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EDITORIAL

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To cite this article: Riccardo Levato and Khoon S Lim 2023 *Biofabrication* **15** 020401

IOP Publishing Biofabrication 15 (2023) 020401 https://doi.org/10.1088/1758-5090/acb50f

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RECEIVED
19 January 2023

ACCEPTED FOR PUBLICATION
20 January 2023

PUBLISHED
1 February 2023

EDITORIAL

Harnessing light in biofabrication

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Keywords: biofabrication, light-based bioprinting, hydrogels, imaging

Abstract

The integration of light-driven technologies into biofabrication has revolutionized the field of tissue engineering and regenerative medicine, with numerous breakthroughs in the last few years. Light-based bioprinting approaches (lithography, multiphoton and volumetric bioprinting) have shown the potential to fabricate large scale tissue engineering constructs of high resolution, with great flexibility and control over the cellular organization. Given the unprecedented degree of freedom in fabricating convoluted structures, key challenges in regenerative medicine, such as introducing complex channels and pre-vascular networks in 3D constructs have also been addressed. Light has also been proven as a powerful tool, leading to novel photo-chemistry in designing bioinks, but also able to impart spatial-temporal control over cellular functions through photo-responsive chemistry. For instance, smart constructs able to undergo remotely controlled shape changes, stiffening, softening and degradation can be produced. The non-invasive nature of light stimulation also enables to trigger such responses post-fabrication, during the maturation phase of a construct. Such unique ability can be used to mimic the dynamic processes occurring in tissue regeneration, as well as in disease progression and degenerative processes in vivo. Bringing together these novel multidisciplinary expertise, the present Special Issue aims to discuss the most recent trends, strategies and novel light-based technologies in the field of biofabrication. These include: 1) using light-based bioprinting to develop in vitro models for drug screening, developmental biology models, disease models, and also functional tissues for implantation; 2) novel light-based biofabrication technologies; 3) development of new photo-responsive bioinks or biomaterial inks.

In the recent years, light-driven technologies have rapidly progressed to expand the toolbox available for biofabrication. Light as a physical stimulus and energy source has been prominent in the fields of biomaterials, tissue engineering and regenerative medicine, as it interacts in a contactless, mechanical stress-free fashion with cells and materials, and able to trigger photo-chemical and biochemical events on demand with high spatial precision. In the field of biofabrication, the aforementioned unique capabilities of light were firstly demonstrated in widespread adoption of light-responsive hydrogels as bioink components in extrusion-based technologies, and more recently to several breakthroughs in creating complex cell-laden architectures, with a degree of freedom of design and resolution superior to conventional extrusion. In fact, growing number of photonics-based technologies, including stereolithographic printing, multiphoton lithography, and more recently volumetric bioprinting, allow the projection of light into different, customizable geometries from single pixels of (sub)micrometer resolution to large 2D and 3D illumination fields. This special issue on 'Harnessing Light in Biofabrication' collects new works describing key applications and innovations in light-based materials, printing technologies, and imaging tools, in the context of biofabrication for tissue engineering and regenerative medicine applications.

In the quest of developing new light-responsive bioinks, the importance of biofunctionality where the materials are required to facilitate cell function (proliferation, migration) and respond to biological and biomechanical cues, is being emphasised in a number of studies. Min *et al* introduced a methacryloyl-modified platelet lysate bioink, which can be photocrosslinked for shape stabilization post extrusion bioprinting, while the abundant biologically active growth factors retained from the platelet lysate facilitated long-term function of the bioprinted cells [1]. Notably, this hydrogel has high potential for rapid clinical translation as it is a blood derivative that can be readily obtained from patient specific sources. Other strategies to modulate cell morphology, proliferation and behaviour in bioprinted hydrogels include incorporating anisotropic microscale elements into the bioink. Prendergast *et al* demonstrated this concept by using microfibers produced from fragmenting light-stabilized electrospun norbornene-modified hyaluronic bioink [2]. These microelements align along the printing direction when sheared through a nozzle, and, in turn, guide cells to acquire elongated morphologies and promote cell-cell interconnections. Using a different approach, Guzzi *et al* described how light-responsive hydrogels and digital light-projection printing can be used in combination with direct ink writing, to locally modulate the degree of crosslinking and the mechanical properties of the printed constructs [3]. By suspending polymer-nanoparticles in photocrosslinkable gelatin-methacryloyl bioinks, zonally patterned stiffness was created in response to digital light processing (DLP) illumination, that enabled control over cell morphology in a zonal meniscal graft.

Photoresponsive hydrogels can also be directly employed as bioresins, a term indicating printable materials for light-based fabrication techniques. Hossain Rakin *et al* developed a methacrylated hyaluronic acid-gelatin methacryloyl blend bioresin, designed specifically to cover a broad range of mechanical properties while still supporting cell viability and applications in stereolithography (SLA) bioprinting [4]. Huh *et al* provided a thorough characterization of the design process needed to optimize a photoresponsive multi-arm poly(ethylene glycol) (PEG) biomaterial for digital light projection printing [5]. In particular, they screened a broad array of cytocompatible photoabsorbers, molecules needed to prevent off-target curing in DLP and SLA biofabrication to maximize print resolutions, where they successfully printed hydrogel constructs with perfusable channels. Compounds able to absorb light can also be selected among stimuli responsive particles, to provide additional functionality to the bioprinted construct. Ajiteru *et al* explored this concept using DLP printing to obtain composite constructs built from two components: a silk fibroin region doped with iron oxide particles, and a gelatin glycidyl region laden with myoblastic cells [6]. This dual material architecture obtained by DLP permitted mechanically stimulation of the cell-laden region through the magnetic silk region using magnetic fields, essentially creating a bioreactor to 'train' the bioprinted muscle cells. While this work highlights the feasibility of multi-material printing in DLP and, more broadly, in vat polymerization techniques, further techniques to fully automate and facilitate multi-material DLP biofabrication are still sought. Bhusal *et al* propose an elegant solution to this challenge, by developing a multimaterial, multi-vat system, in which a rotating stage containing up to four bioresins allows the creation of complex hydrogel-based microfluidic chips and 3D patterns that show local variation in material composition and mechanical properties [7].

Besides applications in cell printing, light-based biofabrication technologies can also be leveraged for its ability to resolve minute geometrical features that can be used to guide cell adhesion and formation of tissue-mimetic structures, after cell seeding post-printing. Carberry *et al* exploited this concept to DLP-print a sacrificial structure from a degradable thioester-containing elastomeric PEG-derivative [8]. The material was used to build a mold for casting structures mimicking the crypts normally found in the intestinal wall, and to finally create a 3D structure to guide the culture and differentiation of cells from intestinal organoids. The mild removal process of the thioester mold permitted transfer of the desired pattern into otherwise delicate and fragile to handle soft hydrogels like Matrigel, a crucial material for culturing organoid-derived intestinal stem cells. Besides soft tissues like the intestine, load-bearing tissues such has articular cartilage, can benefit from the capability of light-based printing to resolve small porous structures. Schoonraad *et al* developed a stiff PEG-based resin as structural material for DLP printing, and sculpted it into an array of aligned pores and pillars, which were then used to inject and stabilize soft, biodegradable hydrogels carrying mesenchymal stromal cells [9]. The DLP-printed composite displayed compressive moduli in the range of native cartilage (□4 MPa), and the materials were further tuned to allow bone- and cartilage-like matrix deposition in *ex vivo* cultures and under dynamic mechanical load.

Together with applications in developing light-driven printing devices, and photosensitive bioresins and bioinks, optical systems have of course clear applications in imaging, monitoring of the print quality, and metrology. Integration of advanced imaging technologies with bioprinting platforms can help improve quality control and shape fidelity in biofabricated constructs. Tashman *et al* demonstrated this concept by developing an Optical Coherence Tomography head that can be paired with an extrusion bioprinter. The device is optimized to operate and resolve printed features not only when fabricated in open air, but also at high spatial resolution during embedded printing in granular, support baths. This is a particularly remarkable feature, as the contrast between the two water-based hydrogels and granular baths, would normally be low [10]. Showing more possibilities, Ma *et al* utilized a DLP printer to generate an anatomical-like blood vessel network with internal microchannels, and leveraged photoacoustic microscopy to image these microstructures. The system displays the ability to resolve the vessel patterns as deep as 3.6 mm into the construct, and to allow imaging and even quantification of healthy and thrombotic blood oxygenation in a label-free fashion [11]. It is thus foreseeable, that new developments in imaging-integrated printers will facilitate translation towards industrial and clinical applications, thanks to their ability to aid standardization and reproducibility.

Overall, all the works collected within this special issue highlighted the vast potential of integrating light into biofabrication approaches, including new chemistry and photocrosslinkable material, light-based bioprinting technologies and light-driven imaging modalities. We hope that the collection of these articles will inspire the community to explore and harness the exciting, multifaceted and versatile features of light, to innovate even more and develop new technologies that will expand the current biofabrication toolbox, further generating significant impact in the field of tissue engineering and regenerative medicine.

We would also like to thank all the authors and reviewer that contributed to this collection, and editorial staff at Institute of Physics and Richard Kelsall for their assistance throughout commissioning this special issue.

Data availability statement

No new data were created or analysed in this editorial.

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