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Toward biomaterial-based implantable photonic devices

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Abstract: Optical technologies are essential for the rapid and efficient delivery of health care to patients. Efforts have begun to implement these technologies in miniature devices that are implantable in patients for continuous or chronic uses. In this review, we discuss guidelines for biomaterials suitable for use *in vivo*. Basic optical functions such as focusing, reflection, and diffraction have been realized with biopolymers. Biocompatible optical fibers can deliver sensing or therapeutic-inducing light into tissues and enable optical communications with implanted photonic devices. Wirelessly powered, light-emitting diodes (LEDs) and miniature lasers made of biocompatible materials may offer new approaches in optical sensing and therapy. Advances in biotechnologies, such as optogenetics, enable more sophisticated photonic devices with a high level of integration with neurological or physiological circuits. With further innovations and translational development, implantable photonic devices offer a pathway to improve health monitoring, diagnostics, and light-activated therapies.

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1 Introduction

Each year, more than 30 million of various medical devices are implanted in the human body, extending and improving the quality of lives of the patients. Among the most implanted are intraocular lens (IOL), stents, artificial joints, cardiac pacemakers, and artificial cochlea. In 2014, more than 20 million IOL procedures were performed worldwide, replacing the natural crystalline lens in the eye in cataract surgery. The development of IOLs was pioneered by Harold Ridley, who as a surgeon in World War II, noticed that poly(methyl methacrylate) (PMMA) fragments from shattered aircraft canopies that penetrated the eyes of pilots remained biologically inert [1–3]. PMMA remained the dominant material for IOLs for at least 40 years, until the advent of acrylics and silicone [4]. The design and materials are chosen based on the lens power as required on a patient-specific basis. Commercial IOLs offer a fixed refractive power, but future IOLs may incorporate active elements for adaptive accommodation.

The artificial retina, or retinal prosthesis, is an optoelectronic device that is implanted in the eye to restore vision for people suffering from incurable blindness because of retinal degeneration, such as age-related macular degeneration and retinitis pigmentosa [5]. While the photoreceptor cells for these patients are nonfunctional, many of the inner retinal neurons remain functional and can be electrically stimulated to elicit visual responses. A number of retinal prostheses have been approved for human use [6, 7]. One such device, the Alpha IMS subretinal implant, uses multiphotodiode arrays and electrodes that sense light and stimulate the biopolar cells of the inner retina [8]. A power supply is needed for this device because ambient light does not generate sufficient photocurrent to stimulate neurons [9]. Recently, a significant improvement over this design has been demonstrated in rats, in which silicon photodiodes are simultaneously powered and activated by pulsed near-infrared (NIR) illumination deliv-

ered by video goggles, obviating the need for an additional power supply [10, 11].

Beyond these ophthalmic applications, photonic and related technologies for other medical applications have been developed. To fulfill the promise of real-time diagnostics and sensing, as well as chronic light delivery to deep tissues, photonic devices are increasingly designed with biocompatible and implantable properties. Devices made from biocompatible materials can be left in the body for prolonged periods of time and used for long-term health monitoring and therapeutics. Direct integration of photonic components into living tissue can enhance light–tissue interactions, enabling new applications in sensing and light generation. Many existing passive (light guiding, refraction, diffraction, etc.) and active (light generation and detection) optical device functions can be realized by using biocompatible materials.

Here, we overview recent developments in implantable photonic devices. First, we review the requirements and challenges associated with biocompatibility when devices are implanted in the human body. Next, we describe progress toward biocompatible photonic devices, including passive devices and light sources. Passive devices include waveguides, lenses, diffractive and holographic components, reflectors, photonic crystals, and plasmonic devices. Active devices are light sources, which include incoherent light-emitting diodes (LEDs) or coherent lasers. We also describe photonic devices that use these functional elements. Fluorescent probes, single plasmonic nanoparticles, and light-activated drugs are reviewed elsewhere [12–16].

2 Biocompatibility Requirements

Photonic technologies are well suited for biomedical applications because of the potential of rapid, precise, and noninvasive or minimally invasive control of biological constituents in the body. While many of these capabilities have been demonstrated *in vitro*, biocompatibility must be considered when designing photonic devices for implantation *in vivo*. Biocompatibility of a material refers to not only the absence of cytotoxicity and minimal health risks for the patient but also the biofunctionality of the material that enables the device to perform its desired function in an implanted position [17, 18]. In this section, we overview the key design criteria of implantable photonic devices, the tissue reactions induced by implantation of these devices, and strategies to overcome the challenge of achieving biocompatibility while maintaining functionality.

2.1 Biocompatible and Biodegradable Materials

The implanted device should integrate with the human body while minimizing tissue reactions that could be harmful for the patient or impair the functionality of the device. Generally, the device is desired to be biodegradable, which would eliminate the need for a follow-up procedure to retrieve the device. Materials that have been used for implantable devices include natural and synthetic materials and hydrogels (Table 1) [17, 19–22].

Natural materials derived from organisms, such as collagen, silk fibroin, and alginate, can be recognized metabolically by the host and be degraded by proteolytic enzymes. The degradation rate of these materials varies significantly depending on the implant location and availability of degradative enzymes [23]. However, biologically derived materials may tend to suffer from batch-to-batch variability, restricted range of mechanical properties, possible immunogenicity, and risk of infection by contamination of bacteria, viruses, or prions [18, 23–26].

Synthetic polymers can be designed to have specific material properties but biocompatibility is a challenge because of the foreign body reaction (FBR) [27]. Examples of synthetic polymers include poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(ethylene glycol) (PEG) [21–23, 28]. Hydrolytically degraded polymers, such as polyesters, may be preferred for implantable devices because of less patient-to-patient variability as compared to the enzyme-catalyzed degradation of natural polymers [23, 29]. The biodegradation mechanisms of various biodegradable polymers are reviewed elsewhere [23, 28–30].

Several photonic devices use inorganic materials, such as gold, silicon, and compound semiconductors such as indium gallium nitride (InGaN). While these materials are not biodegradable, their biocompatibility varies depending on the material, device size, mechanical properties, and the presence of coatings. Silver (Ag) nanoparticles (3–100 nm) are toxic at all sizes, attributed to oxidative stress caused by Ag^+ ions, while gold nanoparticles are generally considered nontoxic at low concentrations (< 0.5 mg/kg daily) at sizes of 3–100 nm [31–33]. While Cd^{2+} ions released from CdSe quantum dots are highly cytotoxic, polymer coated or ZnS shell quantum dots significantly improve biocompatibility [34]. Gallium nitride is an emerging biocompatible semiconductor for use with neural interfaces [35]. In a recent study, silicon transistors, InGaN, and AlInGaP semiconductor LEDs integrated on low modulus silicone substrates had minimal cytotoxicity and no immunogenicity after four weeks of subcutaneous im-

plantation in mice [36]. These flexible and stretchable devices enabled accommodation of natural movements, reducing the risk of inflammation and damage caused by mechanical motion.

When selecting materials for implantable photonic devices, biocompatible properties must be considered alongside the functional requirements, such as structural stability and optical clarity. Mechanical flexibility is also an important characteristic that facilitates noninvasive integration of the device with tissue. An example of a material that meets these requirements is silk fibroin, a protein that has been used for biophotonic applications because of its optical transparency and implant compatibility [19]. Silk films can also be generated with features down to tens of nanometers in size, which is ideal for optical applications such as diffraction gratings. Silk has been used to create various biocompatible optical devices, including microlens arrays, microprism arrays, and diffraction gratings [19, 37–39].

Another class of biocompatible materials are hydrogel-based materials, such as with PEG and poly(vinyl-alcohol) (PVA) [40, 41]. Hydrogels are three-dimensional polymeric networks that retain water, mimicking the body's extracellular matrix (ECM) [40] and are commonly used for tissue engineering applications [41]. They offer unique advantages such as tunable material properties, the possibility of incorporating chemical functional groups, and the ability to encapsulate drugs or cells [21, 40, 41]. For sensing applications, the degree of analyte diffusion through the hydrogel can be controlled by varying the cross-linking density of the gel [17]. However, the mechanical properties of hydrogels, such as low tensile strength and poor adhesion to substrates, make them unsuitable for some applications [18]. By varying the water content or monomer size, the optical transparency of PEG hydrogels can be optimized for light-guiding applications [42, 43].

An emerging class of photonic devices uses living tissues and cells as optical elements, offering the possibility of a biocompatible, reagent-free, and self-healing platform for photonic devices. Such optical devices could repair itself upon damage. Self-healing and regeneration also have drawbacks because the properties of the living optical device change with time and can produce nonreproducible results. On the other hand, these changes can also be used as a sensor providing direct optical measurement of the living constituents of the device. The properties of living materials may not be changed substantially without compromising their viability. The majority of tissues have strong light scattering and absorption, which greatly limits the light propagation. Scattering in rare cases can be beneficial, for example, in random lasers, which require strong scattering for their operation [44–47].

The use of live cells is particularly effective when rendered photonic functionalities by genetic engineering; for example, fluorescent proteins for use as a laser gain medium [48–50] or optogenetic proteins for sensing or inducing synthesis of therapeutic hormones [42]. Natural optical cavities formed by lipid droplets inside adipocyte cells have also been demonstrated [47]. For implantable devices, living cells will likely need to be incorporated into tissue using a substrate capable of sustaining them, such as a hydrogel matrix. Furthermore, the cells should ideally be taken directly from the host to prevent any adverse immune response [51].

2.2 Inflammatory and Foreign Body Responses

The biological response of the human body to implanted devices is a major technical challenge [17]. This response can be classified into three stages [17, 21, 27]: acute inflammation, chronic inflammation, and foreign body response (FBR). The first two stages reciprocate what occurs during normal tissue injury and healing, but the continued presence of the device in the body leads to the FBR.

The initial, acute inflammatory process is caused by adsorption of host proteins to the implant surface and tissue injury caused by the implantation or injection process. This phase, lasting a few days, is characterized by neutrophil infiltration and release of proteases and oxygen free radicals to degrade the foreign body. During the chronic inflammation phase, neutrophils are replaced by monocytes and lymphocytes, which induce the formation of new blood vessels and connective tissue. This phase typically lasts several weeks [28]. While in normal wound healing, chronic inflammation eventually resolves, the FBR follows chronic inflammation when a foreign body is continually present.

This FBR is characterized by the formation of foreign body giant cells, which result from the fusion of macrophages. The characteristic end stage of the FBR involves the fibrous encapsulation of the device by an avascular, collagenous capsule that is typically 50–200 μm in thickness [52]. The degree of fibrous encapsulation depends on a number of factors, including the properties of the implanted material, surface chemistry and roughness, and implant duration and location [53]. The physiological state of the tissue, such as diseased or inflammatory states, can also modulate the degree of FBR [54, 55].

Table 1. List of selected biomaterials that have been used in implementable photonic devices.

Material	Biocompatibility & Biodegradability	Optical property	Application
Silk	Biocompatible and biodegradable with a lifetime in the order of years	Transparent dielectric material	Waveguides [38, 51], gratings [37, 52, 53], photonic crystals [54], reflectors [36], lasers [55], substrate [56]
Poly(ethylene glycol) (PEG) hydrogel	Biocompatible, can be biodegradable	Transparent dielectric material	Waveguides [41, 42]
Agarose hydrogel	Biocompatible	Transparent dielectric material	Waveguides [57, 58]
Polylactic acid (PLA)	Biocompatible and biodegradable with a lifetime in the order of months	Transparent dielectric material	Waveguides, substrate [59]
Poly(lactic-co-glycolic acid) (PLGA)	Biocompatible and biodegradable with a lifetime in the order of weeks	Transparent dielectric material	Waveguides [60]
Poly(methyl methacrylate) (PMMA)	Biocompatible	Transparent dielectric material	Intraocular lens [1–3]
Cells	Endogenous	Laser gain material	Lasers [46, 47, 61–63]
Bacteria	Some strains in symbiosis with human body	Laser gain material	Waveguides [64], lasers [49, 65]
Fluorescent proteins	Biocompatible and biodegradable	Laser gain material	Lasers [47, 66–69]
Riboflavin	Endogenous	Laser gain material	Lasers [55, 59, 70]
Silver and gold	Biocompatible	Plasmonic effects	Plasmonic sensors [12–14, 56, 71]
Lipids	Endogenous	Transparent dielectric material	Gratings [72], lasers [46]
Other non-fluorescent proteins	Endogenous	Transparent dielectric material	Waveguides [73], gratings [74, 75]
Biological tissues	Endogenous	Scattering material	Random lasers [43–46]
DNA	Endogenous	Matrix for active molecules	Lasers [76–80], LEDs [81–84]
Cellulose	Biocompatible and biodegradable	Transparent dielectric material	Waveguides [85], substrate [86]

Few studies have systematically studied the effect of material size and geometry on the FBR. A recent study tested the long-term implant compatibility of spherical materials with diameters ranging from 0.3 to 1.9 mm in rodents and monkeys [56]. While spheres smaller than 0.5 mm had severe fibrotic responses, spheres of 1.5 mm or larger diameters had significantly diminished FBR and were largely devoid of cellular deposition even after six months of implantation. This effect was restricted to spherical shapes and independent of surface area and material composition, which included alginate, stainless steel, glass, polycaprolactone, and polystyrene. These findings suggest that the *in vivo* biocompatibility of implanted devices can be significantly improved by simply increasing their spherical dimensions, but the underlying mechanisms remain unclear and are thought to be related to modulation of macrophage recruitment and polarization. Systematic studies need to be undertaken to understand the FBR to a wider range of shapes and sizes of materials implanted in different locations.

For applications involving smaller devices, microspheres greater than 5 μm in diameter are known to elicit an FBR, while smaller microspheres may be phagocytosed, which can accelerate their biodegradation [28]. As the diameter of a spherical particle is decreased, the surface-to-volume ratio increases, which enhances the surface reactivity [57]. For nanoparticles, the surface layer of adsorbed proteins, often called the "protein corona," is a key determinant of its biological and metabolic fate *in vivo* [58]. The biocompatibility and toxicity of nanomaterials have been comprehensively reviewed elsewhere [57–61].

The inflammatory response, FBR, and fibrous encapsulation can negatively impact the function of implantable medical devices. The device must be able to function in a potentially compromised environment because of the presence of degradative enzymes, reactive oxygen species, and acidic conditions, as low as pH 3, caused by the inflammatory process [27, 28]. Furthermore, the fibrous capsule can be severely limiting, which is particularly the case for *in vivo* biomolecule sensing [62]. The capsule prevents the transport of analytes, such as glucose, to the sensor surface, resulting in a decrease of sensor functionality following implantation. Another challenge is calcification of the implanted device, which can occur with cell injury and accumulation of cellular debris following long-term implantation [17]. Calcification is a major issue that limits the lifetime of bioprosthetic heart valves.

A number of strategies have been explored to minimize the FBR [63]. One approach is using locally delivered drugs to modulate the inflammatory response. Glucocorti-

coids, such as dexamethasone, can inhibit inflammatory mediators leading to reduced fibroblast proliferation and fibrous encapsulation [18, 21, 64]. Angiogenic drugs that enable reperfusion of the capsule have also been used to improve the functional lifetime of biosensing devices [65]. Improving blood flow within the capsule can also enhance transport of analytes to the sensor surface [66]. Another study showed that implants with uniform, highly interconnected 34-μm pores increased vascularization and reduced fibrosis compared to a nonporous implant of the same biomaterial [67].

A particularly successful approach is to minimize the adsorption ("fouling") of nonspecific protein, which triggers and sustains inflammation, to the device [21]. Various nonfouling coatings using hydrophilic materials, such as PEG, PLA, or hydrogels, have been used to encapsulate the device, reducing inflammation and fibrosis [18, 66, 68]. Recently, ultra-low-fouling zwitterionic hydrogels implanted subcutaneously in mice for three months were found to resist the formation of a fibrous capsule and promote angiogenesis in the surrounding-healing tissue [63, 69]. The zwitterionic hydrogels were synthesized from pure carboxybetaine materials, which because of their repulsive hydration forces are resistant to nonspecific protein adsorption [70].

To ensure that a given device is biocompatible, the local and systemic effects of the implanted device must be tested. The International Organization for Standardization (ISO) 10993 provides a series of guidelines, including *in vitro* and *in vivo* test procedures [17, 25]. These include tests for cytotoxicity, irritation, sensitization, carcinogenicity, hemocompatibility, and systemic toxicity [71].

2.3 Other Safety Considerations

Aside from the FBR, there are other practical challenges that should be considered. First, sterilization techniques such as ethylene oxide (EtO) sterilization, gamma radiation, and E-beam sterilization are necessary before implantation to remove harmful microorganisms [72]. The device must be able to withstand these sterilization processes without impairing functionality; for example, silk fibroin can be sterilized using EtO, gamma radiation, or 70% ethanol, while collagen cannot be sterilized under these conditions [73].

Second, power delivery is an important consideration for active photonic devices such as implantable LEDs. To avoid the need for an implantable battery that may need to be replaced, wireless power transmission would be ideal for the patient. Recently, a method for efficient wireless power transfer using mid-field frequencies enabled more than 2 mW of power to be delivered to deep tissues around 5 cm from the source [74]. This power was delivered at the maximum safety standards of 10 W/kg of tissue [74, 75] and is sufficient to power a whole host of implantable devices including miniature LEDs [76].

A final concern, which is unique to photonic devices, is unintended phototoxicity to cells. This could occur if high optical powers are used, for example, to compensate for optical loss in the system, light is focused accidentally to a small area, or if phototoxic ultraviolet (UV) light is needed to form the device, such as UV-cross-linking of *in situ* forming hydrogels [40]. The primary mechanisms of light damage to cells are photothermal and photochemical [77, 78]. Photothermal damage occurs due to light absorption leading to an increase in temperature which can cause denaturation of deoxyribonucleic acid (DNA) and proteins above 67 °C [78]. Importantly, the photothermal damage threshold increases for longer exposure time because heat dissipates over time and space. Photochemical damage is mediated by cellular chromophores that cause the generation of free radicals that cause cellular injury [77]. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) provides guidelines on acceptable limits of exposure to laser radiation, depending on wavelength and duration [79].

3 Optical components

We describe passive optical components made of biocompatible materials. These optical elements include diffraction gratings, photonic crystals, reflectors, plasmonic devices, and photodetectors, which are well-established components traditionally made with inorganic materials, such as glasses, metals, and semiconductors.

3.1 Diffraction grating reflectors

Diffraction gratings are mostly used for spectroscopic applications where they redirect light depending on its wavelength. Diffraction gratings made with materials that are sensitive to specific analytes can be used for sensing. An analyte of interest can change the diffraction efficiency or the grating period, and thus can be detected by measuring the change in the intensity or spectrum of diffracted light.

A diffraction grating has been fabricated with self-assembled lipid multilayers by using parallelized dip-pen nanolithography to deposit 5–100 nm high lines onto a

solid substrate (Fig. 1) [80]. These gratings enabled sensing of proteins with sensitivity down to 5 nM by their intercalation into lipid multilayers, which lowered diffraction efficiency of the gratings.

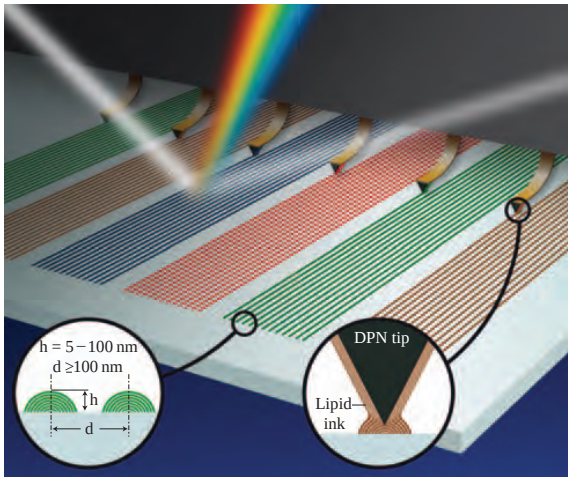

Fig. 1. Dip-pen nanolithography used to fabricate lipid multilayer gratings. Reprinted by permission from [80], Copyright 2010, Macmillan Publishers Ltd.

Silk has been a popular material for fabrication of optical diffractive elements [38, 81, 82]. Gratings are produced by pouring silk fibroin solution to a master mold, allowing it to dry, and detaching the silk layer to form a free-standing grating. A silk grating was shown to have a sensitivity in the refractive index change of $n = 0.007$, which corresponds to a glucose concentration of 5% [83]. In another demonstration [84], the matrix silk was mixed with hemoglobin lysed from red blood cells, and the diffraction intensity depended on the absorption induced by oxygenation. Diffraction gratings and the Fresnel lenses with desired patterns can be manufactured by photopolymerization of silk conjugates with a photoinitiator [85, 86]. The microstructures can be produced in reasonably large (>1 cm) areas. The fabricated structures have similar or superior mechanical properties to native silk fibroin and can readily interface with live cells [85]. Another study used femtosecond laser direct writing to fabricate diffraction gratings in protein films [87, 88]. Bovine serum albumin was coated to a polydimethylsiloxane substrate and a 120-fs titanium–sapphire laser was used to cross-link the protein to form a grating structure.

Silk has also been used to fabricate a microprism retroreflector array (Fig. 2). This device was biodegradable and has been implanted subcutaneously in mice [37]. *In vivo* tests in mice showed up to a threefold enhancement in reflectivity of bare tissue, which would be beneficial for imaging and sensing. Gold nanoparticles and chemotherapeutic drugs were also incorporated into the silk material making a multifunctional device.

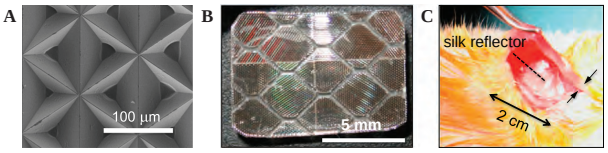

Fig. 2. (A) SEM image of a silk microprism reflector. (B) A microprism array prepared for implantation. (C) The reflector is implanted below mouse skin in the dorsal area. Reprinted from [37], Copyright (2012) National Academy of Sciences, USA.

3.2 Photonic crystals

Similar to diffraction gratings, photonic crystals can be implanted into biological tissues and used for sensing applications [89]. Change in the periodicity or refractive index of the photonic crystal will change the spectrum of reflected light. Further, photonic crystals can provide distinct spectral signatures that could be used as contrast agents without the need for fluorescent tags. Photonic crystals are most frequently made by self-assembly of colloidal particles or by laser recording. For example, monodisperse and highly charged polystyrene and PMMA particles self-assemble into a body-centered cubic or face-centered cubic lattice with a mesoscopic periodicity of 0.1–1.0 µm [90, 91]. Photonic crystals have been also fabricated using laser by silver halide chemistry [92], laser ablation [93], or photopolymerization [94].

Photonic crystals can incorporate functionalized hydrogels which when coming into contact with a target analyte, the volume of the hydrogel changes due to variation in Donnan osmotic pressure. The volumetric alteration of the photonic crystal shifts the bandgap to longer or shorter wavelengths depending on the concentration of the target analyte. The change in the reflection can be measured through the skin or by an optical fiber with reflection spectrometer and correlated with the concentration [95]. Photonic crystals can be functionalized to become sensitive to a wide range of physiologically relevant analytes such as Pb^{2+} ions [96, 97], urea [98], glucose [99], creatinine [100], and ammonia [101] and pH in the physiological range (4.5–9.0) [102, 103]. Glucose sensing with photonic crystals has been demonstrated with a detection limit of ~100 µM in the solution [104] and tear fluid [105]. In one study, the ef-

ficacy of the sensors was tested in an *in vivo* trial by subcutaneous implantation below an eye of a rabbit [104]. In a clinical trial, the photonic crystal integrated on a contact lens was placed beneath the pupil of a human volunteer and the concentration of glucose was monitored after glucose administration [106]. As the concentration of glucose in blood increased from 90 to 140 mg/dL, the holographic sensor produced a 40-nm shift in the reflection peak. Recently, photonic crystals sensors fabricated with chitosan hydrogels have been demonstrated, which is operated in the NIR spectral range [107]. Photonic crystals can potentially be incorporated in hydrogel-based ocular inserts or contact lens sensor for patients with diabetes [108].

Three-dimensional photonic crystals have been fabricated entirely out of silk (Fig. 3) [109]. The silk inverse opals show iridescence or structural color when covered with biological tissue, which may be used for refractive index measurement and for targeted laser-induced heating through photonic crystal-enhanced absorption.

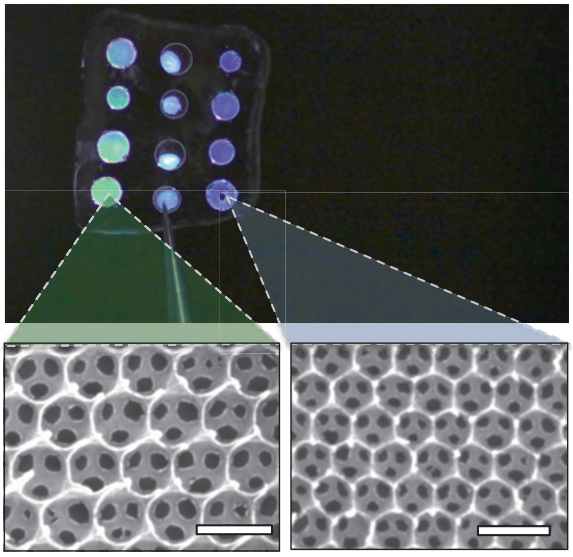

Fig. 3. Silk inverse opals showing structural color. Reprinted by permission from [109], Copyright 2012, Macmillan Publishers Ltd.

3.3 Plasmonic devices

Some applications can benefit from nano- or microscale devices. Plasmonics [110] offers practical ways to miniaturize devices by providing enhanced absorption and scattering properties by optical coupling with free electrons. The use of plasmonic nanoparticles for diagnostic imaging and photothermal therapy have been extensively explored [111–113]. Several photonic devices incorporating plasmonic nanoparticles have been demonstrated. Gold nanoparticles and chemotherapeutic drugs were incorporated into a silk multifunctional polymer device [37]. A biocompatible nanoplasmonic device was assembled with the aid of programmable DNA assembly [114], which can control the chirality of plasmonic nanostructures (Fig. 4) [115, 116]. A 3D photonic crystal of DNA-labeled plasmonic nanoparticles was fabricated by DNA-programmable crystallization with nanometer precision [117]. In another approach, plasmonic nanoparticles are used to optically sense DNA molecules in complex media, where binding of the target DNA causes a spatial extension of the plasmonic nanoparticle dimer inducing spectral shifts [118]. A variety of plasmonic nanostructures such as nanodot, nanohole, and bowtie patters were first fabricated on a silicon substrates and sequentially transferred to a silk substrate [119]. These plasmonic structures can be used as sensors or to enhance fluorescence [120]. A spectral shift sensitivity up to 1200 nm/RIU has been demonstrated for sensing glucose [121].

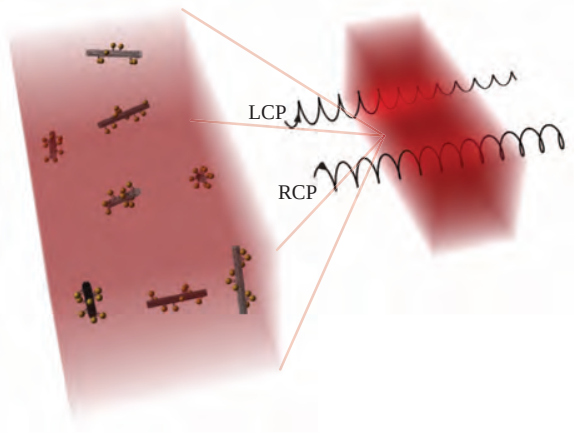

Fig. 4. DNA-based self-assembly of chiral plasmonic nanoparticles. Reprinted by permission from [114], Copyright 2012, Macmillan Publishers Ltd.

3.4 Photodetectors

A photodetector converts light energy to an electrical signal. Most studies on photodetectors have been focused on applications related to retinal prosthetics. Recent efforts have been devoted to develop photodetectors with im-

proved conversion efficiency, mechanical flexibility, and biocompatibility over conventional photodiodes based on inorganic silicon. Organic semiconductors, particularly conjugated polymers (CPs), have shown promise as a potential alternative to silicon [122]. CPs interact with light through conjugated π-electrons, just like natural photoreceptors. Compared to traditional approaches using multiple inorganic elements and electrodes, the promise of a single-component, all-organic, wireless artificial retina that does not require external electrical power is enticing. CPs produce negligible heat and are flexible [123, 124]. Additionally, organic retinal prosthesis based on CPs have been demonstrated [125–127], although their *in vivo* biocompatibility and functional lifetime have yet to be established. Besides the retina, biocompatible photodetectors may be implanted in the body for optical sensing and imaging. The optical signal is detected and converted to an electronic signal, which can then be transmitted wirelessly to an external receiver.

4 Waveguides and waveguide-based devices

Optical implantable waveguides are potentially useful for delivering therapeutic light deep into target tissues and for delivering light to and from other implanted photonic devices. While optical waveguides based on silica fibers [128] or silicon oxynitride planar waveguides [129] in various forms have been implanted in animals, particularly for optogenetic studies in the brain [130], low-loss waveguides can be made from a variety of biocompatible, transparent materials. For low guiding loss, the refractive index of the biomaterial should be higher than that of adjacent tissues, which ranges typically from 1.34 (interstitial fluid) to 1.47. For some applications, however, the light-guiding efficiency is deliberately reduced so that light is extracted to the surrounding tissue through the waveguide surface along the length. Furthermore, optical waveguides may incorporate functional materials, such as dyes, photoactivable chemicals, nanoparticles, and live cells, within the core, cladding, and/or external surface of the waveguide to add a variety of photonic functionalities useful for sensing and therapy. Beside surgical implantation, waveguides may be injected using needles and formed *in situ* using materials, such as guest–host–assembly hydrogels or thermoresponsive hydrogels [131].

4.1 Bio-derived material waveguides

Several bio-derived polymers are good candidates for implantable waveguides. A cellulose waveguide has been developed using cellulose butyrate fibers (refractive index, n = 1.475) as a core and hydroxypropyl cellulose powder (n = 1.337) as a cladding, with a relatively low propagation loss of ~1 dB/cm [132]. The porous cladding layer can serve as a microfluidic channel for drug delivery and biosensing. Silk has a refractive index (n = 1.54) higher than most tissues. Silk optical waveguides were fabricated on a glass substrate [39], on a biocompatible substrate, or as free-standing fibers, with propagation losses as low as 0.25 dB/cm. Native spider silk filament has been shown to guide light, albeit at high loss up to 10.5 dB/cm [133].

Optical waveguides may also be made of endogenous proteins and peptides extracted from host tissues. For example, long needle-like peptide crystals self-assembled from diphenylalanine can guide light and emit fluorescence [134].

It has been demonstrated that a linear array of *Escherichia coli* aligned by optical forces could guide light [135]. Although bacteria would not be considered applicable to implantable devices, this work suggests the possibility of forming an optical waveguide *in situ* inside biological tissue by self-assembly of human cells or biocompatible particles.

4.2 Biodegradable synthetic polymer waveguides

Several biodegradable synthetic polymers are used for medical implants and could also be used for optical waveguides. Planar waveguides were fabricated from PLA and PLGA by first press melting a material to form a transparent film and then using laser cutting to make arbitrary shapes [136]. The waveguides were connected to a conventional optical fiber (Fig. 5a), and green laser light was delivered deep into the skin tissue (Fig. 5b). The light propagation and waveguide loss was tailored by the waveguide shape, so that the light was extracted uniformly along the implantation site (Fig. 5c). Biodegradation of PLGA waveguides tested *in vivo* showed good waveguide transparency in the first week, with loosing of transparency in two or three weeks and complete biodegradation and reabsorption by the body within five weeks (Fig. 5d).

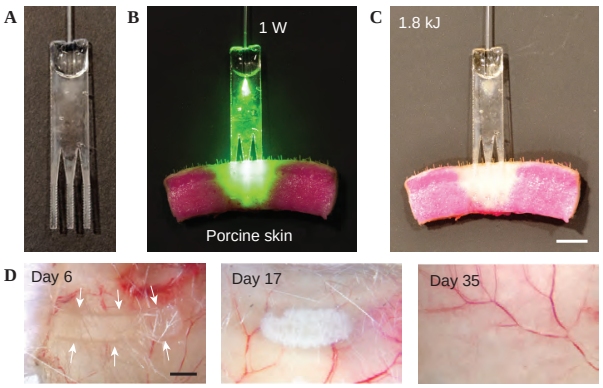

Fig. 5. Biodegradable synthetic polymer waveguides. (A) Planar comb-shaped PLA optical waveguide connected to an optical fiber. (B) Delivery of light through the waveguide deep into the skin tissue. (C) Photobleaching of an applied dye indicates the area of light penetration. (D) Biodegradation of a piece of PLA waveguide *in vivo* during 35 days. Reprinted by permission from [136], Copyright 2016, Macmillan Publishers Ltd.

4.3 Hydrogel waveguides

Hydrogels are commonly used in tissue engineering because of their ability to encapsulate cells, serving as scaffolds for tissue repair and regeneration. Their high water content mimics tissue properties, limiting FBR, and they can be readily functionalized with biologically active materials that can be interfaced with living tissues. An agarose gel (2%, w/v) waveguide containing live cells has been fabricated by soft lithography on top of agarose gel substrates (Fig. 6a) [137]. The difference in the concentration of agarose caused the waveguides to have slightly higher refractive index (n = 1.3357) than the substrate (n = 1.3343) guiding light with an average loss of 13 dB/cm. Hydrogel waveguides were integrated in a microfluidic device composed entirely of agarose gels [138]. A waveguide were fabricated by spin coating low index (n = 1.497) agarose hydrogel at both sides of a high index (n = 1.536) gelatin layer (Fig. 6b).

Cylindrical optical fibers have been fabricated with high-index PEG hydrogels for the core and lower index alginate hydrogels for the shell (Fig. 7a). These biocompatible hydrogel optical fibers had a low propagation loss of 0.42 dB/cm over a fiber length of 1 m. In addition, the permeable nature of the hydrogel materials enabled facile incorporation of small-molecular dyes (Fig. 7b) or nanoparticles to incorporate various functionalities to the fiber, such as plasmonic photothermal heating and light amplification [43]. The flexibility and biocompatibilty of the fibers may be suited for *in vivo* applications (Fig. 7c).

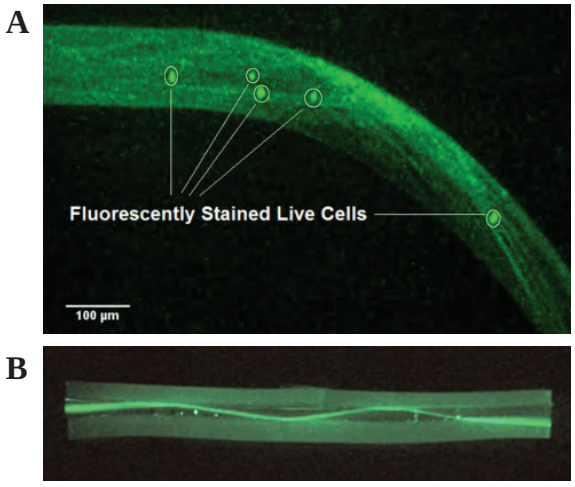

Fig. 6. Hydrogel waveguides. (A) Live cells encapsulated in an agarose hydrogel waveguide. Reprinted by permission from [137], Copyright 2012, The Optical Society. (B) Light guiding in core-cladding hydrogel waveguide. Reprinted by permission from [138], Copyright 2009, Wiley.

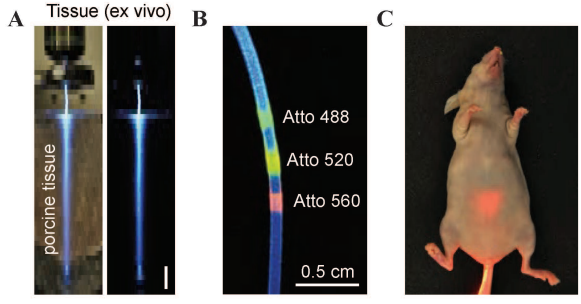

Fig. 7. Hydrogel-based optical waveguide. (A) Light guidance of a fiber in a tissue *ex vivo*. Scale bar, 1 cm. (B) A fluorescence image of a fiber doped with three different fluorophores along the fiber, as indicated. (C) *In vivo* light guidance through a hydrogel fiber administered to the colon through the rectum. Reprinted by permission from [43], Copyright 2015, Wiley.

4.4 Light-guiding hydrogel implants

Hydrogels can be used as photonic materials for guiding light by optimizing their chemical compositions [42]. With an optimal recipe to achieve high transparency and mechanical flexibility, a hydrogel encapsulating cells have been fabricated in a form of slab waveguide. A pigtail optical fiber establishes an efficient optical communication to the cells within the hydrogel (Fig. 8a). Genetically altered HeLa cells that respond to cellular stress by expressing green fluorescent protein (GFP) were implanted subcutaneously in a mouse for sensing of nanotoxicity *in*

vivo. Sensor signal increased when CdTe quantum dots were intravenously injected, but no change was observed with core/shell CdSe/ZnS quantum dots, confirming the role of the ZnS shell in reducing cytotoxicity. In another demonstration, HeLa cells engineered to produce antidiabetic hormone GLP-1 in response to blue light [139] were seeded in a hydrogel waveguide. When implanted in diabetic mice, treatment with blue light significantly improved blood-glucose homeostasis (Fig. 8b). Hydrogels implanted for eight days remained largely functional, with less than 1 dB cm^{-1} loss in optical transmittance, and with more than 65% of the embedded cells remaining viable. A mild FBR was also observed, with the formation of loose connective tissues around the implant. Future research optimizing the light-guiding properties, cell implantation, and FBR-resistant properties [69] may lead to the development of practical, chronically implanted hydrogels for sensing and therapeutic applications.

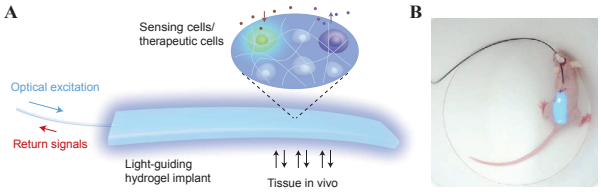

Fig. 8. Hydrogel-based active optical waveguiding devices. (A) A schematic for the cell-integrated optical waveguide. (B) A hydrogel-implanted mouse in a freely moving state with a blue light coupled. Reprinted by permission from [42], Copyright 2013, Macmillan Publishers Ltd.

5 Bio-Lasers

Bio-lasers represent an emerging class of light sources where laser light can be generated *in situ* in target cells and tissues. As with all lasers, three components are needed: an optical cavity that confines light, a gain medium that amplifies light in the cavity, and pump energy to power the gain medium. Bio-lasers implanted or injected in tissue can serve as a local light source in imaging, diagnosis, and therapeutic applications.

5.1 Fluorescent protein and organic dye lasers

Fluorescent proteins (FPs), derived from aquatic organisms such as jellyfish, are widely used as reporters of gene expression in animal models. FPs have high extinction coefficients (20,000–140,000 $M^{-1}cm^{-1}$), good photostability, and high quantum yields of 0.6–0.8 [140]. The lasing of FPs has been demonstrated in different cavity configurations. GFP in a solution [148] or as a dried thin film [141, 142] placed in between two mirrors were shown to provide high optical gain supporting laser generation at low threshold energy down to 100 pJ. A GFP ring laser with 1–2 mm in diameter formed by drying a droplet of GFP on a surface was demonstrated [142]. In another study, DsRed2 was embedded inside a layered high-scattering medium acting as a random one-dimensional cavity [143].

As an alternative to fluorescent proteins, small molecules with π-conjugated fluorophores found naturally in human tissues can be exploited as a gain material for biocompatible photonic devices. Vitamin B_2 (riboflavin) has the highest quantum yield of 0.23 among the molecules present in the human body [144]. Riboflavin was used as a gain medium in a water–glycerol microdroplet whispering-gallery (WG) laser [145]. Riboflavin-doped droplets were generated on a superhydrophobic surface having nearly spherical shape. To prevent evaporation and droplet collapse when implanted into a biological tissue, the droplets were encapsulated in biodegradable PLA microwells. A single-mode distributed feedback laser made from riboflavin-doped gelatin was demonstrated using a micro-patterned, nonbiocompatible polymer substrate with a low refractive index (n = 1.39) [146]. An extension of this design was composed entirely on biocompatible materials including silk [147].

DNA has been used to enhance the functionality of organic dye lasers. Intercalation of dye molecules in DNA strands allowed for dye loading at high concentration and reduced fluorescence quenching, which lowered the threshold for amplified spontaneous emission and lasing [148]. Lasing has been reported in a thin film of DNA doped with Rhodamine 6G dye [149] and in distributed feedback cavities containing DNAs doped with fluorescent dyes [150, 151]. DNA was used as a linker of a donor and acceptor fluorescent dyes in an optofluidic laser as a means to control the efficiency of the Förster resonance energy transfer (FRET) between the gain molecules [152]. The conformational change of the DNA linker by external factors affects the laser output characteristics, such as the wavelength and intensity, and thus can be measured [153].

A laser can also be created directly in a tissue by injecting a fluorescent dye and using the scattering properties of the tissue to induce random lasing [44, 45]. Random lasing occurs when light is trapped in the disordered media, in this case tissue, by multiple scattering forming closed-path optical resonators. Lasing has been achieved in Rhodamine-6G-impregnated human colon, kidney [46], and bovine heart tissue [154]; Rhodamine-800-infiltrated bone tissue [155, 156]; and fluorescent anticancer-drug-infiltrated rodent uterine tissues [157]. The typical output spectrum and spatial profile of random lasers are highly sensitive to the microstructure of the tissue. Random laser emission from more heterogeneous, disorganized, cancerous tissue exhibited more spectral lines than healthy tissues of the same organ [46, 157, 158]. The sensitivity of laser output to scatterers was used to detect nanoscale deformations in bones [156] and stress responses of bovine pericardium [154]. As the random lasing is sensitive to the position of scatterers, this can be used to characterize mechanical properties of tissues. The shift in the spectral peaks of the random lasing in bones that were subject to mechanical stress was used to measure nanoscale deformations [156]. Further studies have been conducted on softer tissues including bovine pericardium and the sac containing the heart [154]. Spectral width of the random lasing has been measured while the stress on the tissue was increased up to 6 MPa. When the tissue is elongated, the collagen fibrils are aligned, reducing the scattering and, therefore, increasing the lasing linewidth.

5.2 Cell lasers

The GFP or organic dyes at high concentration (>100 μM) in the cytoplasm have been shown to provide sufficient gain to generate laser light. In one study [48], a human cell expressing GFP was placed between two laser mirrors and pumped with a nanosecond pulsed laser. At pump energy levels above a few nanojoule, a clear laser output was observed. The laser output spectra varied with changes in the cell size and refractive index, which may be used for cytometry and basic studies of intracellular biological processes. Stable GFP transfection can make the laser replenish the gain medium, rendering it self-healing [50]. Fluorescent dyes obviate the need for genetic transfection [159].

A liquid droplet in the air can confine light by total internal reflection so that the light circulates in the droplet forming whispering gallery modes (WGMs) [160]. Water droplets encapsulating cells and gain dyes have shown to support lasing [161]. While this kind of laser is entirely composed of biocompatible materials for both cavity and gain, the droplet easily breaks when made in contact with tissue. Microdroplet lasers have been encapsulated in a superhydrophobic biocompatible polymer matrix, which renders them potentially implantable [145].

Cell lasers incorporating microresonators have been demonstrated by using fluorescent beads with diameters of about 10 μm (Fig. 9a, b) [47, 162, 163]. The WGM output spectra allowed the individual bead diameters to be determined with 50-pm precision, which can be used as a unique identifier to tag a large number of cells and track them. The position of modes was also used to sense the change in refractive index within the cell. Intracellular lasing was also demonstrated using dye-doped oil droplets injected in cells (Fig. 9c,d). Lasing spectra from deformed droplets was used to measure intracellular forces down to 20 pN/μm^2. An adipocyte, a fat cell, containing a large lipid droplet was also used as a natural optical cavity supporting lasing upon fluorescent dye staining and pumping with external laser [47]. Adipocyte lasers were also demonstrated inside fat tissue using an optical fiber for light delivery and collection. Injectable micro-bio-lasers offer a new possibility of delivering light to tissues.

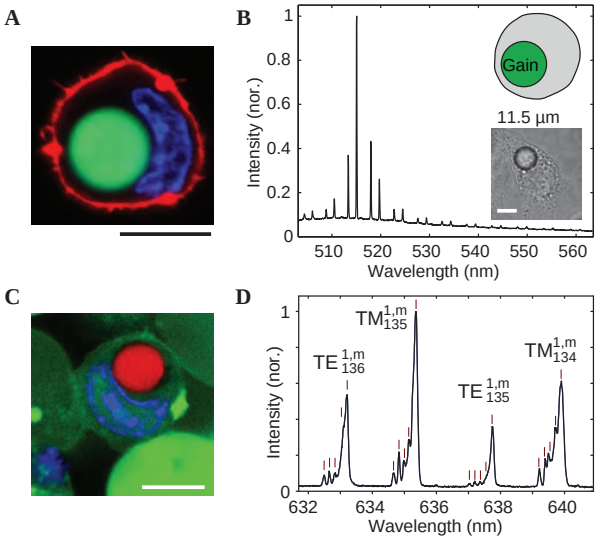

Fig. 9. Intracellular micro-lasers. (A) An intracellular laser based on a fluorescent bead. (B) Lasing emission from an 11.5-μm bead in a cell. Scale bar, 10 μm. (C) A dye-doped high-index oil droplet injected into a cell. (D) Lasing spectrum from a single oil droplet shows split spectral lines because of droplet deformation. Reprinted by permission from [47], Copyright 2015, Macmillan Publishers Ltd.

6 Optoelectronic devices

While in this review we have discussed the development of biomaterial-based devices, many existing medical devices such as the pacemaker or cochlear implant contain sophisticated electronic circuitry that are fully encapsulated, usually with hermetic packaging, to facilitate implantation into the body [71, 72]. The separation of active electronic components from the body's environment creates unique design challenges, including biocompatibility of the packaging material, leakage of internal materials, and particularly for batteryless devices, wireless powering and communication [164]. Recent innovations in wireless powering through radiofrequency (RF) harvesting has enabled miniaturization of devices [165] and delivery of milliwatt levels of electrical power through over 5 cm of tissue [74]. Optical devices could also follow this principle of a sealed wireless capsule containing regular nonbiocompatible optical devices. These may include any device such as light sources (LED and laser), photodetectors including cameras, and imaging devices such as microscope objective. We could also imagine that more complicated systems such as optical coherence tomography (OCT), spectrometer, and confocal microscopes could be implanted into the body. The main limitation here is the size of the device, which could benefit from advances in integrated optical circuits. The light from such device could be coupled to the tissue by using an optical window on the device or having one or multiple optical fibers extending to different parts of the body.

One example of such device currently in use is the capsule endoscopy [166]. A pill-sized camera is ingested by the patient and takes pictures of the intestine while it is traveling through it. The camera contains a light source, batteries, and antenna to transmit data. Typically, the small intestine is imaged in this way because it cannot be reached by endoscopy or colonoscopy. There is no reason why a similar device could be implanted into the body having wireless power transfer for longer operational lifetime.

Other examples are implantable LEDs, which have generated interest for biosensing, photothermal and photodynamic therapy, and optogenetics [167–170]. Of particular interest has been optogenetic applications, which requires integration of miniature light sources deep in the brain to activate specific neurons [169]. To maximize capabilities *in vivo*, functional requirements such as long lifetime, high brightness, small size, mechanical robustness, and flexibility must be met while avoiding cytotoxicity, immunogenicity, sensitization, and chronic toxicity. To date, most conventional light sources implanted *in vivo* are inorganic semiconductor LEDs, such as GaN LEDs, with emission spectra typically in the blue region.

6.1 Semiconductor LEDs

Light activation of photosensitive proteins such as channelrhodopsin for *in vivo* optogenetic applications is traditionally achieved by integration of inorganic semiconductor LEDs to a cranial window in mice [171]. However, the use of wired, externalized LEDs limits opportunities for specific applications such as behavior studies for free-moving animals [172]. Animal movement is restricted by the length and contortion of the power cable, while the bulky size and shape of LEDs limit targeting of deep tissues. To solve these challenges, wireless and micro-scaled LEDs have been developed using wireless power transfer and micro-scaled circuit designs. A major consideration in the design of wireless LEDs is power supply, which is typically transmitted through RF energy harvesting [169, 173] or inductive power [174]. In contrast, wirelessly controlled LEDs use rechargeable batteries and communicate via RFs [173]. The operation range of wirelessly controlled LEDs (4 m) is longer than that of wirelessly powered LEDs (~1–2 m). The average output intensity of wireless LEDs is typically ~10 mW/mm^2 [169, 173], which exceeds (up to 10-fold) the minimum intensity necessary to stimulate rhodopsins.

Wireless LEDs have been directly implanted to deep brain tissues in mice [169, 174, 175]. Flexible and injectable μ-LEDs, with dimensions $0.1 \times 1 \times 1$ mm^3 that are less than 1000th the size of conventional LEDs, are suited for chronic use *in vivo* because of their small sizes, effective thermal management, and reduced tissue damage during the insertion process [169]. These LEDs have shown stable performance for several months following implantation [173]. However, wireless operation on freely moving animals is only possible for short-term experimentation, because a relatively large head-mounted wireless RF receiver is required. Another approach involves a completely implantable wireless optogenetic system, including the LED, RF power source, and controller (total 20 mg, 10 mm^3), that can be implanted throughout the nervous system (Fig. 10a) [176]. Recently, miniaturized wireless optoelectronic systems with high mechanical compliance have enabled implantation to previously inaccessible anatomical locations, such as in the epidural space for illumination of the spinal cord (Fig. 10b) [165].

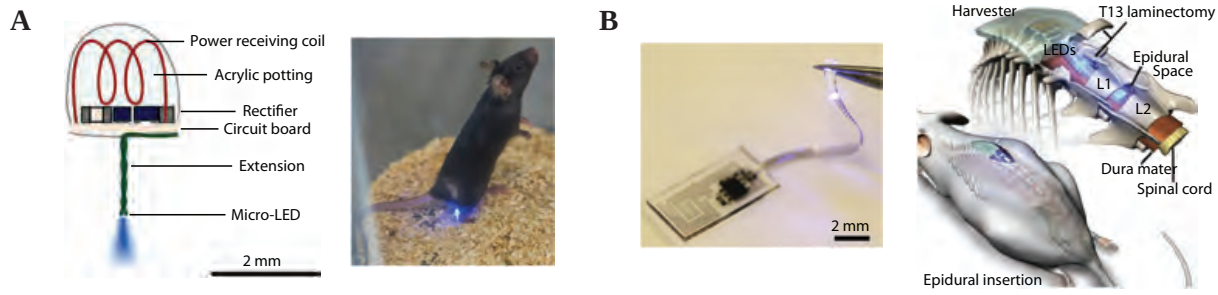

Fig. 10. Wireless LEDs for optogenetics. (A) Left: Schematic of completely implantable micro-LED system. Right: Mouse with subcutaneously implanted micro-LED for stimulation of peripheral nerve endings. Reprinted by permission from [176], Copyright 2015, Macmillan Publishers Ltd. (B) Left: Picture of a soft optoelectronic system including the harvester component and the soft, stretchable connector to an LED. Right: Schematic of implantation of device into the epidural space for spinal illumination. Reprinted by permission from [165], Copyright 2015, Macmillan Publishers Ltd.

6.2 Biomaterial based LEDs

In recent years, there has been great interest in using sustainable, organic light-emitting diodes (OLEDs) for consumer products such as flexible displays [177, 178]. Owing to their flexibility and organic constituents, OLEDs are also attractive candidates for biomedical applications [22, 179]. OLEDs are flexible, easily scalable, and made of organic materials. However, OLEDs are highly sensitive to water and oxidation [180] and leaking of nonbiocompatible organic components could be potentially toxic to the host. There are only a few reports using conventional OLEDs in close contact with biological matter [181]. OLED are mostly used as wearable light sources [182–184] and have not been implanted into tissue. Therefore, there is a need for completely biocompatible and possibly biodegradable LEDs: bio-OLEDs. To reach this goal, all LED components—the substrate, electrodes, conducting and emissive layers—should be made of biomaterials.

To date, a number of individual LED components made using biocompatible, organic materials have been reported. For example, DNA was used as electron/hole transport/blocking layer material [185–187] or as phosphorescent host [188] in OLED devices. Individual nucleobases were also used as electron/hole transport/blocking layer material [189, 190]. In another study, silk fibroin was used as gate dielectric in organic light-emitting transistor (OLET) [191]. Two other necessary components of an OLED are the substrate, which serves as a mechanical support, and electrodes, which enable electrical contacts. As a flexible and biodegradable substrate, bacterial cellulose membrane was used [192], exhibiting high transparency and good mechanical strength. However, for the electrode, an inorganic indium tin oxide (ITO) film was coated to the cellulose membrane. Paper, also a cellulose material, has been recently used for paper electronics [193] and is a potential substrate material. Bio-OLEDs could also be integrated with biomaterials-based electronics to create multifunctional implantable optoelectronic devices. Biocompatible electronics [194, 195] are a much larger and more developed research area than biocompatible photonics. For example, completely biodegradable transistors [196, 197] and other electronic components [22] have been developed. It is likely only a matter of time when the development of bio-OLEDs will follow.

7 Future Perspectives

Diffraction gratings, photonic crystals, reflectors, and plasmonic devices, which are commonly used for *in vitro* sensing, have been fabricated with biocompatible materials. Significant advances have been made in the development of biocompatible optical waveguides to deliver and extract the light from the body as well as having biofunctional components for sensing and therapy. As an alternative to waveguides, light can be generated within the body by bioluminescence or LED sources. Bioluminescence is a process that emits light from chemically stored energy [198]. This natural mechanism is optimized to function in biological systems and could be potentially applied as a weak but natural light source in biocompatible optical devices. For higher optical intensities, biocompatible LEDs and bio-lasers may be used. Energy can be provided to the implanted light source wirelessly without physical link to an external source. Alternatively, it would be beneficial to power these and other photonic devices by internal sources of energy such as biomechanical, biothermal, and biochemical energy. It has been demonstrated

that physiologic motions such as heart beating and respiration can be transduced to electric energy by using piezoelectric transducer [199]. Lasers are another class of light sources that have been successfully integrated with cells and tissues. Their narrow emission spectrum is especially useful in sensing, spectroscopy, and imaging.

While the development of implantable biophotonic devices for clinical applications is in its infancy, many parallels can be drawn to the progress in implantable cardiac pacemakers over the past 60 years. Spurred by 19th century observations that electrical impulses can control heart beating, early pacemakers were external [200], including needle electrodes introduced directly into the heart (1930s), bulky transcutaneous pacemakers powered by AC power (1940s), and battery-operated wearable pacemakers (1950s), before the fully implantable pacemaker was demonstrated in 1958 [201]. One key factor that enabled implantation was encasement of the battery and circuitry with epoxy resin and silicone rubber, which has since been replaced with titanium because of its superior biocompatibility, reduction of electromagnetic interference, and stronger mechanical properties [202].

Today, the use of light for diagnostics, therapy, and surgery is ubiquitous. The pulse oximeter, which measures the patient's arterial oxygen saturation, is universally used in emergency medicine. The wireless capsule endoscope is routinely ingested by patients for imaging of the upper gastrointestinal tract. Emerging flexible optoelectronic technologies can be used for wearable health monitoring, such as quantitative imaging of skin temperature and thermal properties [203]. However, the vast majority of photonic applications in the clinic requires use of external light sources, limiting applications to superficial areas such as the eye or skin. As the development of biocompatible photonic materials continues, implantable photonic devices for human use are likely to emerge, enabling chronic sensing and imaging of difficult to access locations such as the brain [204, 205] and expanding therapeutic applications such as low-level light therapy [206], blue-light antimicrobial treatment [207], and photodynamic therapy [208] beyond superficial skin to deep tissues. The ability to render cells photoactive has opened opportunities for light-based cell therapy and sensing, such as with optogenetics and intracellular lasers. As compared to electrical stimulation of cells, light–tissue interactions are decidedly more diverse and use a range of photonic materials from polymers, semiconductors, organic molecules, and cells.

Small size and mechanical flexibility would be strongly preferred for most applications of implanted devices. The choice of the appropriate material for use *in vivo* will depend not only on the functionality required but also on its biocompatibility profile (Fig. 11). The ability of the device, particularly those encapsulating cells, to integrate into host tissue without impairing functionality and harming the host needs to be evaluated. For chronically implanted devices, FBR-resistant properties enabling long implanted lifespans are essential. For devices implanted for a relatively short time of operation or those that are too small or dispersed, biodegradability and bioresorbability can be implemented to avoid the need to harvest the device after use.

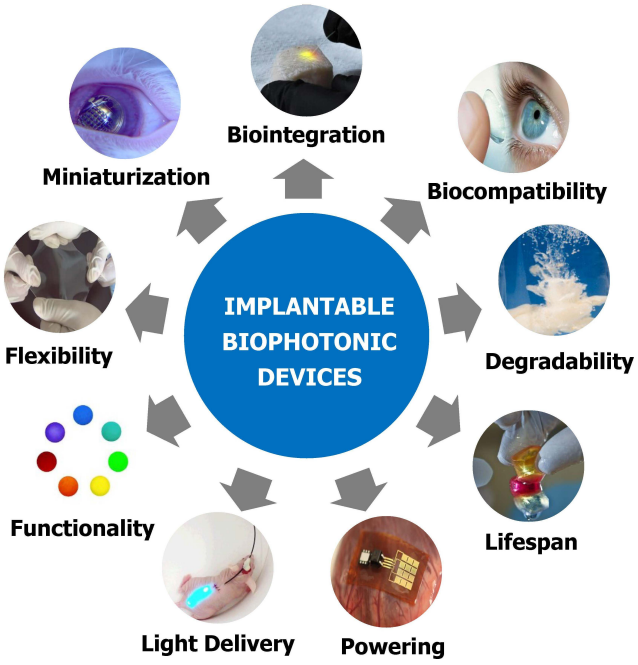

Fig. 11. Factors to consider when designing implantable biophotonic devices.

In principle, it should be possible to realize almost any optical components and functions with biocompatible materials, although biocompatibility may be achieved at the expense of optical performance as compared to conventional photonic technologies. Implantable optical functionalities can serve as building blocks for more complex devices and systems. Most studies conducted to date have focused on proof-of-concept demonstrations on optical benches or animal studies. Further efforts are expected to extend the concepts and techniques demonstrated to date for practical applications in both preclinical and clinical settings. We envision one day opening an optics product catalog featuring a variety of implantable, biocompatible components and devices.

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References

[1] P. A. Asbell, I. Dualan, J. Mindel, D. Brocks, M. Ahmad, and S. Epstein, "Age-related cataract," *Lancet*, vol. 365, no. 9459, pp. 599–609, 2005.

[2] D. J. Apple and J. Sims, "Harold Ridley and the invention of the intraocular lens.," *Surv. Ophthalmol.*, vol. 40, no. 4, pp. 279–292.

[3] H. Ridley, "Intra-ocular acrylic lenses; a recent development in the surgery of cataract.," *Br. J. Ophthalmol.*, vol. 36, no. 3, pp. 113–122, 1952.

[4] R. Lace, C. Murray-Dunning, and R. Williams, "Biomaterials for ocular reconstruction," *J. Mater. Sci.*, vol. 50, no. 4, pp. 1523–1534, 2014.

[5] J. D. Weiland, A. K. Cho, and M. S. Humayun, "Retinal prostheses: Current clinical results and future needs," *Ophthalmology*, vol. 118, no. 11, pp. 2227–2237, 2011.

[6] E. Zrenner, "Fighting blindness with microelectronics.," *Sci. Transl. Med.*, vol. 5, no. 210, p. 210ps16, 2013.

[7] A. T. Chuang, C. E. Margo, and P. B. Greenberg, "Retinal implants: a systematic review," *Br. J. Ophthalmol.*, vol. 98, no. 7, pp. 852–856, 2014.

[8] K. Stingl, K. U. Bartz-Schmidt, D. Besch, A. Braun, A. Bruckmann, F. Gekeler, U. Greppmaier, S. Hipp, G. Hörtdörfer, C. Kernstock, A. Koitschev, A. Kusnyerik, H. Sachs, A. Schatz, K. T. Stingl, T. Peters, B. Wilhelm, and E. Zrenner, "Artificial vision with wirelessly powered subretinal electronic implant alpha-IMS.," *Proc. Biol. Sci.*, vol. 280, no. 1757, p. 20130077, 2013.

[9] D. Palanker, A. Vankov, P. Huie, and S. Baccus, "Design of a high-resolution optoelectronic retinal prosthesis.," *J. Neural Eng.*, vol. 2, no. 1, pp. S105–S120, 2005.

[10] K. Mathieson, J. Loudin, G. Goetz, P. Huie, L. Wang, T. I. Kamins, L. Galambos, R. Smith, J. S. Harris, A. Sher, and D. Palanker, "Photovoltaic retinal prosthesis with high pixel density," *Nat. Photonics*, vol. 6, no. 6, pp. 391–397, 2012.

[11] H. Lorach, G. Goetz, R. Smith, X. Lei, Y. Mandel, T. Kamins, K. Mathieson, P. Huie, J. Harris, A. Sher, and D. Palanker, "Photovoltaic restoration of sight with high visual acuity," *Nat. Med.*, vol. 21, no. 5, 2015.

[12] A. C. Anselmo and S. Mitragotri, "A Review of Clinical Translation of Inorganic Nanoparticles," *AAPS J.* vol. 17, no. 5, pp. 1041-1054, 2015.

[13] T. L. Doane and C. Burda, "The unique role of nanoparticles in nanomedicine: imaging, drug delivery and therapy," *Chem. Soc. Rev.*, vol. 41, no. 7, p. 2885, 2012.

[14] D. Jaque, L. M. Maestro, B. Del Rosal, P. Haro-Gonzalez, A. Benayas, J. L. Plaza, E. M. Rodríguez, and J. G. Solé, "Nanoparticles for photothermal therapies," *Nanoscale*, vol. 6, pp. 1–35, 2014.

[15] J. Zhang, R. E. Campbell, A. Y. Ting, and R. Y. Tsien, "Creating new fluorescent probes for cell biology," *Nat. Rev. Mol. Cell Biol.*, vol. 3, no. 12, pp. 906–918, 2002.

[16] D. E. J. G. Dolmans, D. Fukumura, and R. K. Jain, "Photodynamic therapy for cancer," *Nat. Rev. Cancer*, vol. 3, no. 5, pp. 380–387, 2003.

[17] Y. Onuki, U. Bhardwaj, F. Papadimitrakopoulos, and D. J. Burgess, "A review of the biocompatibility of implantable devices: current challenges to overcome foreign body response.," *J. Diabetes Sci. Technol.*, vol. 2, no. 6, pp. 1003–1015, 2008.

[18] J. M. Morais, F. Papadimitrakopoulos, and D. J. Burgess, "Biomaterials/tissue interactions: possible solutions to overcome foreign body response.," *AAPS J.*, vol. 12, no. 2, pp. 188–196, 2010.

[19] F. G. Omenetto and D. L. Kaplan, "A new route for silk," *Nat. Photonics*, vol. 2, no. 11, pp. 641–643, 2008.

[20] D. F. Williams, "On the mechanisms of biocompatibility," *Biomaterials*, vol. 29, no. 20, pp. 2941–2953, 2008.

[21] J. D. Bryers, C. M. Giachelli, and B. D. Ratner, "Engineering Biomaterials to Integrate and Heal: The Biocompatibility Paradigm Shifts," *Biotechnol. Bioeng.*, vol. 109, no. 8, pp. 1898–1911, 2012.

[22] M. Irimia-Vladu, "'Green' electronics: biodegradable and biocompatible materials and devices for sustainable future.," *Chem. Soc. Rev.*, vol. 43, no. 2, pp. 588–610, 2014.

[23] L. S. Nair and C. T. Laurencin, "Biodegradable polymers as biomaterials," *Prog. Polym. Sci.*, vol. 32, no. 8–9, pp. 762–798, 2007.

[24] A. K. Lynn, I. V. Yannas, and W. Bonfield, "Antigenicity and immunogenicity of collagen," *J. Biomed. Mater. Res. - Part B Appl. Biomater.*, vol. 71, no. 2, pp. 343–354, 2004.

[25] M. N. Helmus, D. F. Gibbons, and D. Cebon, "Biocompatibility: meeting a key functional requirement of next-generation medical devices.," *Toxicol. Pathol.*, vol. 36, no. 1, pp. 70–80, 2008.

[26] R. Langer and D. A. Tirrell, "Designing materials for biology and medicine.," *Nature*, vol. 428, no. 6982, pp. 487–492, 2004.

[27] J. M. Anderson, A. Rodriguez, and D. T. Chang, "Foreign body reaction to biomaterials," *Semin. Immunol.*, vol. 20, no. 2, pp. 86–100, 2008.

[28] J. M. Anderson and M. S. Shive, "Biodegradation and biocompatibility of PLA and PLGA microspheres," *Adv. Drug Deliv. Rev.*, vol. 28, no. 1, pp. 5–24, 1997.

[29] S. Lyu and D. Untereker, "Degradability of polymers for implantable biomedical devices," *Int. J. Mol. Sci.*, vol. 10, no. 9, pp. 4033–4065, 2009.

[30] A. Sannino, C. Demitri, and M. Madaghiele, "Biodegradable cellulose-based hydrogels: Design and applications," *Materials (Basel).*, vol. 2, no. 2, pp. 353–373, 2009.

[31] O. Bar-Ilan, R. M. Albrecht, V. E. Fako, and D. Y. Furgeson, "Toxicity assessments of multisized gold and silver nanoparticles in zebrafish embryos," *Small*, vol. 5, no. 16, pp. 1897–1910, 2009.

[32] R. Shukla, V. Bansal, M. Chaudhary, A. Basu, R. R. Bhonde, and M. Sastry, "Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: A microscopic overview," *Langmuir*, vol. 21, no. 23, pp. 10644–10654, 2005.

[33] N. Khlebtsov and L. Dykman, "Biodistribution and toxicity of engineered gold nanoparticles: a review of in vitro and in vivo studies.," *Chem. Soc. Rev.*, vol. 40, no. 3, pp. 1647–1671, 2011.

[34] C. Kirchner, T. Liedl, S. Kudera, T. Pellegrino, H. E. Gaub, S. Sto, N. Fertig, and W. J. Parak, "Cytotoxicity of Colloidal CdSe and CdSe / ZnS Nanoparticles," *Nano*, vol. 5, no. 2, pp 331-338, 2005.

[35] S. A. Jewett, M. S. Makowski, B. Andrews, M. J. Manfra, and A. Ivanisevic, "Gallium nitride is biocompatible and non-toxic before and after functionalization with peptides," *Acta Biomater.*, vol. 8, no. 2, pp. 728–733, 2012.

[36] G. Park, H. J. Chung, K. Kim, S. A. Lim, J. Kim, Y. S. Kim, Y. Liu, W. H. Yeo, R. H. Kim, S. S. Kim, J. S. Kim, Y. H. Jung, T. Il Kim, C. Yee, J. a. Rogers, and K. M. Lee, "Immunologic and tissue biocompatibility of flexible/stretchable electronics and optoelectronics," *Adv. Healthc. Mater.*, vol. 3, no. 4, pp. 515–525, 2014.

[37] H. Tao, J. M. Kainerstorfer, S. M. Siebert, E. M. Pritchard, A. Sassaroli, B. J. B. Panilaitis, M. A. Brenckle, J. J. Amsden, J. Levitt, S. Fantini, D. L. Kaplan, and F. G. Omenetto, "Implantable, multifunctional, bioresorbable optics," *Proc. Natl. Acad. Sci.*, vol. 109, no. 48, pp. 19584–19589, 2012.

[38] B. D. Lawrence, M. Cronin-Golomb, I. Georgakoudi, D. L. Kaplan, and F. G. Omenetto, "Bioactive silk protein biomaterial systems for optical devices," *Biomacromolecules*, vol. 9, no. 4, pp. 1214–1220, 2008.

[39] S. T. Parker, P. Domachuk, J. Amsden, J. Bressner, J. A. Lewis, D. L. Kaplan, and F. G. Omenetto, "Biocompatible silk printed optical waveguides," *Adv. Mater*, vol. 21, no. 23, pp. 2411–2415, 2009.

[40] J. A. Yang, J. Yeom, B. W. Hwang, A. S. Hoffman, and S. K. Hahn, "In situ-forming injectable hydrogels for regenerative medicine," *Prog. Polym. Sci.*, vol. 39, no. 12, pp. 1973–1986, 2014.

[41] A. S. Hoffman, "Hydrogels for biomedical applications," *Advanced Drug Delivery Reviews*, vol. 64, no. 1, pp. 3–12, 2002.

[42] M. Choi, J. W. Choi, S. Kim, S. Nizamoglu, S. K. Hahn, and S. H. Yun, "Light-guiding hydrogels for cell-based sensing and optogenetic synthesis in vivo," *Nat. Photonics*, vol. 7, no. 12, pp. 987–994, 2013.

[43] M. Choi, M. Humar, S. Kim, and S.-H. Yun, "Step-Index Optical Fiber Made of Biocompatible Hydrogels," *Adv. Mater.*, vol. 27, no. 27 pp. 4081–4086, 2015.

[44] D. S. Wiersma, "Disordered photonics," *Nat. Photonics*, vol. 7, no. 3, pp. 188–196, 2013.

[45] D. S. Wiersma, "The physics and applications of random lasers," *Nat. Phys.*, vol. 4, no. 5, pp. 359–367, 2008.

[46] R. C. Polson and Z. V. Vardeny, "Random lasing in human tissues," *Appl. Phys. Lett.*, vol. 85, no. 7, pp. 1289–1291, 2004.

[47] M. Humar and S. H. Yun, "Intracellular microlasers," *Nat. Photonics*, vol. 9, pp. 572–576, 2015.

[48] M. C. Gather and S. H. Yun, "Single-cell biological lasers," *Nat. Photonics*, vol. 5, no. 7, pp. 406–410, 2011.

[49] A. Jonas and A. Kiraz, "In vitro and in vivo biolasing of fluorescent proteins suspended in liquid microdroplet cavities," *Lab Chip*, vol. 14, pp. 3093–3100, 2014.

[50] M. C. Gather and S. H. Yun, "Lasing from Escherichia coli bacteria genetically programmed to express green fluorescent protein," *Opt. Lett.*, vol. 36, no. 16, pp. 3299–3301, 2011.

[51] E. A. Sykes, A. Albanese, and W. C. W. Chan, "Biophotonics: Implantable waveguides," *Nat. Photonics*, vol. 7, no. 12, pp. 940–941, 2013.

[52] B. D. Ratner and S. J. Bryant, "Biomaterials: where we have been and where we are going.," *Annu. Rev. Biomed. Eng.*, vol. 6, pp. 41–75, 2004.

[53] E. Fournier, C. Passirani, C. N. Montero-Menei, and J. P. Benoit, "Biocompatibility of implantable synthetic polymeric drug carriers: Focus on brain biocompatibility," *Biomaterials*, vol. 24, no. 19. pp. 3311–3331, 2003.

[54] B. D. Ratner, "Healing with medical implants: The body battles back," *Sci Transl Med.*, vol. 7, no. 272, pp. 272fs4.

[55] N. Oliva, M. Carcole, M. Beckerman, S. Seliktar, A. Hayward, J. Stanley, N. Maria, A. Parry, E. R. Edelman, and N. Artzi, "Regulation of dendrimer / dextran material performance by altered tissue microenvironment in inflammation and neoplasia," *Sci. Transl. Med.*, vol. 7, no. 272, 2015.

[56] O. Veiseh, J. C. Doloff, M. Ma, A. J. Vegas, H. H. Tam, A. R. Bader, J. Li, E. Langan, J. Wyckoff, W. S. Loo, S. Jhunjhunwala, A. Chiu, S. Siebert, K. Tang, J. Hollister-Lock, S. Aresta-Dasilva, M. Bochenek, J. Mendoza-Elias, Y. Wang, M. Qi, D. M. Lavin, M. Chen, N. Dholakia, R. Thakrar, I. Lacík, G. C. Weir, J. Oberholzer, D. L. Greiner, R. Langer, and D. G. Anderson, "Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates," *Nat. Mater.*, vol. 14, no. 6, pp. 643–651, 2015.

[57] A. Elsaesser and C. V. Howard, "Toxicology of nanoparticles," *Adv. Drug Deliv. Rev.*, vol. 64, no. 2, pp. 129–137, 2012.

[58] B. Wang, X. He, Z. Zhang, Y. Zhao, and W. Feng, "Metabolism of nanomaterials in vivo: Blood circulation and organ clearance," *Acc. Chem. Res.*, vol. 46, no. 3, pp. 761–769, 2013.

[59] A. Pietroiusti, "Health implications of engineered nanomaterials," *Nanoscale*, vol. 4, no. 4, p. 1231, 2012.

[60] K. Donaldson and C. A. Poland, "Nanotoxicity: Challenging the myth of nano-specific toxicity," *Curr. Opin. Biotechnol.*, vol. 24, no. 4, pp. 724–734, 2013.

[61] A. Nel, T. Xia, L. Mädler, and N. Li, "Toxic potential of materials at the nanolevel.," *Science*, vol. 311, no. 5761, pp. 622–627, 2006.

[62] R. Farra, N. F. Sheppard, L. McCabe, R. M. Neer, J. M. Anderson, J. T. Santini, M. J. Cima, and R. Langer, "First-in-Human Testing of a Wirelessly Controlled Drug Delivery Microchip," *Sci. Transl. Med.*, vol. 4, no. 122, pp. 122ra21, 2012.

[63] D. W. Grainger, "All charged up about implanted biomaterials," *Nat Biotechnol*, vol. 31, no. 6, pp. 507–509, 2013.

[64] P. Wu and D. W. Grainger, "Drug/device combinations for local drug therapies and infection prophylaxis," *Biomaterials*, vol. 27, no. 11, pp. 2450–2467, 2006.

[65] W. K. Ward, M. D. Wood, H. M. Casey, M. J. Quinn, and I. F. Federiuk, "The effect of local subcutaneous delivery of vascular endothelial growth factor on the function of a chronically

implanted amperometric glucose sensor.," *Diabetes Technol. Ther.*, vol. 6, no. 2, pp. 137–145, 2004.

[66] M. Frost and M. E. Meyerhoff, "In vivo chemical sensors: Tackling biocompatibility," *Anal. Chem.*, vol. 78, no. 21, pp. 7370–7377, 2006.

[67] E. M. Sussman, M. C. Halpin, J. Muster, R. T. Moon, and B. D. Ratner, "Porous implants modulate healing and induce shifts in local macrophage polarization in the foreign body reaction," *Ann. Biomed. Eng.*, vol. 42, no. 7, pp. 1508–1516, 2014.

[68] S. Lowe, N. M. O'Brien-Simpson, and L. A. Connal, "Antibiofouling polymer interfaces: poly(ethylene glycol) and other promising candidates," *Polym. Chem.*, vol. 6, no. 2, pp. 198–212, 2015.

[69] L. Zhang, Z. Cao, T. Bai, L. Carr, J.-R. Ella-Menye, C. Irvin, B. D. Ratner, and S. Jiang, "Zwitterionic hydrogels implanted in mice resist the foreign-body reaction.," *Nat. Biotechnol.*, vol. 31, no. 6, pp. 553–6, 2013.

[70] S. Jiang and Z. Cao, "Ultralow-fouling, functionalizable, and hydrolyzable zwitterionic materials and their derivatives for biological applications," *Adv. Mater.*, vol. 22, no. 9, pp. 920–932, 2010.

[71] D. R. Merrill, "Materials considerations of implantable neuroengineering devices for clinical use," *Curr. Opin. Solid State Mater. Sci.*, vol. 18, no. 6, pp. 329–336, 2014.

[72] Y.-H. Joung, "Development of Implantable Medical Devices: From an Engineering Perspective.," *Int. Neurourol. J.*, vol. 17, no. 3, pp. 98–106, 2013.

[73] B. Kundu, N. E. Kurland, S. Bano, C. Patra, F. B. Engel, V. K. Yadavalli, and S. C. Kundu, "Silk proteins for biomedical applications: Bioengineering perspectives," *Prog. Polym. Sci.*, vol. 39, no. 2, pp. 251–267, 2014.

[74] J. S. Ho, A. J. Yeh, E. Neofytou, S. Kim, Y. Tanabe, B. Patlolla, R. E. Beygui, and A. S. Y. Poon, "Wireless power transfer to deep-tissue microimplants," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 111, no. 22, p. 201403002, 2014.

[75] "IEEE Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3 kHz to 300 GHz," New York, 2005.

[76] H. Mei and P. P. Irazoqui, "Miniaturizing wireless implants," *Nat. Biotechnol.*, vol. 32, no. 10, pp. 1008–1010, 2014.

[77] P. N. Youssef, N. Sheibani, and D. M. Albert, "Retinal light toxicity.," *Eye (Lond).*, vol. 25, no. 1, pp. 1–14, 2011.

[78] X. Kong, S. K. Mohanty, J. Stephens, J. T. Heale, V. Gomez-Godinez, L. Z. Shi, J.-S. Kim, K. Yokomori, and M. W. Berns, "Comparative analysis of different laser systems to study cellular responses to DNA damage in mammalian cells.," *Nucleic Acids Res.*, vol. 37, no. 9, p. e68, May 2009.

[79] R. Matthes, C. P. Cain, D. Courant, D. A. Freund, B. A. Grossman, P. A. Kennedy, D. J. Lund, M. A. Mainster, A. A. Manenkov, and W. J. Marshall, "Revision of guidelines on limits of exposure to laser radiation of wavelengths between 400 nm and 1.4 mu m," *Health Phys.*, vol. 79, no. 4, pp. 431–440, 2000.

[80] S. Lenhert, F. Brinkmann, T. Laue, S. Walheim, C. Vannahme, S. Klinkhammer, M. Xu, S. Sekula, T. Mappes, T. Schimmel, and H. Fuchs, "Lipid multilayer gratings," *Nat. Nanotechnol.*, vol. 5, no. 4, pp. 275–279, 2010.

[81] J. J. Amsden, P. Domachuk, A. Gopinath, R. D. White, L. D. Negro, D. L. Kaplan, and F. G. Omenetto, "Rapid nanoimprinting of silk fibroin films for biophotonic applications," *Adv. Mater.*, vol. 22, no. 15, pp. 1746–1749, 2010.

[82] H. Perry, A. Gopinath, D. L. Kaplan, L. D. Negro, and F. G. Omenetto, "Nano-and micropatterning of optically transparent, mechanically robust, biocompatible silk fibroin films," *Adv. Mater*, vol. 20, no. 16, pp. 3070–3072, 2008.

[83] J. J. Amsden, H. Perry, S. V Boriskina, A. Gopinath, D. L. Kaplan, L. Dal Negro, and F. G. Omenetto, "Spectral analysis of induced color change on periodically nanopatterned silk films," *Opt. Express*, vol. 17, no. 23, pp. 21271–21279, 2009.

[84] P. Domachuk, H. Perry, J. J. Amsden, D. L. Kaplan, and F. G. Omenetto, "Bioactive 'self-sensing' optical systems," *Appl. Phys. Lett.*, vol. 95, no. 25, p. 253702, 2009.

[85] N. E. Kurland, T. Dey, S. C. Kundu, and V. K. Yadavalli, "Precise patterning of silk microstructures using photolithography," *Adv. Mater.*, vol. 25, no. 43, pp. 6207–6212, 2013.

[86] R. K. Pal, N. E. Kurland, C. Wang, S. C. Kundu, and V. K. Yadavalli, "Biopatterning of silk proteins for soft micro-optics," *ACS Appl. Mater. Interfaces*, vol. 7, no. 16, pp. 8809–8816, 2015.

[87] Y.L. Sun, W.F. Dong, L.G. Niu, T. Jiang, D.X. Liu, L. Zhang, Y.S. Wang, Q.D. Chen, D.P. Kim, and H.B. Sun, "Protein-based soft micro-optics fabricated by femtosecond laser direct writing," *Light Sci. Appl.*, vol. 3, no. 1, p. e129, 2014.

[88] Y.L. Sun, D.X. Liu, W.F. Dong, Q.D. Chen, and H.B. Sun, "Tunable protein harmonic diffractive micro-optical elements," *Opt. Lett.*, vol. 37, no. 14, pp. 2973–2975, 2012.

[89] Y. Zhao, X. Zhao, and Z. Gu, "Photonic crystals in bioassays," *Adv. Funct. Mater.*, vol. 20, no. 18, pp. 2970–2988, 2010.

[90] R. J. Carlson and S. A. Asher, "Characterization of optical diffraction and crystal structure in monodisperse polystyrene colloids," *Appl. Spectrosc.*, vol. 38, no. 3, pp. 297–304, 1984.

[91] P. A. Rundquist, P. Photinos, S. Jagannathan, and S. A. Asher, "Dynamical Bragg diffraction from crystalline colloidal arrays," *J. Chem. Phys.*, vol. 91, no. 8, pp. 4932–4941, 1989.

[92] A. J. Marshall, J. Blyth, C. A. B. Davidson, and C. R. Lowe, "pH-sensitive holographic sensors," *Anal. Chem.*, vol. 75, no. 17, pp. 4423–4431, 2003.

[93] A. K. Yetisen, Y. Montelongo, N. M. Farandos, I. Naydenova, C. R. Lowe, and S. H. Yun, "Mechanism of multiple grating formation in high-energy recording of holographic sensors," *Appl. Phys. Lett.*, vol. 105, no. 26, p. 261106, 2014.

[94] I. Naydenova, R. Jallapuram, V. Toal, and S. Martin, "A visual indication of environmental humidity using a color changing hologram recorded in a self-developing photopolymer," *Appl. Phys. Lett.*, vol. 92, no. 3, p. 31109, 2008.

[95] A. K. Yetisen, I. Naydenova, F. da Cruz Vasconcellos, J. Blyth, and C. R. Lowe, "Holographic sensors: three-dimensional analyte-sensitive nanostructures and their applications," *Chem. Rev.*, vol. 114, no. 20, pp. 10654–10696, 2014.

[96] S. A. Asher, S. F. Peteu, C. E. Reese, M. Lin, and D. Finegold, "Polymerized crystalline colloidal array chemical-sensing materials for detection of lead in body fluids," *Anal. Bioanal. Chem.*, vol. 373, no. 7, pp. 632–638, 2002.

[97] A. K. Yetisen, Y. Montelongo, M. M. Qasim, H. Butt, T. D. Wilkinson, M. J. Monteiro, and S. H. Yun, "Photonic nanosensor for colorimetric detection of metal ions," *Anal. Chem.*, vol. 87, no. 10, pp. 5101–5108, 2015.

[98] F. Zeng, S. Wu, Z. Sun, H. Xi, R. Li, and Z. Hou, "Urea sensing materials via solidified crystalline colloidal arrays," *Sensors Actuators B Chem.*, vol. 81, no. 2, pp. 273–276, 2002.

[99] C. Zhang, M. D. Losego, and P. V Braun, "Hydrogel-based glucose sensors: effects of phenylboronic acid chemical structure on response," *Chem. Mater.*, vol. 25, no. 15, pp. 3239–3250, 2013.

[100] A. C. Sharma, T. Jana, R. Kesavamoorthy, L. Shi, M. A. Virji, D. N. Finegold, and S. A. Asher, "A general photonic crystal sensing motif: creatinine in bodily fluids," *J. Am. Chem. Soc.*, vol. 126, no. 9, pp. 2971–2977, 2004.

[101] K. W. Kimble, J. P. Walker, D. N. Finegold, and S. A. Asher, "Progress toward the development of a point-of-care photonic crystal ammonia sensor," *Anal. Bioanal. Chem.*, vol. 385, no. 4, pp. 678–685, 2006.

[102] A. K. Yetisen, H. Butt, F. da Cruz Vasconcellos, Y. Montelongo, C. A. B. Davidson, J. Blyth, L. Chan, J. B. Carmody, S. Vignolini, and U. Steiner, "Light-Directed Writing of Chemically Tunable Narrow-Band Holographic Sensors," *Adv. Opt. Mater.*, vol. 2, no. 3, pp. 250–254, 2014.

[103] A. K. Yetisen, "Fundamentals of Holographic Sensing," in *Holographic Sensors*, Springer International Publishing, 2015, pp. 27–51.

[104] S. Kabilan, A. J. Marshall, F. K. Sartain, M.-C. Lee, A. Hussain, X. Yang, J. Blyth, N. Karangu, K. James, and J. Zeng, "Holographic glucose sensors," *Biosens. Bioelectron.*, vol. 20, no. 8, pp. 1602–1610, 2005.

[105] V. L. Alexeev, S. Das, D. N. Finegold, and S. A. Asher, "Photonic crystal glucose-sensing material for noninvasive monitoring of glucose in tear fluid," *Clin. Chem.*, vol. 50, no. 12, pp. 2353–2360, 2004.

[106] A. Domschke, S. Kabilan, R. Anand, M. Caines, D. Fetter, P. Griffith, K. James, N. Karangu, D. Smith, and M. Vargas, "Holographic sensors in contact lenses for minimally-invasive glucose measurements," in *Sensors, 2004. Proceedings of IEEE*, 2004, pp. 1320–1323.

[107] E. Vezouviou and C. R. Lowe, "A near infrared holographic glucose sensor," *Biosens. Bioelectron.*, vol. 68, pp. 371–381, 2015.

[108] N. M. Farandos, A. K. Yetisen, M. J. Monteiro, C. R. Lowe, and S. H. Yun, "Contact lens sensors in ocular diagnostics," *Adv. Heal. Mater.*, vol. 4, no. 6, pp. 792–810, 2015.

[109] S. Kim, A. N. Mitropoulos, J. D. Spitzberg, H. Tao, D. L. Kaplan, and F. G. Omenetto, "Silk inverse opals," *Nat. Photonics*, vol. 6, no. 12, pp. 818–823, 2012.

[110] S. A. Maier, *Plasmonics: fundamentals and applications*. Springer Science & Business Media, 2007.

[111] X. Huang, I. H. El-Sayed, W. Qian, and M. A. El-Sayed, "Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods," *J. Am. Chem. Soc.*, vol. 128, no. 6, pp. 2115–2120, 2006.

[112] K. Sokolov, J. Aaron, B. Hsu, D. Nida, A. Gillenwater, M. Follen, C. MacAulay, K. Adler-Storthz, B. Korgel, and M. Descour, "Optical systems for in vivo molecular imaging of cancer," *Technol. Cancer Res. Treat.*, vol. 2, no. 6, pp. 491–504, 2003.

[113] P. K. Jain, I. H. El-Sayed, and M. A. El-Sayed, "Au nanoparticles target cancer," *Nano Today*, vol. 2, no. 1, pp. 18–29, 2007.

[114] S. J. Tan, M. J. Campolongo, D. Luo, and W. Cheng, "Building plasmonic nanostructures with DNA," *Nat. Nanotechnol.*, vol. 6, no. 5, pp. 268–276, 2011.

[115] A. Kuzyk, R. Schreiber, Z. Fan, G. Pardatscher, E.-M. Roller, A. Högele, F. C. Simmel, A. O. Govorov, and T. Liedl, "DNA-based self-assembly of chiral plasmonic nanostructures with tailored optical response," *Nature*, vol. 483, no. 7389, pp. 311–314, 2012.

[116] Z. Li, Z. Zhu, W. Liu, Y. Zhou, B. Han, Y. Gao, and Z. Tang, "Reversible plasmonic circular dichroism of Au nanorod and DNA assemblies," *J. Am. Chem. Soc.*, vol. 134, no. 7, pp. 3322–3325, 2012.

[117] D. J. Park, C. Zhang, J. C. Ku, Y. Zhou, G. C. Schatz, and C. A. Mirkin, "Plasmonic photonic crystals realized through DNA-programmable assembly," *Proc. Natl. Acad. Sci.*, vol. 112, no. 4, pp. 977–981, 2015.

[118] J. I. L. Chen, Y. Chen, and D. S. Ginger, "Plasmonic nanoparticle dimers for optical sensing of DNA in complex media," *J. Am. Chem. Soc.*, vol. 132, no. 28, pp. 9600–9601, 2010.

[119] D. Lin, H. Tao, J. Trevino, J. P. Mondia, D. L. Kaplan, F. G. Omenetto, and L. Dal Negro, "Direct transfer of subwavelength plasmonic nanostructures on bioactive silk films," *Adv. Mater.*, vol. 24, no. 45, pp. 6088–6093, 2012.

[120] J. Park, Y. Choi, M. Lee, H. Jeon, and S. Kim, "Novel and simple route to fabricate fully biocompatible plasmonic mushroom arrays adhered on silk biopolymer," *Nanoscale*, vol. 7, no. 2, pp. 426–431, 2014.

[121] M. Lee, H. Jeon, and S. Kim, "A highly tunable and fully biocompatible silk nanoplasmonic optical sensor," *Nano Lett.*, vol. 15, no. 5, pp. 3358–3363, 2015.

[122] G. Lanzani, "Materials for bioelectronics: Organic electronics meets biology.," *Nat. Mater.*, vol. 13, no. 8, pp. 775–776, 2014.

[123] N. Martino, D. Ghezzi, F. Benfenati, G. Lanzani, and M. R. Antognazza, "Organic semiconductors for artificial vision," *J. Mater. Chem. B*, vol. 1, pp. 3768–3780, 2013.

[124] R. M. Owens and G. G. Malliaras, "Organic Electronics at the Interface with Biology," *MRS Bull.*, vol. 35, no. 06, pp. 449–456, 2010.

[125] D. Ghezzi, M. R. Antognazza, R. Maccarone, S. Bellani, E. Lanzarini, N. Martino, M. Mete, G. Pertile, S. Bisti, G. Lanzani, and F. Benfenati, "A polymer optoelectronic interface restores light sensitivity in blind rat retinas," *Nat. Photonics*, vol. 7, no. 5, pp. 400–406, 2013.

[126] V. Gautam, D. Rand, Y. Hanein, and K. S. Narayan, "A polymer optoelectronic interface provides visual cues to a blind retina," *Adv. Mater.*, vol. 26, no. 11, pp. 1751–1756, 2014.

[127] D. Ghezzi, M. R. Antognazza, M. Dal Maschio, E. Lanzarini, F. Benfenati, and G. Lanzani, "A hybrid bioorganic interface for neuronal photoactivation.," *Nat. Commun.*, vol. 2, no. 1, p. 166, 2011.

[128] A. N. Zorzos, J. Scholvin, E. S. Boyden, and C. G. Fonstad, "Three-dimensional multiwaveguide probe array for light delivery to distributed brain circuits.," *Opt. Lett.*, vol. 37, no. 23, pp. 4841–3, 2012.

[129] A. N. Zorzos, E. S. Boyden, and C. G. Fonstad, "Multiwaveguide implantable probe for light delivery to sets of distributed brain targets.," *Opt. Lett.*, vol. 35, no. 24, pp. 4133–4135, 2010.

[130] F. Pisanello, L. Sileo, I. A. Oldenburg, M. Pisanello, L. Martiradonna, J. A. Assad, B. L. Sabatini, and M. De Vittorio, "Multipoint-emitting optical fibers for spatially addressable in vivo optogenetics," *Neuron*, vol. 82, no. 6, pp. 1245–1254, 2014.

[131] L. Klouda and A. G. Mikos, "Thermoresponsive hydrogels in biomedical applications," *Eur. J. Pharm. Biopharm.*, vol. 68, no. 1, pp. 34–45, 2008.

[132] A. Dupuis, N. Guo, Y. Gao, N. Godbout, S. Lacroix, C. Dubois, and M. Skorobogatiy, "Prospective for biodegradable microstructured optical fibers," *Opt. Lett.*, vol. 32, no. 2, pp. 109–111, 2007.

[133] N. Huby, V. Vié, A. Renault, S. Beaufils, T. Lefevre, F. Paquet-Mercier, M. Pézolet, B. Bęche, T. Lefčvre, F. Paquet-Mercier, M. Pézolet, and B. Bęche, "Native spider silk as a biological optical fiber," *Appl. Phys. Lett.*, vol. 102, no. 12, p. 123702, 2013.

[134] X. Yan, Y. Su, J. Li, J. Früh, and H. Möhwald, "Uniaxially oriented peptide crystals for active optical waveguiding," *Angew. Chemie Int. Ed.*, vol. 50, no. 47, pp. 11186–11191, 2011.

[135] H. Xin, Y. Li, X. Liu, and B. Li, "Escherichia coli-Based Biophotonic Waveguides.," *Nano Lett.*, 2013.

[136] S. Nizamoglu, M. C. Gather, M. Humar, M. Choi, S. Kim, K. S. Kim, S. K. Hahn, G. Scarcelli, M. Randolph, R. W. Redmond, and S. H. Yun, "Bioabsorbable Polymer Optical Waveguides For Deep-Tissue Photomedicine," *Nat. Commun.*, vol. 7, pp. 10374, 2016.

[137] A. Jain, A. H. J. J. Yang, and D. Erickson, "Gel-based optical waveguides with live cell encapsulation and integrated microfluidics," *Opt. Lett.*, vol. 37, no. 9, pp. 1472–1474, 2012.

[138] A. K. Manocchi, P. Domachuk, F. G. Omenetto, and H. Yi, "Facile fabrication of gelatin-based biopolymeric optical waveguides," *Biotechnol. Bioeng.*, vol. 103, no. 4, pp. 725–732, 2009.

[139] H. Ye, M. Daoud-El Baba, R.-W. Peng, and M. Fussenegger, "A synthetic optogenetic transcription device enhances blood-glucose homeostasis in mice.," *Science*, vol. 332, no. 6037, pp. 1565–1568, 2011.

[140] N. C. Shaner, R. E. Campbell, P. A. Steinbach, B. N. G. Giepmans, A. E. Palmer, and R. Y. Tsien, "Improved monomeric red, orange and yellow fluorescent proteins derived from Discosoma sp. red fluorescent protein," *Nat. Biotechnol.*, vol. 22, no. 12, pp. 1567–1572, 2004.

[141] H. J. Oh, M. C. Gather, J. J. Song, and S. H. Yun, "Lasing from fluorescent protein crystals," *Opt. Express*, vol. 22, no. 25, pp. 31411–31416, 2014.

[142] M. C. Gather and S. H. Yun, "Bio-optimized energy transfer in densely packed fluorescent protein enables near-maximal luminescence and solid-state lasers," *Nat. Commun.*, vol. 5, p. 5722, 2014.

[143] T. M. Drane, H. Bach, M. Shapiro, and V. Milner, "Femtosecond pumped lasing from the fluorescent protein DsRed in a one dimensional random cavity," in *SPIE LASE*, 2013, vol. 8611, no. 1997, p. 86110G–86110G–6.

[144] W. Holzer, J. Shirdel, P. Zirak, A. Penzkofer, P. Hegemann, R. Deutzmann, and E. Hochmuth, "Photo-induced degradation of some flavins in aqueous solution," *Chem. Phys.*, vol. 308, no. 1, pp. 69–78, 2005.

[145] S. Nizamoglu, M. C. Gather, and S. H. Yun, "All-biomaterial laser using vitamin and biopolymers," *Adv. Mater.*, vol. 25, no. 41, pp. 5943–5947, 2013.

[146] C. Vannahme, F. Maier-Flaig, U. Lemmer, and A. Kristensen, "Single-mode biological distributed feedback laser," *Lab Chip*, vol. 13, no. 14, pp. 2675–2678, 2013.

[147] Y. Choi, H. Jeon, and S. Kim, "A fully biocompatible single-mode distributed feedback laser," *Lab Chip*, vol. 14, pp. 642-645. 2015.

[148] Y. Kawabe, L. Wang, S. Horinouchi, and N. Ogata, "Amplified Spontaneous Emission from Fluorescent-Dye-Doped DNA–Surfactant Complex Films," *Adv. Mater.*, vol. 12, no. 17, pp. 1281–1283, 2000.

[149] L. Sznitko, A. Szukalski, K. Cyprych, P. Karpinski, A. Miniewicz, and J. Mysliwiec, "Surface roughness induced random lasing in bio-polymeric dye doped film," *Chem. Phys. Lett.*, vol. 576, pp. 31–34, 2013.

[150] L. Sznitko, J. Mysliwiec, P. Karpinski, K. Palewska, K. Parafiniuk, S. Bartkiewicz, I. Rau, F. Kajzar, and A. Miniewicz, "Biopolymer based system doped with nonlinear optical dye as a medium for amplified spontaneous emission and lasing," *Appl. Phys. Lett.*, vol. 99, no. 3, p. 31107, 2011.

[151] A. Camposeo, P. Del Carro, L. Persano, K. Cyprych, A. Szukalski, L. Sznitko, J. Mysliwiec, and D. Pisignano, "Physically Transient Photonics: Random versus Distributed Feedback Lasing Based on Nanoimprinted DNA," *ACS Nano*, vol. 8, no. 10, pp. 10893–10898, 2014.

[152] Y. Sun, S. I. Shopova, C.-S. Wu, S. Arnold, and X. Fan, "Bioinspired optofluidic FRET lasers via DNA scaffolds," *Proc. Natl. Acad. Sci.*, vol. 107, no. 37, pp. 16039–16042, 2010.

[153] X. Zhang, W. Lee, and X. Fan, "Bio-switchable optofluidic lasers based on DNA Holliday junctions," *Lab Chip*, vol. 12, no. 19, pp. 3673–3675, 2012.

[154] J. C. Briones-Herrera, N. Cuando-Espitia, F. M. Sánchez-Arévalo, and J. Hernández-Cordero, "Evaluation of mechanical behavior of soft tissue by means of random laser emission," *Rev. Sci. Instrum.*, vol. 84, no. 10, p. 104301, 2013.

[155] Q. Song, S. Xiao, Z. Xu, J. Liu, X. Sun, V. Drachev, V. M. Shalaev, O. Akkus, and Y. L. Kim, "Random lasing in bone tissue," *Opt. Lett.*, vol. 35, no. 9, pp. 1425–1427, 2010.

[156] Q. Song, Z. Xu, S. H. Choi, X. Sun, S. Xiao, O. Akkus, and Y. L. Kim, "Detection of nanoscale structural changes in bone using random lasers," vol. 1, no. 5, pp. 1401–1407, 2010.

[157] F. Lahoz, I. R. Martín, M. Urgellés, J. Marrero-Alonso, R. Marín, C. J. Saavedra, a Boto, and M. Díaz, "Random laser in biological tissues impregnated with a fluorescent anticancer drug," *Laser Phys. Lett.*, vol. 12, no. 4, p. 45805, 2015.

[158] R. C. Polson and Z. V Vardeny, "Cancerous tissue mapping from random lasing emission spectra," *J. Opt.*, vol. 12, no. 2, p. 24010, 2010.

[159] S. Nizamoglu, K. Lee, M. C. Gather, K. S. Kim, M. Jeon, S. Kim, M. Humar, and S. H. Yun, "A simple approach to biological single-cell lasers via intracellular dyes," *Adv. Opt. Mater.*, vol. 3, no. 9, pp. 1197–1200, 2015.

[160] K. J. Vahala, "Optical microcavities," *Nature*, vol. 424, no. 6950, pp. 839–846, 2003.

[161] A. Jonas, A. Kiraz, A. Jonáš, M. Aas, Y. Karadag, S. Manioğlu, S. Anand, D. McGloin, H. Bayraktar, and A. Kiraz, "In vitro and in vivo biolasing of fluorescent proteins suspended in liquid

microdroplet cavities," *Lab Chip*, vol. 14, pp. 3093–3100, 2014.

[162] M. Humar and S. H. Yun, "Microlasers Inside Live Cells," in *CLEO: QELS_Fundamental Science*, 2015, p. JTh5A. 2.

[163] M. Schubert, A. Steude, P. Liehm, N. M. Kronenberg, M. Karl, E. C. Campbell, S. J. Powis, and M. Gather, "Lasing within live cells containing intracellular optical micro-resonators for barcode-type cell tagging and tracking," *Nano Lett.*, vol. 15, no. 8, pp. 5647–5652, 2015.

[164] G. Jiang and D. D. Zhou, "Technology advances and challenges in hermetic packaging for implantable medical devices," in *Implantable Neural Prostheses 2*, Springer, 2010, pp. 27–61.

[165] S. Il Park, D. S. Brenner, G. Shin, C. D. Morgan, B. A. Copits, H. U. Chung, M. Y. Pullen, K. N. Noh, S. Davidson, S. J. Oh, J. Yoon, K.-I. Jang, V. K. Samineni, M. Norman, J. G. Grajales-Reyes, S. K. Vogt, S. S. Sundaram, K. M. Wilson, J. S. Ha, R. Xu, T. Pan, T. Kim, Y. Huang, M. C. Montana, J. P. Golden, M. R. Bruchas, R. W. Gereau, and J. A. Rogers, "Soft, stretchable, fully implantable miniaturized optoelectronic systems for wireless optogenetics," *Nat. Biotechnol.*, vol. 33, pp. 1280–1286, 2015.

[166] G. Iddan, G. Meron, A. Glukhovsky, and P. Swain, "Wireless capsule endoscopy," *Nature*, vol. 405, no. 6785, p. 417, May 2000.

[167] S. K. Bisland, L. Lilge, A. Lin, R. Rusnov, and B. C. Wilson, "Metronomic photodynamic therapy as a new paradigm for photodynamic therapy: rationale and preclinical evaluation of technical feasibility for treating malignant brain tumors.," *Photochem. Photobiol.*, vol. 80, pp. 22–30, 2004.

[168] A. F. Bagley, S. Hill, G. S. Rogers, and S. N. Bhatia, "Plasmonic photothermal heating of intraperitoneal tumors through the use of an implanted near-infrared source," *ACS Nano*, vol. 7, no. 9, pp. 8089–8097, 2013.

[169] T.-I. T. Kim, J. G. McCall, Y. H. Jung, X. Huang, E. R. Siuda, Y. Li, J. Song, Y. M. Song, H. A. Pao, R.-H. R.-H. Kim, C. Lu, S. D. Lee, I.-S. Song, G. Shin, R. Al-Hasani, S. Kim, M. P. Tan, Y. Huang, F. G. Omenetto, J.A Rogers, and M.R. Bruchas, "Injectable, Cellular-Scale Optoelectronics with Application sfor Wireless Optogenetics," *Science*, vol. 340, no. 6129, pp.211-216, 2013.

[170] S. Y. Lee, K. Il Park, C. Huh, M. Koo, H. G. Yoo, S. Kim, C. S. Ah, G. Y. Sung, and K. J. Lee, "Water-resistant flexible GaN LED on a liquid crystal polymer substrate for implantable biomedical applications," *Nano Energy*, vol. 1, no. 1, pp. 145–151, 2012.

[171] D. Huber, L. Petreanu, N. Ghitani, S. Ranade, T. Hromádka, Z. Mainen, and K. Svoboda, "Sparse optical microstimulation in barrel cortex drives learned behaviour in freely moving mice," *Nature*, vol. 451, no. 7174, pp. 61–64, 2008.

[172] M. Hashimoto, A. Hata, T. Miyata, and H. Hirase, "Programmable wireless light-emitting diode stimulator for chronic stimulation of optogenetic molecules in freely moving mice," *Neurophotonics*, vol. 1, no. 1, p. 11002, 2014.

[173] J. G. McCall, T. Kim, G. Shin, X. Huang, Y. H. Jung, R. Al-Hasani, F. G. Omenetto, M. R. Bruchas, and J. A. Rogers, "Fabrication and application of flexible, multimodal light-emitting devices for wireless optogenetics," *Nat. Protoc.*, vol. 8, no. 12, pp. 2413–2428, 2013.

[174] R. Ameli, A. Mirbozorgi, J. L. Neron, Y. LeChasseur, and B. Gosselin, "A wireless and batteryless neural headstage with optical stimulation and electrophysiological recording," in *Engineering in Medicine and Biology Society (EMBC), 2013 35th Annual International Conference of the IEEE*, 2013, pp. 5662–5665.

[175] C. T. Wentz, J. G. Bernstein, P. Monahan, A. Guerra, A. Rodriguez, and E. S. Boyden, "A wirelessly powered and controlled device for optical neural control of freely-behaving animals.," *J. Neural Eng.*, vol. 8, no. 4, p. 046021, 2011.

[176] K. L. Montgomery, A. J. Yeh, J. S. Ho, V. Tsao, S. Mohan Iyer, L. Grosenick, E. a Ferenczi, Y. Tanabe, K. Deisseroth, S. L. Delp, and A. S. Y. Poon, "Wirelessly powered, fully internal optogenetics for brain, spinal and peripheral circuits in mice," *Nat. Methods*, vol. 12, pp. 969–974, 2015.

[177] T. Someya, "Flexible electronics: tiny lamps to illuminate the body.," *Nat. Mater.*, vol. 9, no. 11, pp. 879–880, 2010.

[178] J. Liang, L. Li, X. Niu, Z. Yu, and Q. Pei, "Elastomeric polymer light-emitting devices and displays," *Nat. Photonics*, vol. 7, no. 10, pp. 817–824, 2013.

[179] M. Irimia-Vladu, E. D. Głowacki, G. Voss, S. Bauer, and N. S. Sariciftci, "Green and biodegradable electronics," *Mater. Today*, vol. 15, no. 7–8, pp. 340–346, 2012.

[180] A. P. Ghosh, L. J. Gerenser, C. M. Jarman, and J. E. Fornalik, "Thin-film encapsulation of organic light-emitting devices," *Appl. Phys. Lett.*, vol. 86, no. 22, p. 223503, 2005.

[181] J. T. Smith, B. O'Brien, Y.-K. Lee, E. J. Bawolek, and J. B. Christen, "Application of flexible oled display technology for electro-optical stimulation and/or silencing of neural activity," *Disp. Technol. J.*, vol. 10, no. 6, pp. 514–520, 2014.

[182] H.W. Guo, L.T. Lin, P.H. Chen, M.H. Ho, W.T. Haung, Y.J. Lee, S.H. Chiou, Y.S. Hsieh, C.Y. Dong, and H.W. Wang, "Low-fluence rate, long duration photodynamic therapy in glioma mouse model using organic light emitting diode (OLED)," *Photodiagnosis Photodyn. Ther.*, vol. 12, no. 3, pp. 504–510, 2015.

[183] S. K. Attili, A. Lesar, A. McNeill, M. Camacho-Lopez, H. Moseley, S. Ibbotson, I. D. W. Samuel, and J. Ferguson, "An open pilot study of ambulatory photodynamic therapy using a wearable low-irradiance organic light-emitting diode light source in the treatment of nonmelanoma skin cancer," *Br. J. Dermatol.*, vol. 161, no. 1, pp. 170–173, 2009.

[184] A. K. Bansal, S. Hou, O. Kulyk, E. M. Bowman, and I. D. W. Samuel, "Wearable Organic Optoelectronic Sensors for Medicine," *Adv. Mater.*, pp. 1–7, 2014.

[185] J. A. Hagen, W. Li, A. J. Steckl, and J. G. Grote, "Enhanced emission efficiency in organic light-emitting diodes using deoxyribonucleic acid complex as an electron blocking layer," *Appl. Phys. Lett.*, vol. 88, no. 17, pp. 2004–2007, 2006.

[186] Q. Sun, D. W. Chang, L. Dai, J. Grote, and R. Naik, "Multilayer white polymer light-emitting diodes with deoxyribonucleic acid-cetyltrimetylammonium complex as a hole-transporting/electron-blocking layer," *Appl. Phys. Lett.*, vol. 92, no. 25, p. 251108, 2008.

[187] Q. Sun, G. Subramanyam, L. Dai, M. Check, A. Campbell, R. Naik, J. Grote, and Y. Wang, "Highly Efficient Quantum-Dot Light-Emitting Diodes with DNA-CMTA as a Combined Hole-Transporting and Electron-Blocking Layer," vol. 3, no. 3, pp. 737–743, 2009.

[188] M. J. Cho, U. R. Lee, Y. S. Kim, J. Shin, Y. M. Kim, Y. W. Park, B. Ju, J. Jin, and D. H. Choi, "Organic soluble deoxyribonucleic acid (DNA) bearing carbazole moieties and its blend

with phosphorescent Ir (III) complexes," *J. Polym. Sci. Part A Polym. Chem.*, vol. 48, no. 9, pp. 1913–1918, 2010.

[189] E. F. Gomez, V. Venkatraman, J. G. Grote, and A. J. Steckl, "DNA Bases Thymine and Adenine in Bio-Organic Light Emitting Diodes," *Sci. Rep.*, vol. 4, p. 7105, 2014.

[190] E. F. Gomez, V. Venkatraman, J. G. Grote, and A. J. Steckl, "Exploring the Potential of Nucleic Acid Bases in Organic Light Emitting Diodes," *Adv. Mater.*, vol. 27, pp. 7680, 2015.

[191] R. Capelli, J. J. Amsden, G. Generali, S. Toffanin, V. Benfenati, M. Muccini, D. L. Kaplan, F. G. Omenetto, and R. Zamboni, "Integration of silk protein in organic and light-emitting transistors," *Org. Electron.*, vol. 12, no.7

[192] C. Legnani, C. Vilani, V. L. Calil, H. S. Barud, W. G. Quirino, C. A. Achete, S. J. L. Ribeiro, and M. Cremona, "Bacterial cellulose membrane as flexible substrate for organic light emitting devices," *Thin Solid Films*, vol. 517, no. 3, pp. 1016–1020, 2008.

[193] D. Tobjörk and R. Österbacka, "Paper electronics," *Adv. Mater.*, vol. 23, no. 17, pp. 1935–1961, 2011.

[194] M. Muskovich and C. J. Bettinger, "Biomaterials-Based electronics: Polymers and interfaces for biology and medicine," *Adv. Healthc. Mater.*, vol. 1, no. 3, pp. 248–266, 2012.

[195] P. Meredith, C. J. Bettinger, M. Irimia-Vladu, A. B. Mostert, and P. E. Schwenn, "Electronic and optoelectronic materials and devices inspired by nature," *Reports Prog. Phys.*, vol. 76, no. 3, p. 34501, 2013.

[196] C. J. Bettinger and Z. Bao, "Organic Thin-Film Transistors Fabricated on Resorbable Biomaterial Substrates," *Adv. Mater.*, vol. 22, no. 5, pp. 651–655, 2010.

[197] M. Irimia-Vladu, P. A. Troshin, M. Reisinger, L. Shmygleva, Y. Kanbur, G. Schwabegger, M. Bodea, R. Schwödiauer, A. Mumyatov, and J. W. Fergus, "Biocompatible and Biodegradable Materials for Organic Field-Effect Transistors," *Adv. Funct. Mater.*, vol. 20, no. 23, pp. 4069–4076, 2010.

[198] C. H. Contag and M. H. Bachmann, "Advances in in vivo bioluminescence imaging of gene expression," *Annu. Rev. Biomed. Eng.*, vol. 4, no. 1, pp. 235–260, 2002.

[199] C. Dagdeviren, B. D. Yang, Y. Su, P. L. Tran, P. Joe, E. Anderson, J. Xia, V. Doraiswamy, B. Dehdashti, and X. Feng, "Conformal piezoelectric energy harvesting and storage from motions of the heart, lung, and diaphragm," *Proc. Natl. Acad. Sci.*, vol. 111, no. 5, pp. 1927–1932, 2014.

[200] O. Aquilina, "A brief history of cardiac pacing," *Images Paediatr. Cardiol.*, vol. 8, no. 2, pp. 17–81, 2006.

[201] R. Magjarevic and F. P. Bozidar, "Implantable Cardiac Pacemakers - 50 Years from the First Implantation," *Slov. Med. J.*, vol. 79, no. 01, pp. 55–67, 2010.

[202] G. Honari, S. G. Ellis, B. L. Wilkoff, M. a. Aronica, L. G. Svensson, and J. S. Taylor, "Hypersensitivity reactions associated with endovascular devices," *Contact Dermatitis*, vol. 59, no. 1, pp. 7–22, 2008.

[203] L. Gao, Y. Zhang, V. Malyarchuk, L. Jia, K.I. Jang, R. Chad Webb, H. Fu, Y. Shi, G. Zhou, L. Shi, D. Shah, X. Huang, B. Xu, C. Yu, Y. Huang, and J. A. Rogers, "Epidermal photonic devices for quantitative imaging of temperature and thermal transport characteristics of the skin," *Nat. Commun.*, vol. 5, p. 4938, 2014.

[204] T. D. Yoshida Kozai, N. B. Langhals, P. R. Patel, X. Deng, H. Zhang, K. L. Smith, J. Lahann, N. A. Kotov, and D. R. Kipke, "Ultrasmall implantable composite microelectrodes with bioactive surfaces for chronic neural interfaces," *Nat. Mater.*, vol. 11, no. 12, pp. 1065–1073, 2012.

[205] H. Takehara, A. Nagaoka, J. Noguchi, T. Akagi, H. Kasai, and T. Ichiki, "Lab-on-a-brain: Implantable micro-optical fluidic devices for neural cell analysis in vivo," *Sci. Rep.*, vol. 4, p. 6721, 2014.

[206] H. Chung, T. Dai, S. K. Sharma, Y.-Y. Huang, J. D. Carroll, and M. R. Hamblin, "The Nuts and Bolts of Low-level Laser (Light) Therapy," *Ann. Biomed. Eng.*, vol. 40, no. 2, pp. 516–533, 2012.

[207] T. Dai, A. Gupta, C. K. Murray, M. S. Vrahas, G. P. Tegos, and M. R. Hamblin, "Blue light for infectious diseases: Propionibacterium acnes, Helicobacter pylori, and beyond?," *Drug Resist. Updat.*, vol. 15, no. 4, pp. 233–236, 2012.

[208] M. T. Wan and J. Y. Lin, "Current evidence and applications of photodynamic therapy in dermatology," *Clin. Cosmet. Investig. Dermatol.*, vol. 7, pp. 145–163, 2014.