BIOPHOTONICS

Implantable waveguides

The development of hydrogel patches that both guide light and accommodate optogenetic cells could usher in a new breed of implantable systems for in-body optical sensing and therapy.

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Inside our bodies, millions of cells function in tandem to execute innumerable biological tasks. Proteins interact with nucleic acids, ions, small molecules, lipids and other proteins to mediate the functions of cells. Disruptions to these interactions by synthetic materials, genetic malfunctions or other means can cause problems in cells and give rise to abnormal biological states and disease. If we could peer into these biological processes in real time, we would be able to monitor physiological changes and disease progression, allowing us to design improved therapeutic systems to counteract undesirable effects.

Light-based techniques for whole-animal imaging offer precise, rapid and non-invasive methods of visualizing biological functions in living organisms[1]. Unfortunately, light transmission *in vivo* is severely limited by the absorption and scattering of light at ultraviolet, visible and, to a lesser extent, near-infrared wavelengths by biological molecules and structures in bone, fat, muscle and skin[2]. As a result, optical signals can penetrate only a few centimetres or so into biological tissue[3]. This hampers the use of light-based detection techniques in the body, because many optical probes are excited by and emit light at ultraviolet and visible wavelengths[4,5]. Hence, schemes for propagating light through tissue are currently needed to allow physiological processes in the body to be monitored in real-time with a high resolution.

In this issue of *Nature Photonics*, Myunghwan Choi and co-workers[6] present an intriguing hydrogel construct that overcomes this light transmission barrier and serves as an implantable biosensor and drug delivery system that can be used to sense exposure to toxins and to treat diseases in living animals. The implantable system consists of a polyethylene glycol diacrylate (PEGDA) hydrogel patch measuring 4 mm (length) × 1 mm (width) × 40 mm (height). This patch can be loaded with implanted cells and used to guide light delivered by an optical fibre cable. Importantly, the hydrogel can accommodate genetically modified cells, which can be programmed to respond to light in a specific manner, allowing them to function as an optical sensor or an optically activated therapeutic agent.

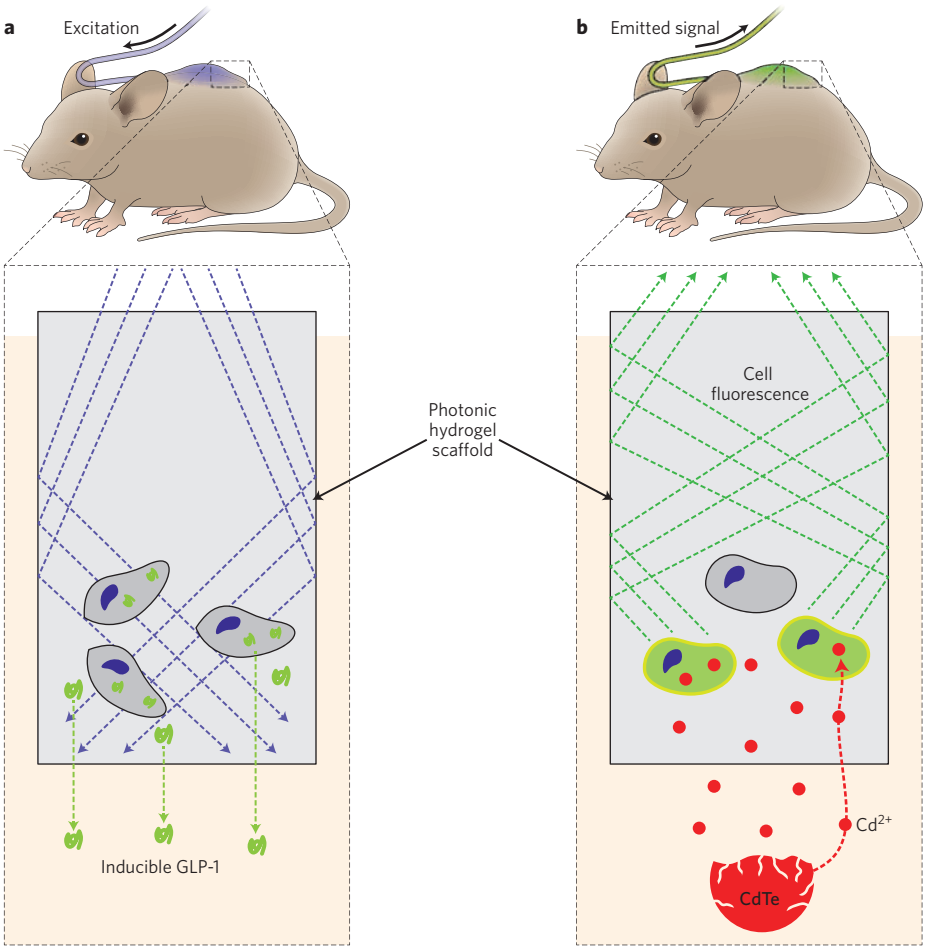

Figure 1 | Schematics of implantable hydrogel patches. **a**,**b** Illustration of use of implantable hydrogel patch (grey) for optical therapy (**a**) and sensing (**b**) in biological tissue (orange). The hydrogel creates a low resistance path for light (dashed purple and dashed green lines). It can also be used to accommodate genetically enhanced cells that can be induced to release therapeutic agents in response to external light stimuli (**a**) and emit fluorescence in the presence of certain chemicals (**b**).

The researchers showed that light transmission through their hydrogel can be modulated by tuning the size of the PEGDA patch, the number of diacrylate bonds and the cell density. Longer PEGDA chains and greater hydrogel crosslinking through diacrylate bonds were found to cause more frequent mismatching in the refractive index of the hydrogel, whereas higher quantities of cells led to greater light scattering. By optimizing these properties, Choi *et al.* found that light can travel up to 4 cm through a 10% weight by volume hydrogel consisting of 5-kDa PEGDA and having fewer than 10^5 cells. Interestingly, at this composition, the hydrogel did not impede movement when implanted in mice, nor did

it trigger an immunological or inflammatory reaction up to 12 days after surgery. The tolerance of biological systems to the hydrogel is vital for its long-term function and to ensure that the implanted waveguide will not be degraded by immune cells.

Utilizing their optimized design, Choi *et al.* demonstrated that their hydrogel can be used for biosensing and bio-modulating applications when it is implanted *in vivo* (Fig. 1). As a proof of concept, they created a biosensor for nanotoxicity measurements by impregnating their PEGDA hydrogel with genetically altered HeLa cells that co-express green fluorescent protein when the heat shock protein HSP70 is produced in response to metal-induced cellular stress. By injecting mice with cadmium telluride quantum dots, which are known to degrade easily[7], they showed that the liberated cadmium and telluride ions are able to (i) diffuse through the hydrogel, (ii) cause the co-expression of HSP70 and green fluorescent protein in the reporter cells, and (iii) produce a fluorescent (500 nm) signal that can be detected by a fibre optic interfaced to the hydrogel.

Their study also demonstrated that the system could be used to induce insulin expression in patients. This was achieved by seeding the hydrogel with HeLa cells that when exposed to light produce GLP-1, a secretory protein that stimulates the release of insulin. Using a glucose tolerance test in type-2 diabetic mice, the researchers showed that illuminating the implanted construct with 455-nm light for 10 s led to the release of GLP-1 from the photoresponsive cells, resulting in basal blood glucose levels in the mouse being restored within 90 min of excitation. Although these two demonstrations are just examples of applications of hydrogel systems, genetically modified cells have been engineered for a variety of applications ranging from the treatment of cancer to the prevention of gout. This suggests that the implantable hydrogel could be used for many biological and clinical applications[8].

In summary, Choi *et al.* have developed an interesting medium that fulfils two important goals — it functions as an implantable waveguide for light and as a substrate capable of supporting living cells. Incorporation of reporter cells within this hydrogel creates a self-sustained, reagent-free platform that can be used to detect and respond to physiological changes in a host.

To push this new technology towards clinical use, some improvements should be made. First, reporter cells should be produced from cells taken from the host to prevent immune reactions that may adversely impact the function of the implant. Second, the light propagation distance in the hydrogel needs to be extended beyond 4 cm to realize effective optical transmission in the human body, which is clearly much larger than a mouse. Finally, the efficacy of hydrogels with different porosities should be explored *in vivo* to validate the versatility of the proposed biosensor in different tissues and its use with various target biomolecules.

The rising popularity of light for investigating and influencing biological processes is creating a demand for biologically relevant tools capable of delivering light in the body. Choi and co-workers have successfully created a biocompatible fibre optic system that achieves these desired properties and further functions as a real-time biosensor and photoresponsive drug delivery vehicle. These abilities indicate the potential utility of PEGDA hydrogels for long-term use *in vivo* and its applicability as a substrate for applications such as ontogenetics. With refinement, the proposed hydrogel system could help researchers probe complex developmental processes and understand the progression of diseases *in vivo,* and it may one day allow clinicians to monitor the health of patients more precisely and to produce better drug treatment strategies. ❐

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