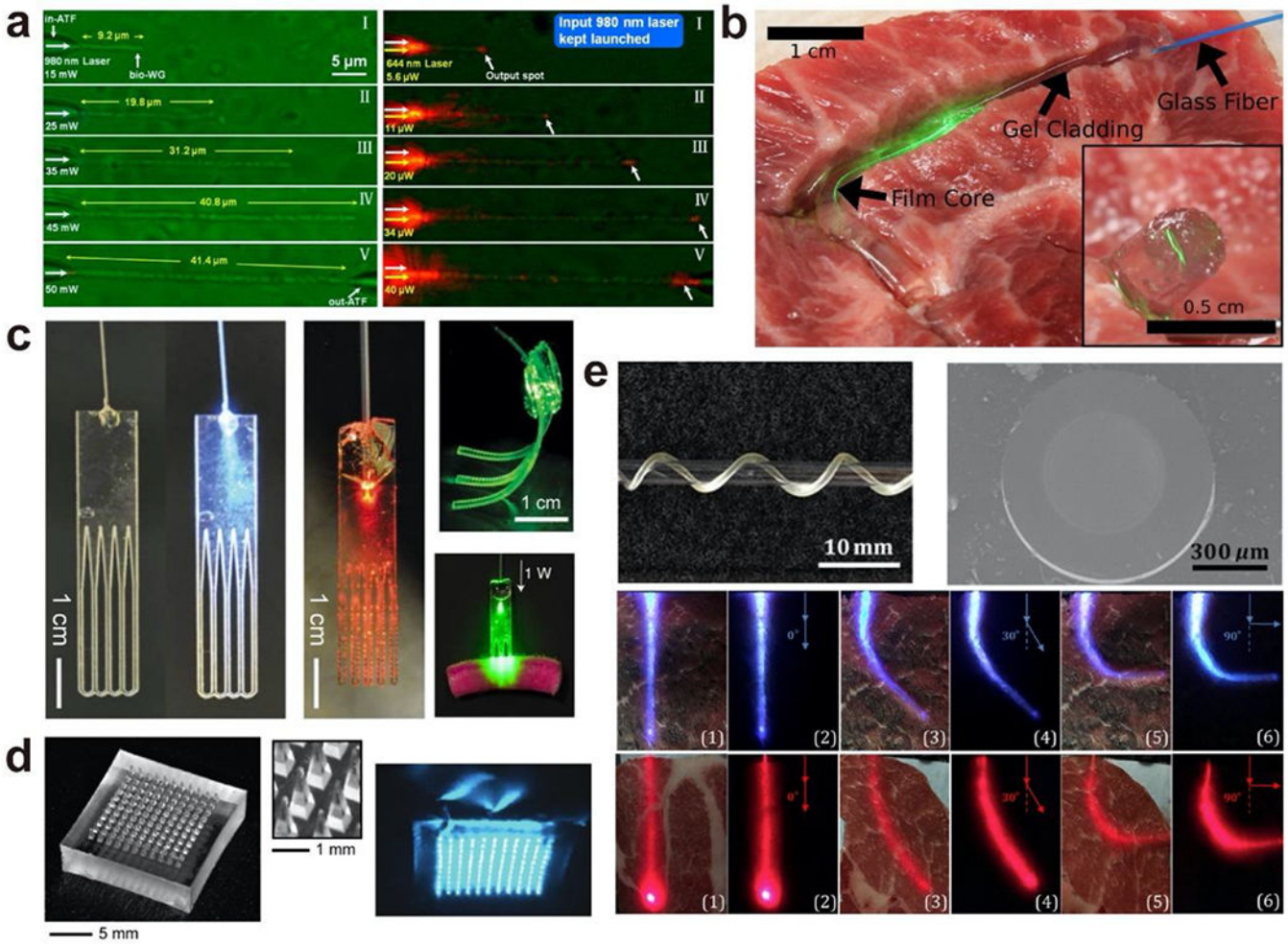

Fig. 5.

Representative biocompatible optical waveguides comprised of cells and polymeric biomaterials (a) E. coli-based biophotonic waveguide. Adapted with permission from [665]. Copyright (2013) American Chemical Society; (b) Step-index optical waveguides made from silk. Adapted with permission from [639]. Copyright (2015) Optical Society of America; (c) Bioabsorbable optical waveguides made from poly(L-lactic acid) (PLLA) or polyethylene glycol (PEG). Adapted with permission from [656]. Copyright (2016) Nature Publishing Group; (d) Optical microneedle array made from poly(lactic acid) (PLA). Adapted with permission from [655]. Copyright (2016) Optical Society of America; (e) Biodegradable step-index optical fiber made from citrate-based polymers: poly(octamethylene citrate) (POC) as cladding while poly(octamethylene maleate citrate) (POMC) as core. Adapted with permission from [653]. Copyright (2017) Elsevier.

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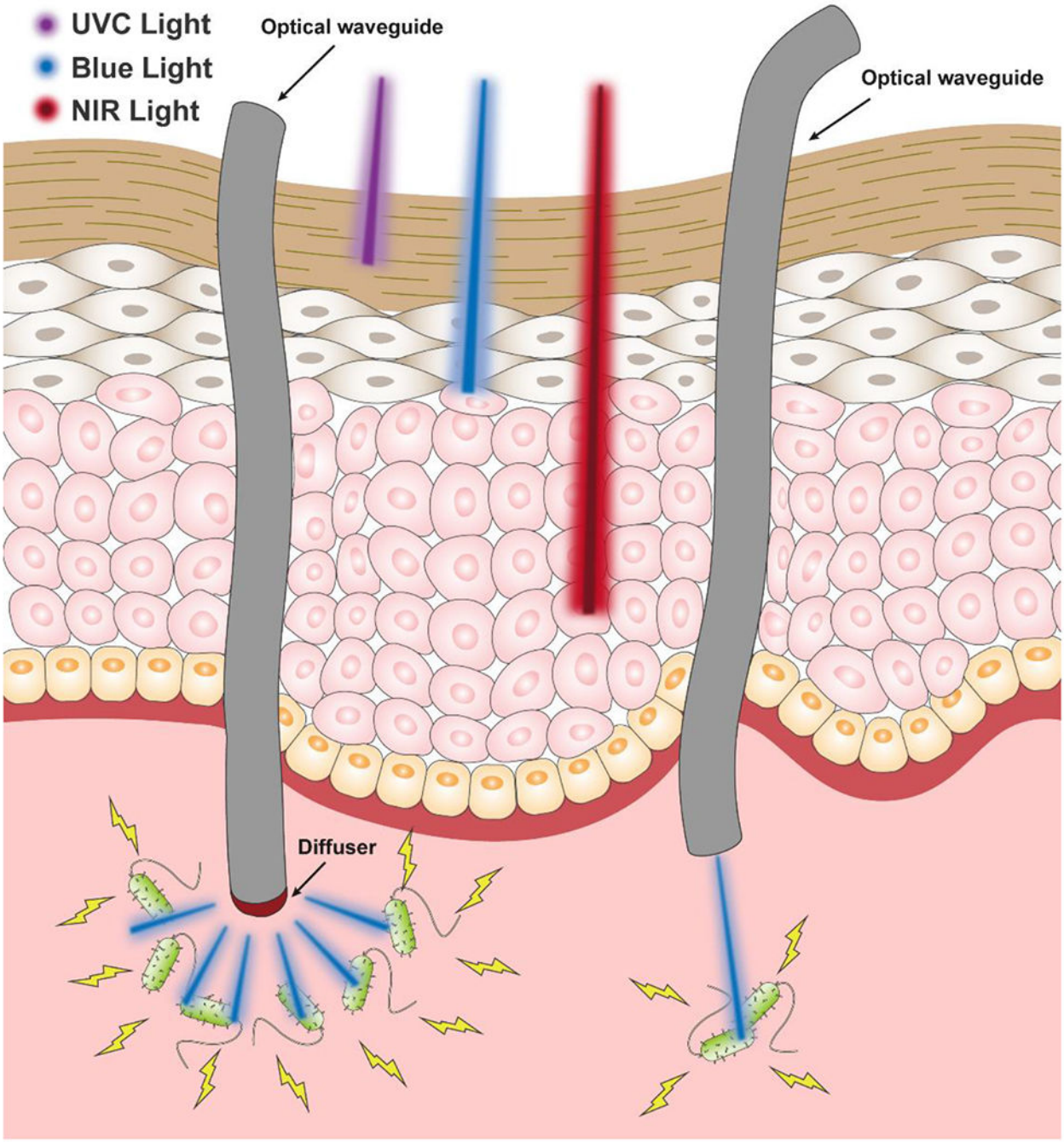

Fig. 6.

Schematic illustration of the penetration depths of various therapeutic lights (UVC, blue, and NIR) in tissues and the optical waveguide-mediated light delivery for phototherapy. Left: diffused light delivery through a diffuser/diffusing tip at a large lesion; Right: precise light delivery at a specific target site.

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Table 1.

Types of phototherapy and respective limitations

Phototherapy	Description	Mechanism of Action	Limitations
PDT	Light activates a topical or injected PS in the presence of a substrate produce ROS and radical ions[50, 51]	ROS and free radicals destroy macromolecules critical to cell function[54, 55]	ROS are not cell selective[51, 57] Poor biocompatibility or phototoxicity of PSs[23, 73, 74, 77, 623, 624]
PTT	Irradiation of photothermal agents (PTAs) with light	Local hyperthermia leads to denaturation of proteins, cell aggregation, loss of membrane integrity, and cross-linking of DNA[408]	Thermal effects are not cell selective[408] Photobleaching, poor biocompatibility or toxicity of PTAs[408, 426, 437, 497, 583] High temperatures, power density, or overexposure to light irradiation may damage host tissue
Direct Ultrafast (Ultrashort) Pulsed Laser	Ultrafast pulses of light with power on the order of GW. Femtosecond lasers are the most commonly used[535]	Viruses: Induced viral capsid aggregation and inhibition of viral replication and transcription[534, 535] DNA damage and relaxation of supercoiled DNA in bacteria and fungi[535] Activation of endogenous porphyrins to generate ROS[535, 637] Increase in cell membrane permeability increasing sensitivity to drug treatment[637]	Induced resistance has been reported[23–25] Requires specialty equipment and training
Direct Dual-Wavelength Laser	Two different wavelengths of laser are applied to infected site. Low power and red/NIR light can be used[536]	Reduced membrane potential[537] ROS production by endogenous chromophores[537] Aberrant electron transport chain processes and energy production[536]	Requires specialty equipment and training Mechanism of action, safety, and efficacy are largely underexplored
Direct UV	Direct light (100 - 400 nm) irradiation. UVC (100 - 280 nm) is the most commonly employed[22, 539, 541]	Inhibited DNA replication due to formation of thymine dimers[539] Possible damage to aromatic amino acids in proteins[638]	Limited tissue penetration depth[22] Risk of carcinogenesis, burns, and retinal damage upon prolonged exposure[539] Induced resistance has been reported[22]
Direct Blue Light	Direct light (400 - 500 nm) irradiation. An aerobic environment may be necessary[578]	May activate endogenous PSs (e.g. porphyrins, flavins, cytochromes) in microbes to generate ROS[27]	Poor tissue penetration[27] Risk of eye damage upon prolonged exposure[27]

PDT: photodynamic therapy; NIR: near-infrared; ROS: reactive oxygen species; PS: photosensitizer; UV: ultraviolet; GW: gigawatts; PTT: photothermal therapy; PTA: photothermal agent; DNA: deoxyribose nucleic acid

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Table 2.

Representative studies administering phototherapy via optical waveguides for infection treatment

Infection Model	Treatment	Results	Reference
Osteomyelitis induced by *S. aureus* in tibia of SD rats	*In vivo*: Percutaneous administration of 635 ± 10 nm laser (fluence of 75 J/cm^2) at 250 mW/cm^2 for 4 hours post-IP injection of ALA (300 mg/kg)	Significant inhibition of bacterial growth after 24 hours No significant difference after 48 hours compared to ALA treatment only	[711]
Human root canals infected with *E. faecalis*	*Ex vivo:* Methylene blue (25 μg/mL) incubation for 5 minutes followed by illumination with 665 nm light (fluence 222 J/cm^2)	97% killing after 7 days of sample incubation relative to no treatment controls.	[714]
In vivo and clinical *H. pylori* infection	*In vivo:* Several 15-minute treatments of 31 to 46 kJ of 408 nm light to porcine stomachs	Clinical results revealed transient decrease in infection 8 hours after treatment according to UBT	[715]
	Clinical: 15, 30, 45, or 60-minute treatment time; UBT and bacterial counts were evaluated at time of enrollment, 5 days, and 5 weeks after treatment, respectively.	CFU reduction was highest and only significant in the antrum (97.7% killing) The highest reduction in microbe count was observed in the 30-minute treatment group	
In vitro and clinical *H. pylori* infection	*In vitro:* 2 cm^2 spot size of 405 nm light (4, 8, 16, and 32 J/cm^2 fluence) for 5 minutes	*In vitro:* 32 J/cm^2 energy density caused a 5-log reduction of bacterial viability 7 days post-treatment	[585]
	Clinical: 1 cm^2 spot size of 405 nm light (40 J/cm^2 fluence) for 4.5 minutes in the antrum	Clinical: CFUs/gram of tissue demonstrated significant (91%) bacterial kill relative to non-treated samples	
Periodontitis induced by *P. gingivalis* in SD rats	6, 12, 24, 48 J of 630 nm light for 1, 2, 4, and 8 minutes with toluidine blue (0.01, 0.1, and 1 mg/ml) for bacterial kill measurements	No detectable bacteria in 1 mg/mL toluidine blue with light treatment group and significant reductions (at least one $\log_{10}$) in viable count of all other treatment groups.	[210]
	48 J of 630 nm light was administered for 8 min using toluidine blue (0.01, 0.1, and 1 mg/ml) for bone loss measurements	Significant differences in reduction in bone loss in 0.1 and 1 mg/mL toluidine groups using 48 J of light	
Clinical COVID-19 pulmonary infection	Blue and/or red light administered via endobronchial or pulmonary arterial routes proposed for antiviral, antibacterial, anti-inflammatory, and vasculoprotective effects	Proposed study design	[311]
Intubated patients with COVID-19 pulmonary infection and/or acute respiratory distress syndrome	Direct trachea-bronchial UVC irradiation (2.0-2.5 mW) for 6 minutes every 4 hours for 24 hours	Proposed study design	[561]

S. aureus: Staphylococcus aureus; SD: Sprague-Dawley; IP: intraperitoneal; ALA: 5-Aminolevulinic acid hydrochloride; *E. faecalis: Enterococcus faecalis;* InGaN: indium gallium nitride; UBT: urea breath test; CFU: colony forming unit; *P. gingivalis: Porphyromonas gingivalis*