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New players in phototherapy: photopharmacology and bio-integrated optoelectronics

Johannes Morstein and Dirk Trauner

Photodynamic therapy and phototherapy are used in the clinic to treat dermatological conditions, cancer, macular degeneration, and a variety of other diseases. Despite their long history and widespread application, the scope of these therapeutic approaches has been limited by a lack of specificity and challenges with light delivery. In recent years, much progress has been made in these regards. Photopharmacology has provided drug-like molecules that change their efficacy upon irradiation and allow for the optical control of a wide range of defined biological targets. Many photopharmaceuticals are now used *in vivo* and some show promising results in preclinical development. At the same time, new bioelectronics for subdermal light delivery have been engineered that could enable phototherapy deep in tissue, for example within the human brain. These developments could increase the impact of photodynamic therapy in human precision medicine.

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Introduction

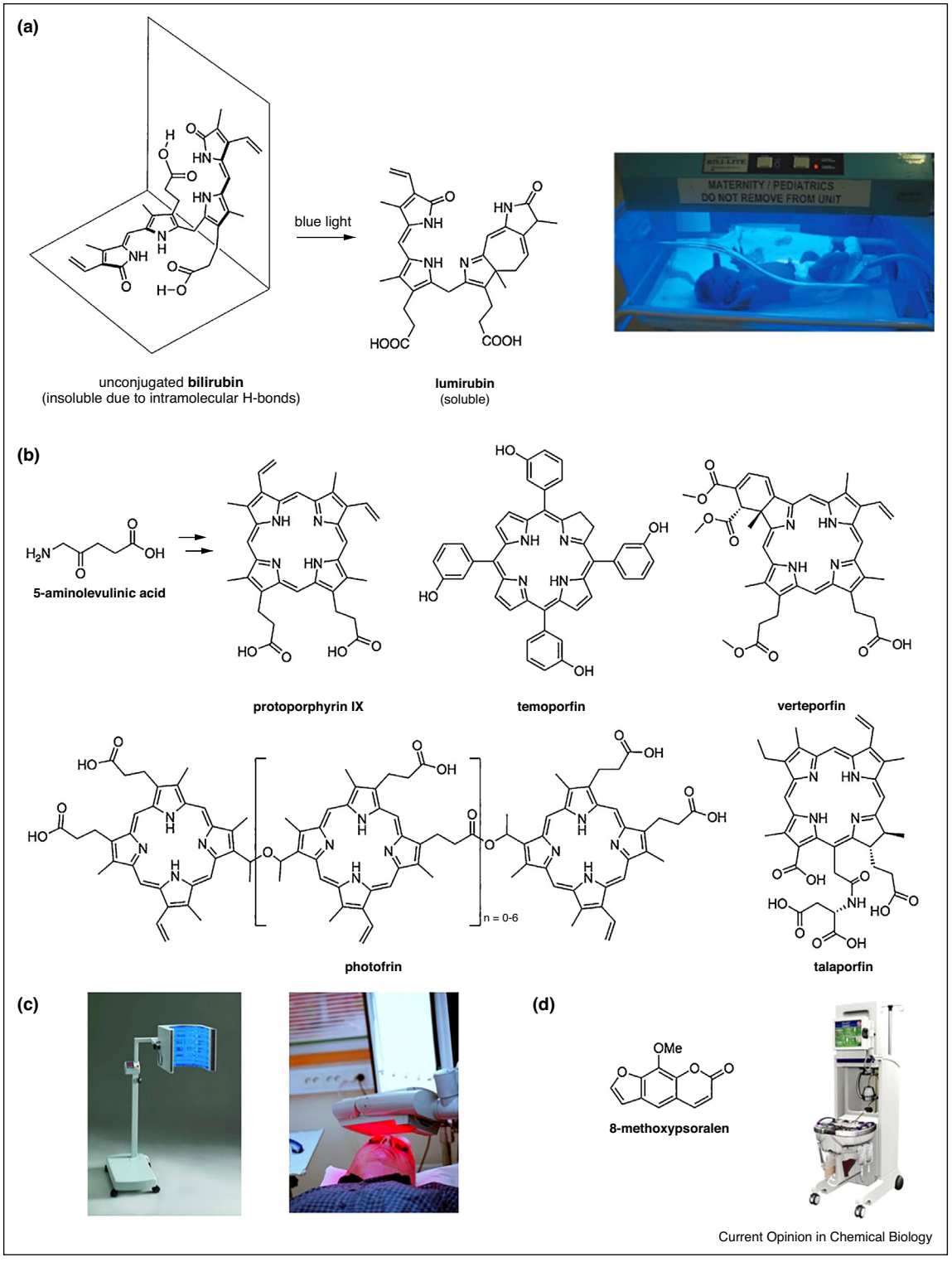
Phototherapy was used in ancient civilizations to treat various skin conditions, such as psoriasis and vitiligo, as well as rickets and psychosis [1]. At the turn of the 20th century, phototherapy was first systematically investigated by Niels Finsen, who was awarded the Nobel Prize in 1903 for the treatment of Lupus Vulgaris, a cutaneous form of tuberculosis, with light [2]. Around the same time, Raab and Tappeiner reported the combined effects of light and dye molecules, giving rise to the field of photodynamic therapy (PDT). Both types of photomedicine are now commonly used in the clinic but have certain limitations [3]. New pharmacology and new light technology could significantly expand the reach of PDT in the future. In photopharmacology, photocaged and photoswitchable drugs allow for the optical control of specific molecular targets. These photopharmaceuticals can be used *in vivo* and some are under preclinical investigation [4••]. In addition, PDT could benefit from new forms of light delivery, driven by optogenetics that include stretchable [5], wirelessly powered [6,7], and biodegradable electronics [8]. In this account, we provide a brief overview of the current state and limitations of PDT and discuss the potential impact of emerging technologies.

From phototherapy to photodynamic therapy

Phototherapy (or light therapy) relies on photochemical processes that occur in endogenous biomolecules. In some cases, these processes can be highly specific. An example is the blue light induced isomerization of lipophilic and insoluble **bilirubin** to a soluble isomer that can be conjugated and excreted. This strategy is used to treat neonatal jaundice (Figure 1a) [9,10]. In other cases, the underlying photochemical processes are less clear and could result from a combination of multiple processes, including UV-A induced generation of reactive oxygen species (ROS) or UV-B induced inflammation [11,12]. In photodynamic therapy (PDT), photosensitizers are combined with light to locally increase the UV-A induced generation of ROS: After excitation, photosensitizers can undergo intersystem crossing to triplet states, which react with triplet oxygen to produce highly reactive singlet oxygen. Alternatively, electron transfer from an excited state to molecular oxygen produces superoxide anion, which can undergo protonation and dismutation or form hydrogen peroxide. Hydrogen peroxide in turn may be reduced to a highly reactive hydroxyl radical and hydroxide anion. Most photosensitizers used in PDT are porphyrin derivatives (Figure 1b). They include **protoporphyrin IX**, which is endogenously produced after delivery of its biosynthetic precursor **5-aminolevulinic acid**. Alternatively, they can be externally provided, for example, in the case of **temoporfin**, **verteporfin**, **photofrin**, and **taloporfin**, which tend to accumulate in proliferating cells. While **protoporphyrin IX** is activated with blue light, the latter work with more deeply penetrating red light.

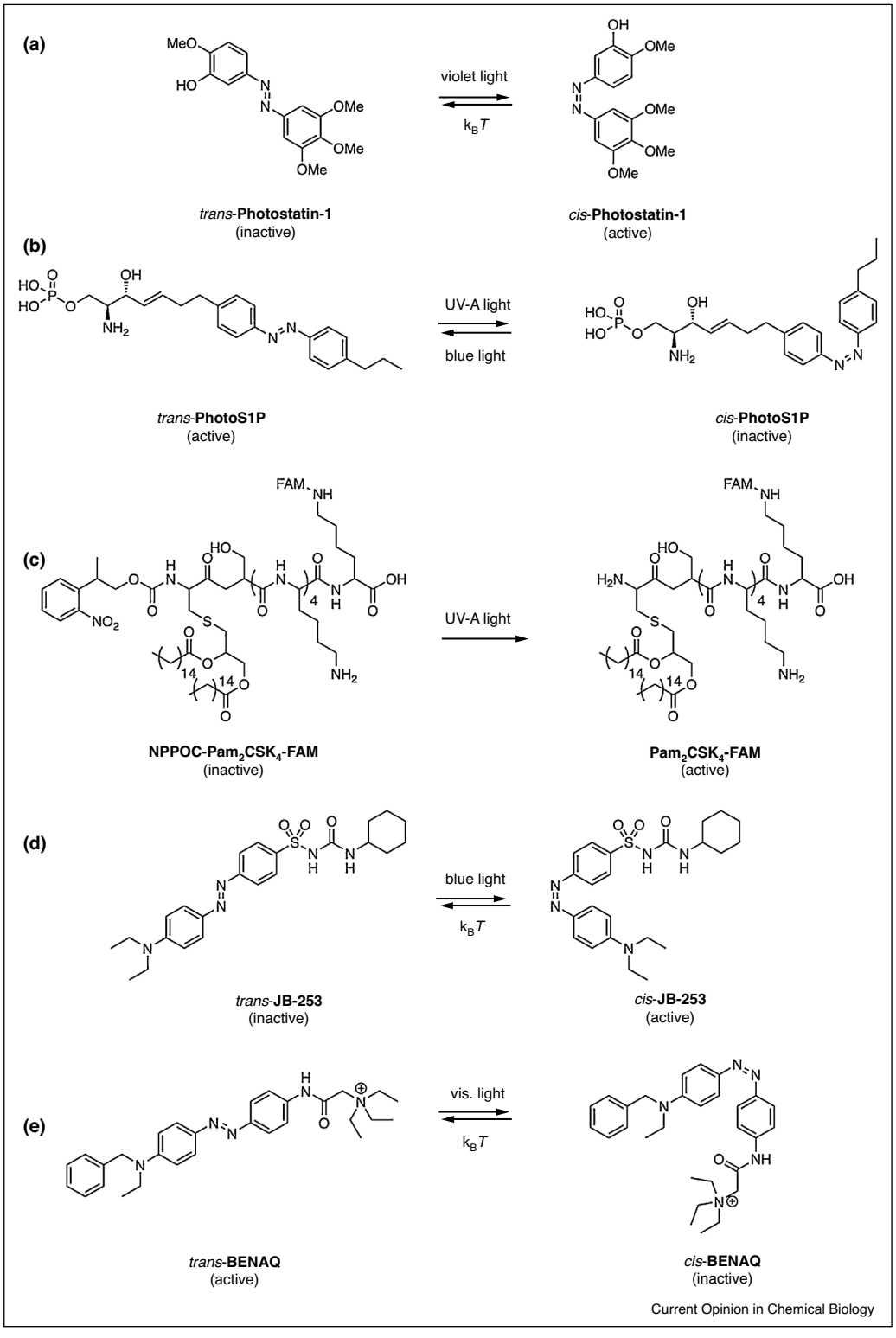
PDT is now commonly used in the clinic for a variety of pathologies, such as cancers, dermatological, and ophthalmic diseases [13]. These include esophageal cancer, non-small cell lung cancer, actinic keratosis, and the wet form of age-related macular degeneration. Most approved procedures use transdermal light-delivery (Figure 1c).

Figure 1



Phototherapy and PDT.
(a) Light-induced isomerization of bilirubin during phototherapeutical treatment of neonatal jaundice and treatment of a newborn with blue-light irradiation [10]. **(b)** Biosynthesis of protoporphyrin IX from 5-aminolevulinic acid and other representative porphyrin-based photosensitizers used in PDT. **(c)** Devices for transdermal delivery of light in PDT [19]. **(d)** 8-methoxypsoralen which is used in photopheresis and an apparatus for photopheresis treatment.

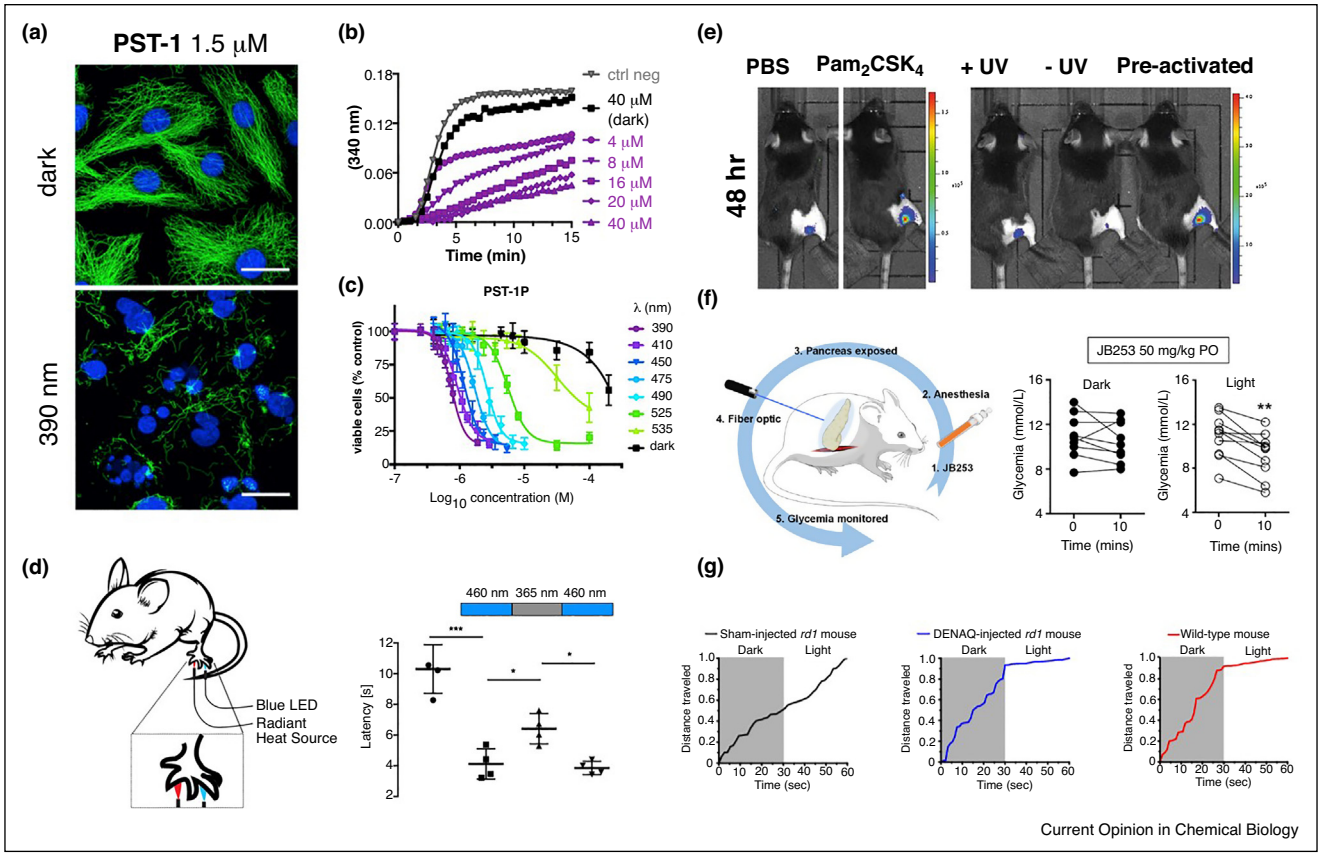
Figure 2



Representative photopharmaceuticals in preclinical trials or *in vivo* studies.
(a) Photostatin-1 enables optical control of microtubule dynamics. It can be switched to its active form upon irradiation with violet light. **(b) PhotoS1P** enables photocontrol of S1P biology and S1P-dependent pain behavior. **(c) NPPOC-Pam$_2$CSK$_4$-FAM** (FAM: Carboxyfluorescein) allows for the optical control of innate immunity. **(d)** The photoswitchable sulfonylurea **JB-253** enables the optical control of glucose stimulated insulin secretion. It can be switched to its active form upon irradiation with blue light. **(e) BENAQ** is a photoswitchable ion channel blocker used in preclinical development for vision restoration.

However, endoscopic techniques are also used to shine light to a region of interest [14]. In addition to 'classic' PDT, a number of modalities have emerged that extend the reach of PDT. For example, photopheresis is an extracorporeal form of PDT which is used to treat cutaneous T-cell lymphomas and prevent graft versus host disease (Figure 1d) [15]. In this procedure, white blood cells are separated from patients, treated with UV-A irradiation in the presence of 8-methoxypsoralen, which undergoes intercalation and photochemical addition to thymine bases, and returned to the patient together with the red blood cells and platelets. In photoimmunotherapy, PDT is combined with immunotherapy to enhance the effects of PDT [16]. Other approaches are meant to increase the specificity of PDT. These include Metronomic PDT, where a low dose of light and photosensitizer are applied to induce cell-specific apoptosis, or PDT Molecular Beacons, where a quencher is switched off through a specific enzymatic activity (e.g. proteolytic cleavage of the quencher) [17••]. However, despite these efforts to improve PDT, some underlying challenges remain: the effectiveness in PDT depends on a variety

Figure 3



In vivo applications of photopharmacology.
(a) Light-induced disruption of microtubule dynamics with **photostatin-1** (**PST-1**). Reprinted with permission from Ref. [20]. Copyright 2015 Elsevier Ltd. **(b) PST-1** shows dose-dependent inhibition of tubulin polymerization under 390 nm irradiation (violet dose response curves). Data shown are an *in vitro* polymerization assay — greater absorbance corresponds to greater degree of polymerization. **(c) PST-1** exhibits minimal toxicity in the dark-adapted form and the concentration of the active form can be increased using different wavelengths of green, blue, and violet light ('color dosing'). **(d)** Optical control of S1P receptor 3 dependent nociception in wild type mice with **PhotoS1P**. The inactive form of **PhotoS1P** (*cis*) does not induce increased thermal hypersensitivity (Hargreaves radiant heat assay). Pain responses can be triggered with blue light and partially reversed using UV-A light. Reprinted with permission from Ref. [21]. Copyright 2019 Nature Publishing Group. **(e)** A photocaged Toll-like receptor agonist (**NPPOC-Pam$_2$CSK$_4$-FAM**) enables the optical control of innate immunity *in vivo*. Reprinted with permission from Ref. [25]. Copyright 2017 Nature Publishing Group. The migration of tagged dendritic cells (luminescent) was measured after injection of PBS, Pam$_2$CSK$_4$ or **NPPOC-Pam$_2$CSK$_4$-FAM** (with or without UV irradiation). **(f)** Optical control of glucose metabolism *in vivo* using **JB-253**. Reprinted with permission from Ref. [22]. Copyright 2017 Nature Publishing Group. After gavaging mice with **JB-253**, the pancreas was exposed and irradiated with blue light. Increased glycemia was observed after irradiation. **(g)** Restoration of visually guided behavior in blind rd1 mice through injection of a photoswitchable ion channel blocker. Mice are conditioned to associate light with a foot shock and freeze. Blind mice do not respond to light but DENAQ-injected blind mice respond (DENAQ is a photoswitchable ion channel blocker structurally closely related to **BENAQ**). Reprinted with permission from Ref. [26]. Copyright 2014 Elsevier Ltd.

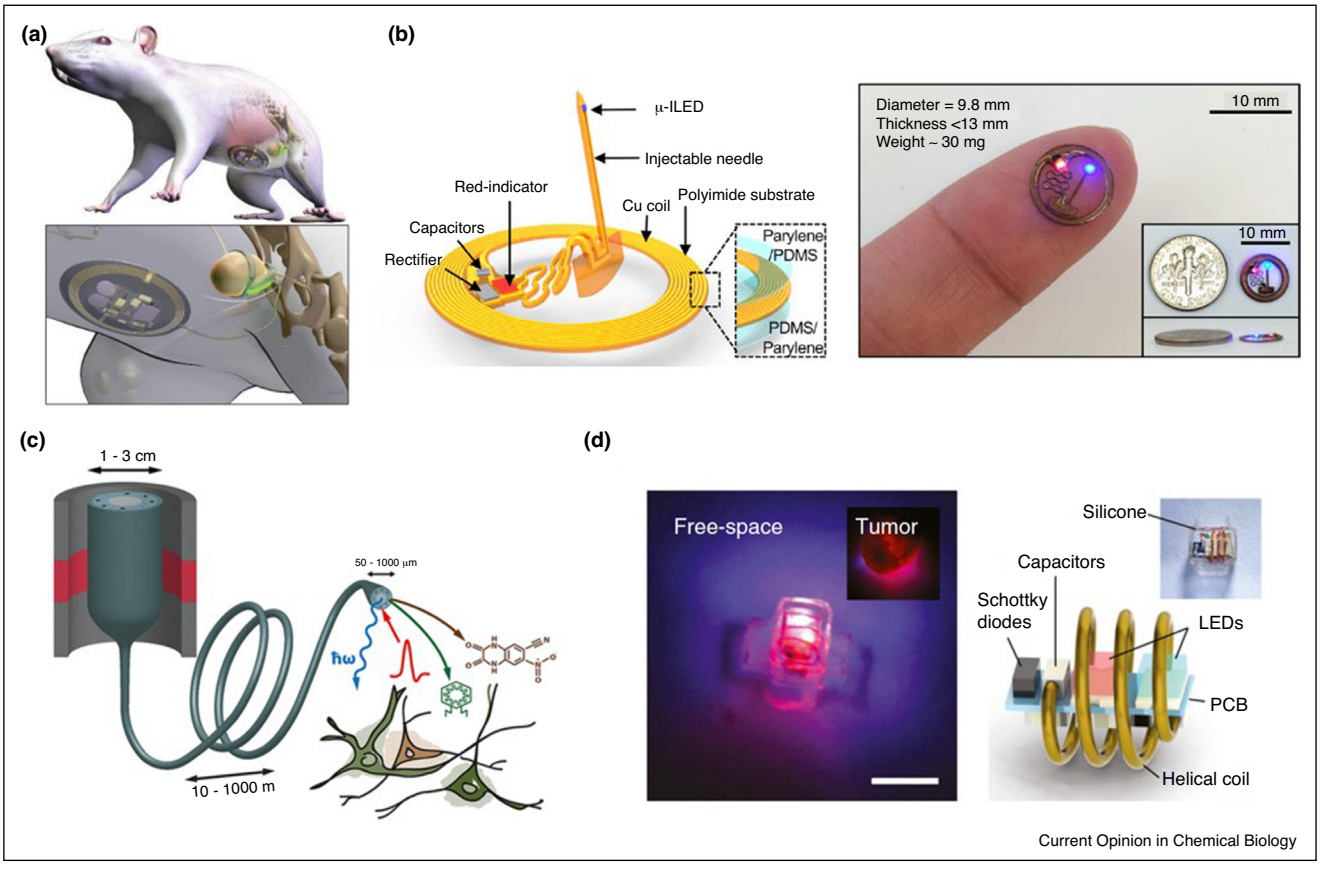
of factors, including light intensity and the concentration of photosensitizer, molecular oxygen, and the presence of ROS scavengers [1]. Treatment with photosensitizers often leads to systemic side effects [18] and relatively few pathologies are susceptible to ROS.

Photopharmacology as a new form of photodynamic therapy

Photoactivatable drugs ('Photopharmaceuticals') could provide an alternative to the unselective and 'unsophisticated' reactive oxygen species generated in conventional PDT. Photopharmacology has been used for the light-dependent modulation of a wide range of biological targets, including ion channels, GPCRs, transporters, pumps, enzymes, and cytoskeleton elements [4••]. In contrast to conventional drugs, photopharmaceuticals (Figure 2a–e) can be administered in their inactive form and activated through irradiation with light. Importantly, both the action spectrum and the thermal half-life of the active form can be tuned to tailor these compounds to their targets. The benefit of photopharmaceuticals over photosensitizers are the clearly defined pharmacodynamics and the simplification of the overall system. For example, the effect of photopharmaceuticals does not depend on the availability of oxygen or the presence ROS scavengers.

To date, the preclinical development of photopharmaceuticals has progressed furthest for vision restoration. However, treatment of cancer, diabetes, and pain, as well as photoimmunotherapies have also shown promising results. Photopharmacological cancer treatments could rely on compounds that interfere with cell proliferation in a light-dependent fashion. One type are the so-called

Figure 4



Emerging technologies for light delivery.
(a) Soft, fully internal, and wirelessly powered optoelectronic implant for the optical control of bladder function in rats. Reprinted with permission from Ref. [33•]. Copyright 2019 Nature Publishing Group. A stretchable optoelectronic stimulation and sensing module is wrapped around the bladder and allows for monitoring changes in bladder volume as well as optogenetic stimulation of opsin-expressing neurons. **(b)** Injectable microscale LED for subdermal light delivery in the brains of mice. Reprinted with permission from Ref. [34]. Copyright 2017 Elsevier Ltd. **(c)** Multimodal optical fibers for the simultaneous delivery of light, electrical current, viruses, and organic molecules. Reprinted with permission from Ref. [31]. Copyright 2018 American Chemical Society. **(d)** A wireless photonic device for photodynamic therapy of solid tumors. Reprinted with permission from Ref. [32•]. Copyright 2018 National Academy of Sciences.

'**photostatins**'. [20] These compounds are azosters of combretastatin A4 (and colchicine) and inhibit microtubule dynamics. They can be activated with violet or blue light and reversibly relax back to their inactive state after a few minutes (Figure 3a–c).

Optical control of pain responses was recently demonstrated with a photoswitchable analog of the signaling lipid sphingosine-1-phosphate (**PhotoS1P**; Figure 3d). [21] This allowed for the reversible activation of S1P receptor 3-dependent pain hypersensitivity in mice via activation of TRPV1 in somatosensory neurons. Notably, the inactive form of the photoswitch did not induce behavioral effects, while the activated form evoked responses comparable to unmodified S1P. A photocaged Toll-like receptor agonist (**NPPOC-Pam$_2$CSK$_4$-FAM**) has enabled light-activated innate immune responses (Figure 3e). Photoswitchable sulfonylureas (e.g. **JB-253**) have successfully been employed for the optical control of K_{ATP} channels in pancreatic β-cells and *in vivo* for the optical control of glucose stimulated insulin secretion (Figure 3f) [22].

Notable progress in the translational use of photopharmaceuticals has been made in the field of visions restoration, where photoswitchable ion channel blockers have been used in animal models for the restoration of visually guided behavior (Figure 3g) [23]. In addition to the therapeutic success in a number of preclinical models, the toxicity and metabolic liability of the lead-compound **BENAQ** has been positively evaluated [24]. Of course, in the case of vision restoration light delivery is not an issue since the eye largely consist of transparent tissue.

The impact of bio-integrated electronics

Photodynamic therapy and photopharmacology both require light delivery to the site of therapeutic action. While transdermal light delivery is straightforward, light (especially at short wavelengths) does not penetrate tissue efficiently, due to melanin pigmentation of the skin and the presence of other highly absorbing molecules, such as heme and flavoproteins. Therefore, new technologies for subdermal electronics could greatly benefit PDT. Fortunately, there has been enormous progress toward this goal in recent years, which was largely driven by demand in optogenetics [27]. Optogenetics is an attempt to control biological function with genetically encoded and engineered photoreceptors. While its therapeutic usefulness remains to be determined, it has already revolutionized modern biology (especially neurobiology), and has prompted the development of highly sophisticated light delivery methods.

One of the most important engineering goals has been a reduction in size and weight of bioelectronics as these properties directly correlate with biocompatibility [28]. Much progress to this end was made using internal and wirelessly powered electronic platforms (Figure 4a,b) [6,7]. Some bio-integrated electronics could even be injected with a syringe and unfolded after injection [29]. This could lead to yet less invasive procedures. Other properties that were markedly improved in recent years include shape and *in vivo* stability of bioelectronics [30]. In particular, stretchability was achieved in many devices developed recently. In addition to these advances, multimodality has been achieved for optical fibers allowing for simultaneous delivery of light, compounds, and electrical current (Figure 4c). [31] Some of these new devices are now undergoing evaluation for PDT applications, for example, to reach tumor tissue (Figure 4d) [32•].

Conclusion

Phototherapy and photodynamic therapy have been successfully used in humans for more than a century and are now routinely used in the clinic. The widespread use and expansion of this strategy as a therapeutic modality for many pathologies is hampered both by the inability to achieve molecular target specificity and also by challenges in subdermal light delivery. Photopharmacology, by contrast, allows for the light-mediated modulation of defined biomolecules and has the capacity to improve precision in photo-directed therapeutic strategies. Combined with new technologies for light delivery, this could enable entirely new applications of PDT in the clinic. The translational potential of these strategies as clinical therapies will be realized through the collective and collaborative effort of chemists, biologists, engineers, and clinicians.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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