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Soft nano and microstructures for the photomodulation of cellular signaling and behavior

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Abstract

Photoresponsive soft materials are everywhere in the nature, from human's retina tissues to plants, and have been the inspiration for engineers in the development of modern biomedical materials. Light as an external stimulus is particularly attractive because it is relatively cheap, noninvasive to superficial biological tissues, can be delivered contactless and offers high spatiotemporal control. In the biomedical field, soft materials that respond to long wavelength or that incorporate a photon upconversion mechanism are desired to overcome the limited UV-visible light penetration into biological tissues. Upon light exposure, photosensitive soft materials respond through mechanisms of isomerization, crosslinking or cleavage, hyperthermia, photoreactions, electrical current generation, among others. In this review, we discuss the most recent applications of photosensitive soft materials in the modulation of cellular behavior, for tissue engineering and regenerative medicine, in drug delivery and for phototherapies.

Keywords

Photoisomerization; Photothermal; Photodynamic; Photocleavage; Photovoltaic/Optoelectronic; Smart Soft Materials; Phototherapies; Regenerative Medicine; Cell Behavior; Drug Delivery

1. Introduction

Soft matter is present everywhere in nature and it has been the inspiration for engineers in the development of modern materials. Nature's soft materials are composed of lipids, saccharides, peptides, and nucleotides that assemble into multiresponsive dynamic structures such as biological tissues, fat, muscles, etc. The term "soft" comes from their relatively low Young's modulus, in the range of 10^4 to 10^9 Pa, in comparison with other classes of materials [1]. Artificial materials that can recapitulate the mechanical properties of biological materials such as polymers, gels, colloids, or liquid crystals, are of great interest

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for the design and fabrication of modern tools with applications in biomedicine [2], nanotechnology [3], and robotics [4,5]. However, prevalent applications require of soft materials with multifunctional dynamic properties just as found in nature. Synthetic soft materials undergoing rapid conformational changes in response to internal/external stimulus such as pH, ionic strength, temperature, or irradiation are of high scientific interest [6].

Biomedical soft materials that respond to internal stimulus such as pH, metabolite concentration or temperature may benefit from undesired foreign disturbances, however, naturally occurring physiological and pathological stimuli offer poor control over the dynamics of the material. Electrical currents, magnetic fields, ultrasound, and light are among the most popular external stimuli technologies investigated for biomedical soft materials [7]. For instance, electrical stimulation has been applied to manipulate the behavior of electroconductive soft materials [8-10]. However, this external stimulation approach requires a device/electrode wired to the system to deliver the electrical currents, which is often damaging to biological tissues [11]. The heat dissipation and reactive oxygen species (ROS) production through soft magnetic materials has been widely exploited in the biomedical field utilizing wireless magnetic fields as external stimuli [12,13]. The weak magnetic properties and low electrical conductivity of tissue allow magnetic fields to reach deep into the body with no attenuation of the signal [14-17]. Magnetic field stimulus strategies are limited by the potential off-target heating effects and the challenges in scaling high-frequency magnetic coils, which impede their universal adoption in clinical practices. The use of soft materials for stimulation with ultrasound has open the possibility for a technology with higher spatial resolution, however, even in the form of focused ultrasound, it has a broad radius of action on the order of millimeters to centimeters [18,19], resulting in undesired perturbation of biological tissues. Special attention in the biomedical field has been given to photoresponsive soft materials. Light provides a unique combination of wireless energy delivery with high spatial and temporal resolution [20]. Additionally, low-cost light sources can be tuned for their wavelength/frequency, intensity and chirality offering well-controlled stimulation [21]. A clear disadvantage of photosensitive soft materials in the biomedical field is the poor optical penetration of biological tissues at short wavelengths. To overcome this deficiency soft materials that respond to light in the near infrared wavelengths and nanotechnologies for photon upconversion have been developed. In general, photosensitive soft materials are designed to respond to light stimuli through specific light-triggered mechanisms as are photoisomerization, photocleavage, photocrosslinking, photothermal, photodynamic, photovoltaic, among others [22]. Photoisomerization implies a conformational change upon light illumination about a bond with restricted rotation, in general a double bond. In organic molecules with double bonds, such as azobenzenes, it involves isomerization between the *trans* and *cis* orientations upon irradiation with light of different wavelengths [23]. Isomers exhibit geometric structural differences, for instance, planar *trans* orientation of azobenzenes is more hydrophobic than the nonplanar *cis* orientation. While the microscopic geometrical change can be translated into macroscopic motion to control material shape or exert mechanical stress, the change in wettability can be used to trigger assembly-disassembly of nanocarriers and tune material interactions with drugs, proteins and cells [23,24]. Photocleavage involves the fission or splitting of chemical bonds upon light illumination.

Photocleavage can be used to modulate the degree of gel crosslinking and soften a gel, remove protecting groups to expose targeting ligands or to trigger dissociation for controlled drug release [21,25]. Photocrosslinking is the light-induced formation of bonds linking polymer chains. It can be used to *in situ* control hydrogel gelation and stiffness, for cell encapsulation in mild conditions and for phototriggered shrinking of polymer multilayer particles followed by drug release [22,26,27]. A photothermal material is able to convert light energy into thermal energy [28]. Polymers and soft materials exhibiting photothermal conversion capacity can be used to, upon light illumination, stimulate temperature sensitive cells or kill specific cell populations such as tumor or bacteria cells. Photothermal materials can be also coupled with thermoresponsive materials, *i.e.*, materials able to experience geometric or physicochemical changes following temperature variations, to control cells or trigger drug release [29,30]. Photodynamic effect refers to the generation of reactive oxygen species or free radicals upon illumination of a photosensitizer [31]. The local increase of concentration of these cytotoxic species is generally used to kill cancer or bacteria cells [32]. Finally, photovoltaic effect is the conversion of light energy into electrical power. Photovoltaic biomaterials are often used in soft electronic tools and interfaces and to stimulate electrogenic cells such as neurons and muscle [33,34]. Here, we will review the most recent advances in photoresponsive soft materials for the modulation of cellular behavior, in tissue engineering and regenerative medicine, for the delivery of therapeutics and for phototherapies (Scheme 1).

2. Photoresponsive soft materials for controlling cell function

The extracellular matrix (ECM) is a crucial, non-cellular component in tissues and organs that surrounds them and acts as the cell's physical environment, modulating their behavior [35]. As such, ECM serves as nature's template for the development of new biomaterials and scaffolds that frequently try to emulate its natural properties, sensitivity and dynamic behavior [36,37]. The ECM has intrinsic biochemical and mechanical cues that regulate cell phenotype and function, tissue morphogenesis, homeostasis and response to injury [38]. Furthermore, each tissue has a unique ECM composition and topography that interacts dynamically and reciprocally with the cells [39]. Since static scaffolds often fail to mimic the ECM dynamicity, it is of outmost importance to develop stimuli responsive scaffolds able to change their biochemical and/or physical properties in response to biocompatible stimuli [40]. In this vein, molecular photoswitches, such as azobenzene or spiropyran, and other reversible chemistries have been incorporated into hydrogels to control polymer chain conformation and thereby emulate the dynamic nature of the ECM [41]. The development of new biomaterials to study the influence of isolated materials properties on cell behavior, and to understand the interplay of multiple factors on cellular function is fundamental for basic cell biology studies and for generating new *in vitro* models [42,43]. Moreover, as the ECM is a crucial mediator for most of the intracellular events, abnormalities in the ECM lead to the development of most mammalian diseases [44]. Thus, gaining knowledge on ECM-cell interactions may lead to the development of new therapeutic options. Cells' interactions with surfaces depends on material's properties such as chemistry, surface energy and charge, wettability, roughness, morphology, rigidity and deformability [45]. Different nano and microscale engineering techniques such as layer-by-layer assembly

[46], microcontact printing [47], and electrospinning [48] can be used to synthesize soft biomaterials with controlled biochemical and physical properties. Soft photoresponsive nanomaterials and biointerfaces have been also developed for engineering precise and dynamic cell microenvironments, manipulate cell behavior and trigger specific cellular responses [26,49,50]. Different photoresponsive reactions, such as photocrosslinking, photocleavage and photoisomerization, have been employed to elicit specific material responses such as stiffness change, degradation or shape change [26]. In the following subsections, the use of different photo-responsive soft materials for controlling cell behavior will be reviewed.

2.1. Cell adhesion, spreading and morphology

Cell adhesion, *i.e.*, the ability of a cell to attach to other cells or to a surface through specialized protein complexes, is the first of many physiological and pathological processes such as morphogenesis, wound healing, and tumor progression [51,52]. Material characteristics such as topography [53], stiffness [54], surface physicochemical properties (e.g. wettability, polarity and charge) and pro-adhesive protein adsorption [45,55], influence cell adhesion, often in a cell-line specific fashion, and may be controlled to obtain a particular cellular response. Depending on the application, preventing or promoting selective cell adhesion may be desired. Photoresponsive materials may take advantage of photoisomerization, photocleavage or photothermal effects for controlling cell adhesion [56]. In reference [57], Wu *et al.* presented a photocured thiolated hyaluronic acid (HA) hydrogel and its *in-situ* remodeling capacities with light stimuli and small molecule diffusion. Synthetic thiolated HA polymers were crosslinked by UV irradiation in the presence of a radical photoinitiator, which lead to the radical-mediated photooxidation of thiols into disulfide. The obtained hydrogels presented both self and photoinduced healing properties. The authors further explored the hydrogel remodeling via photodegradation, being able to obtain patterns of soft gel areas within the stiff gel by employing a photomask. Hydrogel reversible remodeling was possible by free thiol molecules such as glutathione at physiologically relevant concentrations. Photocrosslinked thiolated HA hydrogels with Young's modulus in the range 260–680 Pa were able to sustain human mesenchymal stem cells (hMSCs) adhesion and spreading, but adhesion was impaired in hydrogels with larger crosslinking densities. In reference [58], Karimipour *et al.* developed spiropyran (SP)-based photoswitchable acrylic nanofibers for dynamic control of cell adhesion and detachment. The authors used emulsion polymerization to synthesize photoresponsive poly (methyl methacrylate-*co*-hydroxy ethyl methacrylate-*co*-spiropyran ethyl acrylate) terpolymer that was further used to create nanofibers and film coatings by electrospinning and drop-casting techniques, respectively. Reversible photoswitching between orthogonal, hydrophobic, colorless SP and hydrophilic, zwitterionic and colored merocyanine (MC) can be achieved upon illumination with UV and visible light. It was found that the higher exposure surface and porosity of the nanofibrillar structure can be occupied by hydrophobic air leading to higher water contact angle (higher hydrophobicity) in the SP nanofibers relative to the SP films. Furthermore, it explains the faster photoswitching rate of MC to SP found in the nanofibers in comparison to the films. Switchable glioma cancer C6 cells attachment and detachment on nanofibrillar samples was achieved upon visible light and UV light illumination. In another approach using SP-functionalized polymer, He *et al.* developed

a photoresponsive interface able to spatiotemporally modulate wettability, cell adhesion and detachment in a reversible manner [59]. SP molecules were introduced into the hydrophobic block of an amphiphilic diblock copolymer composed of poly (methyl methacrylate) (PMMA) and polyethylene glycol (PEG). Then, the copolymer was immobilized on a glass substrate by spin-coating. The surface exhibited reversible changes in wettability with the alternating irradiation of UV and visible light. Interestingly, due to the diblock structure of the copolymers the direction of change was opposite to the polarity change in the photoisomerization of SP. The obtained surface is cell repellent and can be turned into cell-adhesive upon UV-light illumination. Cell detachment can be further induced by visible light irradiation.

Smart surfaces may be further modified with target bioactive ligands such as DNA or peptides to obtain selective cell adhesion. In reference [60] Zhang *et al.* developed photoswitchable selective protein/cell adhesion surfaces via self-assembled monolayers (SAMs) based on sugar(galactose/mannose)-modified azobenzene derivatives. The inactive *cis*-state of the monosaccharide-azobenzene modified surface can be switched upon visible light illumination to the *trans*-state where the hydrophilic saccharide protrudes. This allows selective binding of lectins (proteins that recognize sugars) and cells that highly express sugar receptors, such as HepG2 cells that overexpress the galactose-selective asialoglycoprotein receptor and macrophage cells that express mannose receptor. The smart surface can be switched off by UV-light illumination, which induces photoisomerization towards the *cis*-state and exposure of the hydrophobic azobenzene moiety, leading to weakened affinity towards biomacromolecules and cells. In another approach for the reversible capture and release of targeted cells, Li *et al.* developed a photoresponsive SP-coated nanostructured surface with both structural and molecular recognition (Fig. 1a-d) [61]. The first arises from the interaction between the nanofractal silica surface and the protrusions of the cell surface that improves cell capture capability. The latter is regulated by phototriggered wettability changes. The ring-closed SP form can be switched to the ring-opened MC form upon UV illumination, leading to a surface wettability transition from hydrophobic to hydrophobic. The MC form can be switched back again to the SP form upon visible light exposure. However, in general, the light-triggered wettability transition on photoresponsive surfaces is limited, reducing cell release efficiency. Thus, the authors amplified the wettability transition by introducing photo-irresponsive and hydrophilic 2-hydroxyethyl methacrylate (HEMA) to the spiropyran derivatives (SPMA) (Fig. 1b). As HEMA provides more free space for SPMA isomerization, the phototriggered wettability switch is facilitated. Furthermore, HEMA hydrophilicity resists nonspecific cell adhesion. Biotinylated bovine serum albumin (BSA) can be adsorbed onto hydrophobic poly-(HEMA-*co*-SPMA) through hydrophobic interactions, and detached from the surface upon UV-light illumination (Fig. 1c). Using streptavidin as a linker, biotinylated epithelial cell adhesion molecule antibody can be further connected to biotinylated BSA as a cell capture agent (Fig. 1d). The designed surface presented high specific isolation of epithelial cell adhesion molecule-positive cells and high resistance to non-specific adhesion. Cell specificity can be also achieved by other targeting ligands such as aptamers, *i.e.* single-stranded short nucleotide sequences [62]. In this vein, Huang *et al.* employed *o*-nitrobenzyl phosphate ester photoprotected nucleic acids for photopatterning of nucleic acid tethers on

polyacrylamide hydrogel films [63]. Stiffness differences between the patterned regions and the surrounding hydrogel matrix were observed. Mucin 1 protein (MUC-1) is a glycoprotein which is overexpressed in some human cancer cells membranes. By using anti MUC-1 DNA aptamers, HeLa cells were deposited on domains with circular shape.

Though adherent cells are mainly cultured on two-dimensional (2D) substrates, *in vivo* they are embedded in a three-dimensional (3D) dynamic environment composed by ECM and cells. Thus, developing dynamic and controllable 3D microenvironments is desired to better mimic *in vivo* conditions. In this context, Nagata *et al.* presented a 3D microfiber scaffold with photoresponsive polymer surfaces for regulating cell adhesion by means of light stimulation [66]. The authors employed a core-sheath electrospinning technique to form bilayer fibers composed of an inner core of PMMA with a diameter of ca. 1 μm and a 30 nm thickness outer sheath of copolymers of SPMA and PMMA (poly (SPMA-*co*-MMA)). Adhesion of bovine aortic endothelial cells on the core-sheath nanostructures could be regulated by the light-induced chemical changes. While hydrophobic SP in the sheath layer prevented cell adhesion, the isomerization to hydrophilic MC upon UV exposure promoted cell adhesion, probable due to an enhanced interaction with amino acids in ECM proteins and formation of stable complexes. In another study, Ma *et al.* developed a 3D cell culture system with controlled cell adhesion and detachment based on photoresponsive smart hydrogel microspheres [67]. Hydrogel microspheres consisting of PEG and β -cyclodextrin (β -CD) modified poly (methyl vinyl ether-*alt*-maleic acid) were allowed to assemble with *trans*-azobenzene modified arginine-glycine-aspartate (RGD) integrin-binding peptide via host-guest interactions. Upon UV irradiation, photoisomerization of *trans*-azobenzene to *cis*-azobenzene leads to unbinding of the β -CD and azobenzene-RGD complex and subsequent cell detachment.

It is worth noting that cells are able to sense and respond to spatial variations or gradients in environmental physicochemical properties. In fact, rather than being homogeneous materials, several body tissues exhibit local gradual variations and a directional dependence in their biochemical and physical/structural properties [68]. These inhomogeneities may be reflected in patterning or in the change of concentration of biochemical cues along a direction, and also in patterning and gradients of structural and physical characteristics such as topography, mechanical or optical properties [69]. Thus, anisotropic biomaterials are of interest for tissue engineering applications. Moreover, as they allow to study the effect on cell behavior of a wide range of values of a determined property on the same surface, materials with gradient properties are very appealing for cell biology studies [70]. In reference [71], Ender *et al.* developed a photochemical strategy to generate gradients of integrin-binding peptide RGD on amyloid-like fibril scaffolds. A self-assembling β -sheet forming peptide was connected to an RGD motif using a photocleavable nitrobenzil linker. Then, the fibrils were spray-coated on glass substrates and the RGD motif was cleaved in a dose-dependent manner by a gradual irradiation with UV-light. A homogeneous distribution of nanofibrils with a cm-length scale gradient of RGD was obtained. A gradient of A459 adenocarcinoma epithelial lung cells adhesion was obtained, with less cells on the sections exposed to longer UV irradiation, *i.e.*, lower RGD concentration. Gradients and patterned mechanical properties with submicrometer resolution have been obtained on photodegradable hydrogels by means of photolithography [72]. Even gradients of distinct

parameters have been developed to study their cooperative influence on cell behavior. Rape *et al.* developed a HA hydrogel with orthogonally pattern gradients of substrate stiffness and fibronectin density using distinct wavelengths of light and a gradient photomask [73].

Multifunctional scaffolds and external stimuli can be combined to synergistically guide cell behavior and enhance desired outcomes. In reference [64], Milos *et al.* combined optical stimulation with topographical cues of the substrate to regulate neuronal growth (Fig. 1e-g). Thiophene-based polymer poly(3-hexylthiophene-2,5-diyl) (P3HT) was used due to its electrical and photoelectrical properties and biocompatibility [74]. Optically active P3HT micropillars array platform was obtained by push-coating technique (Fig. 1e). Micropillars topography allowed a close contact with cells, as shown in the actin cytoskeleton staining and in the SEM images (Fig. 1f). Neurons seeded on P3HT micropillars presented neurites ~ 40 % larger than on flat P3HT substrates or glass, showing the effect of micro and nano scale topography in promoting neurite growth. Moreover, while neurites of neurons seeded on flat substrates without topographical cues presented a random angle distribution, neurites of neurons seeded on the micropillar array were mostly aligned at 0, 45 and 90° relative to the direction of the pattern. Photostimulation of neurons seeded on optically inert substrates (glass or hybrid organic/ceramic polymer OrmoComp) had no observable effect on axon length. However, cells growing on P3HT substrates and stimulated with a green LED presented significantly larger axons than non-stimulated cells or cells stimulated with a red LED with negligible overlap with P3HT absorption (Fig. 1g). All in all, micro/nano topography of a photoresponsive substrate and wireless, noninvasive light stimulation can be combined to modulate the growth of rat primary cortical neurons *in vitro*.

Being able to separate or trap individual or a group of cells on substrates at a high density in a simple and accurate manner is essential for high-throughput single cell analysis and organ-on-chip technologies. However, retrieval of adherent cells may restrict target cell recovery. On the other hand, trapping weakly adherent and non-adherent cells may be troublesome. In reference [75] Jarzbska *et al.* developed a photoresponsive material with strong trapping capability based on photo-cleavable PEG-lipid. The material consisted of a long PEG chain, which is known to inhibit cell adhesion, connected to a photo-cleavable linker moiety and an oleyl group able to interact with lipid bilayers of cell membranes. In order to improve cell trapping, different spacers were placed between the photo-cleavable linker moiety, finding the best results with oligo (ethylene glycol) spacers. The obtained material was used to coat a collagen surface. Then, UV-light and a photomask were used for light-guided micropatterning, removing oleyl groups via photo-induced cleavage. Model immunocytes were selectively trapped in non-irradiated areas as single cells, and were further released from the substrates following UV light illumination. The same group reported the reversible, photoresponsive and spatioselective trapping of nonadherent cells by SP-functionalized PEG-lipids conjugates [65]. SP was attached to different PEG-lipid conjugates to find the optimal for photoswitchable cell trapping. SP-conjugated PEG – lipid were immobilized on collagen-coated substrates. In the ‘closed’ and hydrophobic SP form the PEG-lipid may form hydrophobic assemblies and hamper interaction between cells and lipid moieties (Fig. 1h). Upon UV light illumination, isomerization to the ‘open’ hydrophilic MC form induced the PEG-lipid to be disperse in solution, allowing the lipid moiety to interact with cells. The substrate enabled fast and switchable non-adherent and

adherent cells immobilization and release upon UV and visible light irradiation, respectively (Fig. 1i-j). Spatially selective photo-switching was also demonstrated illuminating part of the surface area. Using a different approach, Yamaguchi *et al.* developed a photocleavable RGD-PEG conjugate surface for light-guided patterning and recovery of adherent cells [76]. The RGD peptide that binds to integrins and leads to cell adhesion and spreading can be released from the surface upon exposure to nontoxic levels of light, allowing for cell recovery. Facile patterning of cell adhesive and non-adhesive regions and further cell release was achieved with light.

Cell shape and cell membrane curvature dynamically change in response to complex intracellular and extracellular cues, affecting several curvature-dependent intracellular processes such as endocytosis, exocytosis and actin dynamics [77]. Though prefabricated nano and micro structured static surfaces are useful for studying curvature-dependent processes, they fail to mimic dynamicity aspects of cell membrane curvature and cell-ECM interactions. In this regard, De Martino *et al.* developed a light-responsive azobenzene-based polymer structure in which the shape changed from vertical pillar to an elongated vertical bar upon green light illumination [78]. Ordered arrays of vertical micropillars of poly (dispersed Red 1 methacrylate) (pDR1m) were fabricated on glass coverslips by soft lithography. By means of green polarized light, a *trans-cis* isomerization can be induced and an athermal transition from glassy azopolymer to a fluid state is achieved. This leads to a distinct mass migration along the direction of the light polarization and a pillar to ellipsoidal bar shape transition. The light-triggered reshaping process induced dynamic changes in human bone osteosarcoma epithelial cells (U2OS) membrane curvatures, promoting accumulation of actin fibers and actin nucleation factor in locations with high curvature. Rossano *et al.* employed pDR1m as a substrate to display dynamic concentric rings patterns to fibroblastic NIH-3T3 cells by means of a focused laser beam of a confocal microscope [79]. Cells were strongly influenced by 10 μm crest-to-crest distance circular patterns but perceived 5 and 15 μm circular patterns as flat surface. As fast as 2 h after pattern inscription, cells reconfigure their shape and align along pattern direction assuming a circular disposition. Fibroblasts cultivated on 10 μm patterned substrates possessed a significantly softer cell body than cells on flat surfaces. Moreover, cells presented a less organized actin network and shorter focal adhesion, probably due to substrate curvature impairment maturation of the cytoskeleton.

A brief summary of strategies for controlling cell adhesion reviewed in this subsection is presented in Table 1.

2.2. Cell migration and mechanobiology studies

Both individual and collective cell migrations play crucial roles in several physiological and pathological processes [80]. For instance, single-cell migration towards or between tissue compartments takes place with leukocytes migration during inflammation. Collective cell migration, *i.e.*, the movement of physically and functionally connected cells in a coordinated manner, is essential in embryogenesis, wound healing and is involved in many disease processes such as cancer metastasis [81]. Different external cues such as substrate topography [82] and gradients of substrate stiffness or soluble chemoattractants [83] are

known to interplay with cell intrinsic cues in order to regulate cell migration [84]. Smart photoresponsive materials offer the possibility of mimicking the dynamic microenvironment of cells and allow the *in-situ* control of extrinsic cell migration regulators.

The programmable and adaptive nature of photoresponsive liquid crystal networks (LCN) coatings has been used to study the effect of *in situ* changes of micro and nanoscale topographical cues in cell adhesion and migration (Fig. 2a-c) [85]. A mixture of methacrylate functionalized azobenzene and liquid crystalline monomers were photopolymerized. Illumination using a photomask leads to local *trans* to *cis* transition of azobenzene and local formation of protrusions and increased in nanoroughness. Cell adhesion and migration were analyzed either on surfaces with fixed microscale hexagonally arranged pillars (Fig. 2b-c), or on flat surfaces where nanoscale topography was changed *in situ* by UV-light illumination. A decrease in mean cell speed was observed after illumination, correlated with the increase in nanoroughness. In another approach using photoresponsive azobenzene-based materials, Isomäki *et al.* developed a light-responsive cell culture bilayer interface for reversible cell guidance [86]. The platform consisted on a thin layer of azobenzene-based molecular glass coated with a thin polydimethylsiloxane (PDMS) layer (Fig. 2d and 2e). Surface relief gratings (SRGs) were easily photo-inscribed and photo-erased, therefore allowing for reversible photomodulation (Fig. 2f). The inscribed gratings can guide epithelial cell orientation and migration along the topography. For small groups of cells, grating erasure led to rearrangement of phosphorylated focal adhesion kinase, an effect which was not visible for confluent layers of cells. In reference [87], Liu *et al.* developed a near-infrared (NIR) light-responsive optomechanical actuator for controllable modulation of collective cell migration. A thermoresponsive copolymer hydrogel composed of *N*-isopropylacrylamide (NIPAM) and acrylamide (AM) was doped with gold nanorods, which can transform NIR light illumination into heat, leading to hydrogel contraction and increase in Young's modulus. Following surface functionalization with cell adhesive ligands, it was shown that applying contraction forces to cells by means of NIR light illumination, significantly increased random cell motility in comparison to controls. Using a microcontact printing strategy, patterned presentation of adhesive ligands and further cell alignment was achieved. Directed collective cell migration was stimulated by NIR light. Wu *et al.* designed a photo-responsive hydrogel with reversible tunable mechanical properties for optically controlling collective cell migration (Fig. 2g-j) [88]. The hydrogels were made of four-armed PEG-maleimide molecules crosslinked by the photoswitchable protein Dronpa145N (Fig. 2g and 2 h). Dronpa145N forms tetrameric species under violet light illumination and can be rapidly switched to the monomeric state under cyan light illumination, leading to a gel-sol transition and softening of the hydrogel (Fig. 2g and 2i). Cell adhesive ligand RGD was introduced to Dronpa145N proteins for promoting cell attachment to the hydrogels to perform a wound healing cell migration assay. The authors found a correlation between stiffness of the hydrogels and cell migration and were able to modulate cell migration rate in real time (Fig. 2j).

Although extrinsic factors such as chemical and mechanical cues may affect collective cell migration, intrinsic conditions such as cell density and colony shape may also play an important role [89,90]. In order to study and resolve the interplay between mechanical, chemical and geometrical factors, Yamamoto *et al.* developed a photoactivable

hydrogel platform to study cell migration under standardized conditions [91]. The substrate consisted on a poly(acrylamide) hydrogel, which allowed controlling mechanical properties, functionalized with poly-d-lysine, which allowed for controlling ECM proteins adsorption, and photocleavable PEG, which allowed to control colony geometry by photopatterning. Even though 2D cell migration has been studied in detail, elucidating how cells migrate in the complex 3D environments of living tissues is important for understanding several biological processes and for tissue engineering applications [92]. In reference [93], Cao *et al.* studied how endothelial cells (ECs) migrate into photoresponsive HA hydrogels with tunable stiffness under the presence of proinflammatory macrophages (M1). HA was grafted with methacrylate moieties, which crosslinking is insensitive to environmental stimuli and thus maintain hydrogel integrity, and with coumarin, which dimers formed at 365 nm can be decomposed by irradiation at 254 nm leading to a decrease in hydrogel compressive modulus and increase in mesh size and swelling. Hydrogels irradiated or not at 254 nm were placed in a Boyden chamber and ECs were seeded on top, while pro-inflammatory macrophages were seeded in the well. After 7 days, a significant larger displacement of ECs was found in the softer hydrogel irradiated at 254 nm than in the stiffer one.

The process by which cells are able to sense mechanical cues from their environment and transduce these cues into biochemical signals is called mechanotransduction. Active biomaterials that can apply dynamic mechanical cues to cells and tissues in a controllable manner are very appealing for mechanobiology studies [94]. Different light manipulation strategies have been employed to temporarily modulate mechanical properties in synthetic matrices. Lee *et al.* incorporated an azobenzene crosslinker to a polyacrylamide-based hydrogel to obtain a scaffold with photo-switchable mechanical properties for minimally invasive mechanotransduction *in vitro* studies [95]. Softening and stiffening of the hydrogel was induced by near-UV and visible blue light, respectively, leading to changes in primary human MSCs spreading and morphology. Brown *et al.* synthesized soft hydrogels via strain-promoted azide – alkyne cycloaddition (SPAAC) reaction and exploited the ability of azadibenzocyclooctyne to undergo a photocrosslinking reaction for on-demand stiffening of the 3D scaffold [96]. Taking advantage of the favorable kinetics of the SPAAC reaction at physiological conditions, C2C12 mouse myoblasts were encapsulated in the 3D hydrogels and further subjected to dynamic stiffening of the extracellular environment. Cells sensed and responded changing their spreading and localization of Yes-associated protein 1. In reference [97] Homma *et al.* designed a hydrogel composed of an azobenzene acrylate and *N,N*-dimethyl acrylamide copolymer that undergoes stiffness changes by photo-induced phase transition. The combination of hydrophilic *N,N*-dimethyl acrylamide and hydrophobic azobenzene acrylate allows the copolymer to phase separate in aqueous solution with the increase of temperature. Furthermore, the photoisomerization of azobenzene that causes changes in hydrophilicity shifts the phase separation temperature. The authors tuned the amount of azobenzene so the phase transition solely occurs by light irradiation and azobenzene photoisomerization at around 37 °C. Upon UV and visible light illumination, the hydrogel undergoes reversible swelling-deswelling and softening-stiffening. Human breast cancer MCF-7 cells seeded on the gels showed varied responses in gene expression levels of E-cadherin upon stiffening at different timepoints.

Measuring scaffold stiffness *in situ* may be time consuming, invasive and difficult for some systems such as microfluidic chips. In this vein, Li *et al.* developed a photoresponsive and photonic hydrogel for *in situ* light-manipulation and monitoring of scaffold stiffness via color change [98]. The photonic hydrogel was synthesized by copolymerizing a coumarin-containing acrylate monomer and PEG diacrylate in the presence of mono-dispersed silica nanoparticles (Fig. 3a-c). Coumarin reversible dimerization upon illumination was used to dynamically control hydrogel stiffness. Silica nanoparticles form periodic structures during hydrogel formation leading to a photonic band gap that reflects light at specific wavelengths depending on the center-to-center distance between nearest particles (Fig. 3a). Light-induced changes in hydrogel mechanical properties are associated with swelling-deswelling processes that lead to changes in the distance between silica nanoparticles and thus, to a change in hydrogel color (Fig. 3d-f). The authors demonstrate the feasibility of applying this photonic hydrogel strategy to microfluidic chips and cell culture microarrays. As in many physio and pathological processes cells are exposed to transient, cyclic forces, Chandorkar *et al.* developed a patterned beating hydrogel system that can be spatiotemporally controlled using NIR light trigger [99]. By mixing *N*-isopropyl acrylamide and *N*-ethyl acrylamide a volume phase transition temperature around 37 °C was achieved. Gold nanorods were added for photothermal heating and the surface was coated with cell adhesive proteins for cell attachment. Local nN-scale mechanical actuation (beats) with specific amplitude and variable frequencies was achieved by using a NIR laser (Fig. 3g). L929 fibroblast cells exhibited changes in migration, nuclear translocation of the mechanosensory protein myocardin related transcription factor A and increased secretion and alignment of fibronectin upon actuation (Fig. 3h and 3i). Liu *et al.* reported a modular semisynthetic approach to create protein-polymer hydrogel biomaterials for cyclic stiffness modulation upon user-specified stimuli [100]. By employing a dual-chemoenzymatic modification strategy, the authors created different fusion protein-based gel crosslinkers with stimuli-dependent intramolecular association. Taking advantage of reversible dissociation between light, oxygen, and voltage sensing domain 2 (LOV2) protein and J α helix upon blue light illumination, the authors obtained hydrogels with phototunable mechanical properties. Moreover, they showed that cyclic mechanical loading drive fibroblasts to myofibroblasts transdifferentiation.

A brief summary of strategies for controlling cell migration and for performing mechanobiology studies reviewed in this subsection is presented in Table 2.

2.3. Cell differentiation and stimulation

Cell differentiation, *i.e.* the process in which cells become more specialized, is the result of the integration of different stimuli in a spatiotemporal manner [101]. Studying how extrinsic mechanical and biochemical cues guide cell fate is not only essential for understanding development and disease, but also for designing new therapeutic strategies [35,102].

Administration and delivery of growth factors [103], small molecules [104], and even ions [105], are among the most common strategies for inducing cell differentiation. In reference [106], Zhang *et al.* developed NIR-responsive multishell upconverting nanoparticles (UCNPs) constructs for spatiotemporal control of small-molecule release and neural stem

cell differentiation (Fig. 4a and 4b). UCNPs are lanthanide-doped optical nanomaterials able to up-convert two or more lower energy-photons into one high energy photon [107]. The multishell structure was optimized to maximize NIR to UV upconversion and was further coated with a mesoporous silica shell that acted as a reservoir of small molecules. The resulting UCNPs were functionalized with a UV photoresponsive polymeric shell containing SP groups as a capping system and then, a colloidal stabilizing polymer layer of polyacrylic acid was further grafted (Fig. 4a). Using this UCNPs and NIR light illumination, retinoic acid, a neuronal differentiation factor, was delivered to human-induced pluripotent stem cell-derived neural stem cells and neuronal differentiation was promoted in a remotely controlled manner (Fig. 4b). Mechanical and biophysical cues can also guide cell differentiation. It is known that, under certain conditions, electrical stimulation can promote cardiac, neuronal or osteogenic commitment. As such, optoelectronic materials that can convert light into electrical signal are very appealing for neuronal cells studies and nerve regeneration as they provide a less invasive and wireless stimulation option. In reference [108], Yuan *et al.* developed a tri-component polymeric fibrous platform with optoelectronic properties for neuronal differentiation. A mixture of polycaprolactone and photoactive P3HT was electrospun and biocompatible electroconductive polypyrrole was further polymerized on the nanofibers surface. It was shown that, in comparison to nonfunctionalized nanofibers, tri-component material enhanced neuron-like PC12 cells differentiation and increased cell survival due to reactive oxygen/nitrogen species scavenging of polypyrrole. As substrate topography is another cue known to guide cell behavior, Wu *et al.* studied the effect of different micro/-nanoscale structures of semiconducting polymer P3HT on neuronal differentiation [109]. Self-assembled nanofibers with 100 nm average diameter, electrospun microfibers with ~ 1 μm diameter and patterned stripes with width of 3, 25, and 50 μm obtained by photolithography were tested against control homogeneous films (Fig. 4c). The combination of topographical and photoconductive stimulation enhanced neuronal differentiation and directed growth of rat pheochromocytoma PC12 cells (Fig. 4d). Other non-metallic photocatalysts such as carbon nitride or graphene oxide have been used as coating of polycaprolactone/gelatin electrospun fibers for neuronal stimulation [110].

Though most engineered scaffolds present fixed mechanical properties to the cells, the stiffness of muscle tissue changes during regeneration. To address this issue, Madl *et al.* developed a photoresponsive hydrogel system with dynamically-tunable mechanical properties [111]. Multi-armed PEG macromers functionalized with azide or bicyclo [6.1.0] nonyne were crosslinked by biorthogonal SPAAC. In order to enable controlled softening of the hydrogels, UV photocleavable *ortho*-nitrobenzyl ester moieties were introduced between PEG and a subset of azide groups used in crosslinking. While culturing skeletal muscle stem cells on soft hydrogels with healthy muscle mechanical properties enabled cell proliferation, culturing on stiff hydrogels impaired proliferation and myogenic progression. Experiments with dynamic hydrogels showed that culturing for 3 days on a stiff substrate was enough to impair cell proliferation and block commitment. Biophysical and biochemical cues' ability for guiding cell fate and commitment can be empowered by controlling spatiotemporal signal presentation. In reference [112], De Martino *et al.* used azopolymeric photoactive interfaces as a kind of 'cell gym' on a chip for presenting/withdrawing morphological signals to living cells. Light-induced topographical changes were obtained

by illuminating a pDR1m spin-coated substrate with a 514 nm laser from a single photon confocal microscope. Cyclic cellular and nuclear stretches could be induced by surface topography dynamic changes from a parallel pattern to flat or grid. Culture experiments with human MSCs revealed the possibility of rerouting or reversing stem cell fate by the dynamic modulation of morphological signals. In an intent to emulate natural tissue's ability to control multidirectional differentiation of MSCs, Yan *et al.* developed a photocontrolled UCNPs-based substrate functionalized with photocleavable 4-(hydroxymethyl)-3-nitrobenzoic acid modified PEG (marked as *P1*) and RGD modified PEG (marked as *P2*) [113]. While the latter can capture MSCs, the former blocks interaction between MSCs and substrate enabling the cells to maintain their stem-cell properties due to the anti-adhesive effect. Cell-matrix interactions can be tuned upon NIR irradiation and photocleavage of *P1*. Power density of the NIR irradiation correlates with percentage of *P1* detachment. Thus, low-power and high-power NIR irradiation led to adipogenic and osteogenic differentiation of MSCs, respectively, due to different cell-substrate forces and cytoskeletal tension. In another approach of cell differentiation by mechanotransduction, Zhang *et al.* developed light switchable tethers which length can be reversibly modulated by switching light responsive protein pdDronpa in between monomer and dimer states (Fig. 4e) [114]. Upon illumination of 488 and 405 nm light, tether length could be reversibly switched between 'long' (175 or 245 nm) and 'short' (105 nm) states, respectively, inducing distinct mechanical signals without changing the biochemical conditions. This results in contrasting cellular behaviors, as cells located in the area under irradiation of 405 nm light expressed osteogenic markers and adipogenic markers were observed under 488 nm light excitation (Fig. 4f and 4 g).

Being able to manipulate cell signaling in a precise and minimally invasive manner is crucial for cell basic research and for developing therapies for different diseases such as neurological disorders or cancer [115,116]. For instance, recently, cell stimulation has been achieved by means of magnetic discs that transduced alternating magnetic fields into mechanical forces [17,117], and piezoelectric micromotors that convert ultrasound input into an electrical signal [118]. Even long-range cell stimulation has been reported using a system comprising a circular magnetic array and a nanoscale magnetic torque actuator that can deliver piconewton-scale forces to cells over a working range of ~ 70 cm [119]. Minimally invasive stimulation of cells can be also achieved using 3D scaffolds. Tay *et al.* reported the synthesis of 3D magnetic hydrogels composed of hyaluronic acid that were able to stimulate mechanosensitive primary dorsal root ganglions in the presence of magnetic fields [120]. It has been reported that low levels of red and NIR light can promote intracellular Ca^{+2} elevation in neuron and cancer cells [121]. Different optogenetic approaches can be used to gain control over different Ca^{+2} modulated physiological processes [122]. Moreover, photoactive organic substrates that can transduce energy from light into heat or electricity have been employed to stimulate cells and trigger membrane depolarization [123]. In reference [124], Bossio *et al.* synthesized P3HT NPs by the re-precipitation method and used their photocatalytic activity to generate intracellular reactive oxygen species (ROS) upon visible light irradiation. The ROS generation did not affect cell viability and triggered intracellular calcium ion flux of Human Embryonic Kidney cells (HEK293). Though organic photovoltaic interfaces present a good performance in light

mediated excitation and silencing of neuronal cells, limited adhesion of conjugated polymers in aqueous environments and absorption spectrum restricted to the visible range are clear disadvantages against inorganic materials. To address this issue, Leccardi *et al.* developed a photovoltaic interface composed of chemically modified organic materials in order to improve adhesion in aqueous environments and optimize photo-electrical stimulation efficiency [125]. The resulting prosthesis presented no cytotoxicity and was able to stimulate explanted degenerated mice retinas upon NIR light illumination.

A brief summary of strategies for controlling cell differentiation and for cell stimulation reviewed in this subsection is presented in Table 3.

3. Photoresponsive soft materials in tissue engineering, wound healing and implants

The loss of tissues and organs due to trauma, diseases, congenital defects and an aging world population leads to an increasing demand of organ and tissue repair or replacement [126,127]. By applying the principles of engineering and life sciences the tissue engineering and regenerative medicine field aims to deal with the regeneration or replacement of diseased or damaged tissues and organs [128]. As the development, regeneration and fabrication of a tissue/organ involve very complex processes, the combination of several strategies such as multifunctional scaffolds and biomaterials, drug and growth factors delivery, gene therapies, immunomodulation and external stimulus (*i.e.* electrical, magnetic, optical) is often required [129]. The spatiotemporal tunability of photoresponsive biomaterials is very appealing in a range of biomedical applications where tissue-like properties and programmable responses are required, such as tissue engineering and drug delivery [130-132].

Along with photoresponsive scaffolds and biomaterials, photobiomodulation (PBM) therapies, *i.e.* the use of non-ionizing light in the visible and near infrared spectrum for cell modulation, have presented promising results in the tissue engineering field [133]. There are several proposed underlying mechanisms of action for PBM such as activation of light sensitive ion channels and light-mediated effects on important molecules [134]. However, as red and NIR photons are predominantly absorbed by cells' mitochondria, it is likely that the main mechanism of actions involves light absorption by cytochrome *c* oxidase and retrograde mitochondrial signaling (*i.e.*, a mechanism by which mitochondria communicate with the cell nucleus affecting gene expression) [134-136]. Visible and NIR light would induce changes in the concentration of signaling molecules such as adenosine triphosphate, cyclic adenosine monophosphate, ROS, calcium and nitric oxide, and the activation of transcription factors. All these activities can lead to cytoprotection, enhanced cell proliferation, migration and differentiation, and modulation of inflammation, with positive effects in tissue repair and regeneration. For instance, it has been shown that an illumination with a diode laser of 830 nm wavelength and 40 mW power significantly enhanced bone repair when associated with bone morphogenetic proteins (BMP) in a critical size femoral defect (CSFD) rat model [137]. It has also been shown the positive effects of laser PBM in cartilage defect in animal models of knee osteoarthritis [138] and in promoting

angiogenesis *in vitro* in a co-culture model of endothelial cells and *in vivo* in a chick embryo chorioallantoic membrane model [139]. PBM has also been used in combination with stem cell (SC) therapy for temporomandibular joint disc disorders [140]. In a different approach, Khosravipour *et al.* showed that *in vitro* PBM preconditioning of human adipose derived stem cells (hADSCs) increased cell viability and bone repair in a CSFD rat model [141]. The combination of human umbilical cord mesenchymal stem cells (hUCMSCs) transplantation and PBM presented a synergistic effect on the recovery of motor function and reduced lesion volume after spinal cord injury (SCI) in a rat model [142]. Biomaterials and PBM may be used together as synergistic strategies for increasing tissue regeneration. Paiva Margi *et al.* systematically reviewed studies that combined ceramic biomaterials and PBM in the healing process of animal models of bone defects [143]. The authors found that the combination of the appropriate biomaterials and PBM parameters presented enhanced healing effects. Thus, the association of biomaterials and PBM may have huge potential in tissue engineering approaches. The use of photoresponsive soft materials for tissue engineering, regeneration and implants will be discussed in the following subsections.

3.1. Bioactive molecules, Angiogenesis, and immunomodulation

Growth factors (GFs) are bioactive molecules able to control several cellular processes such as proliferation, migration, or differentiation, on targeted cells by specifically binding transmembrane receptors [144]. As GFs play a crucial role in tissue development and regeneration, their use in tissue engineering approaches is promising [145]. However, short-term burst-type diffusion from the delivery site and short half-life due to proteolysis limit GFs effectiveness [103,144]. Therefore, developing biomaterials and strategies that improve GFs stability and control their release is of utmost importance [146]. For instance, Zhao *et al.* developed a photoresponsive supramolecular HA hydrogel with controlled EGF delivery for wound healing applications [147]. HA (an important component of ECM) chains were conjugated with azobenzene (photoisomerization properties) and β -cyclodextrin (high binding-affinity with *trans*-azobenzene) groups (Fig. 5a). The hydrogel dynamic network could be controlled by photostimulation, transitioning to a soft or stiff state upon exposure to UV or visible light, respectively (Fig. 5b). EGF release from the loosened hydrogel is fast, thereby increasing its delivery at the wound site (Fig. 5c). Photoresponsive hydrogels with UV irradiation presented good biocompatibility properties assessed through hemolysis assay and through *in vitro* viability studies in L-929 mouse fibroblasts. Furthermore, illuminated photoresponsive hydrogels presented enhanced wound healing and angiogenesis in rat full-thickness skin defect model with respect to the controls (Fig. 5d). In addition to skin's protein and cell delivery, photoresponsive hydrogels may be used for tissue engineering approaches of other tissues/organs. In reference [148], the authors employed metal–ligand coordination interactions and photochemistry of cobalamins [149] for developing an injectable, photoresponsive hydrogel capable of delivering cells and neuroprotective proteins to enhance axon regeneration. Via SpyTag/Spy Catcher technology the C-terminal adenosylcobalamin binding domain (CarH_c) from the B₁₂-dependent photoreceptor protein (CarH) was fused with a polyhistidine-tag (His6-tag), which can complex with transition metal ions such as Co⁺², Cu⁺², Ni⁺² or Zn⁺². The addition of coenzyme B₁₂ or adenosylcobalamin (AdoB₁₂) that binds CarH_c induces its tetramerization and leads to self-assembly of the metal–ligand complexes into molecular

networks in the dark (sol–gel transition). The C–Co bond within AdoB₁₂ is sensitive to green (522 nm) and white light. Upon light exposure, following cleavage of the C–Co bond, the tetramers dissociate into monomers causing a gel–sol transition and the release of 4',5'-anhydroadenosine (cleavage product of the coenzyme B₁₂). As Zn⁺² is relatively abundant in biological systems, Zn⁺²-coordinated hydrogels were used for cell encapsulation and *in vivo* applications. The obtained injectable, self-healing and photodegradable hydrogel was able to encapsulate 3T3 fibroblasts and hMSCs with good viability and was suitable to release the cells within 8 min of light exposure. Leukemia inhibitory factor, a neuroprotective cytokine that facilitates axon growth, laden hydrogels led to prolonged cellular signaling and enhanced axonal regeneration in a mouse optic nerve injury model.

Oxygen diffusion and nutrient supply is a clear limitation for the size and complexity of tissue engineered constructs [151]. As such, angiogenesis, the formation process of new blood vessels, is crucial for supporting functional recovery and graft integration with the host tissue [129]. In that vein, several approaches employing photoresponsive materials have been proposed. In reference [152], Lodola *et al.* employed polymer-mediated optical stimulation for wireless modulation of endothelial colony-forming cells (ECFCs) proliferation and function. Thin films of P3HT, a biocompatible organic semiconductor widely used for phototransduction applications, were obtained by spin coating, and further coated with fibronectin. ECFCs were isolated from human peripheral blood samples and seeded on top of polymer and control glass substrates. The cultures were optically stimulated by application of milliseconds excitation pulses of a 525 nm LED for 4 to 36 h. The photoexcitation of the P3HT leads to enhanced proliferation and increased tubulogenesis of ECFCs *in vitro*. The authors propose the Ca⁺²-permeable transient receptor potential vanilloid 1 (TRPV1) channel and the pro-angiogenic genes expression mediated via NF-κB as the molecular pathway leading to these macroscopic results. In a different approach, Nair *et al.* employed hydrogels containing a phototriggerable vascular endothelial growth factor (VEGF) peptidomimetic system for light-controlled angiogenesis [153]. The 15 amino acid peptide was functionalized with a 3-(4,5-dimethoxy-2-nitrophenyl)-2-butyl (DMNPB) photoremovable protecting group that temporarily inhibits its angiogenic activity. Then, it was incorporated into maleimide cross-linked bioactive PEG hydrogels along with human umbilical vein endothelial cells (HUVECs). By exposing the modified hydrogels to 405 nm light, the formation of new vessel structures at the illuminated sites of the 3D culture was promoted, achieving spatial control of the angiogenic process. Spatiotemporal control of sprouting directionality can also be accomplished without growth factors. In reference [154], Fedele *et al.* employed an azopolymer photopatterning approach for real-time presentation of topographical cues to HUVECs spheroids. The authors used pDR1m, an azopolymer capable of controlling the material surface profile by a light-induced mass migration, and a confocal microscope to deliver topographical signals during early-stage angiogenesis. The *in-situ* photo-inscribed pattern was able to guide cell migration, with the spheroid's cores acquiring a polarized shape and the sprouts following the topographical cues.

The immune system plays a crucial role in controlling wound healing and guiding tissue regeneration [155]. Inflammatory processes may lead to scar formation, fibrosis and structural changes hampering tissue healing and compromising its functionality. Thus, immunomodulatory therapies may prevent tissue/organ damage and induce a pro-

regenerative environment to enhance regeneration [129,156]. In that regard, Kang *et al.* designed a photoresponsive nanocarrier for controlling intracellular calcium levels and, therefore, modulate macrophage polarization towards an activated pro-inflammatory (M1) or anti-inflammatory and pro-healing (M2) phenotype [157]. NIR light has more tissue penetration and presents minimal cytotoxicity in comparison to UV light. The UCNP were coated with a mesoporous silica shell and were loaded with calcium regulators, *i.e.*, calcium supplier or chelator. The nanocarrier was further chemically modified with a gating structure to gain control over the release of calcium regulators. This was achieved by a serial coupling of a photocleavable 4-(hydroxymethyl)-3-nitrobenzoic acid linker and RGD peptide-bearing molecular cap via cyclodextrin-adamantine host-guest complexation. Moreover, RGD peptide enhances cellular uptake of the nanocarriers through binding to integrin receptors of the cells. Under NIR light excitation, the upconverted light emission from the UCNP triggered the cleavage of the cap, enabling the on-demand release of calcium regulators. Even when the NIR light was applied through an intervening layer of porcine skin tissue, an elevation or depletion of intracellular calcium ions was induced, promoting a M1 or M2 polarization of macrophages, respectively. It is worth noting that the same group reported the use of a similar photoresponsive nanocarrier system for controlling stem cell differentiation *in vivo* via remote control of intracellular calcium, an strategy that could accelerate stem cell-based regenerative therapies [158]. Dynamic control of macrophage polarization *in vivo* could help the treatment of inflammatory diseases and aid tissue regeneration. Macrophage immunomodulation can be also achieved by means of smart biomaterials and controlling cell-ECM interactions. To this end, Wang *et al.* developed a photoresponsive nanocomposite HA hydrogel with tunable cell adhesion sites [150]. Adhesive peptide RGD were loaded into photodegradative alkoxyphenacyl-based polycarbonate nanocarriers (Fig. 5e). HA was functionalized with acrylate groups to act as binding sites for RGD peptides through a Michael addition between acrylate and cysteine thiol groups. Moreover, HA polymer chains were modified with a cysteine-contained biodegradable matrix metalloproteinase (MMP) crosslinker peptide for encapsulating murine macrophages. The authors showed that upon pulsed UV light exposure, RGD release and conjugation to the HA hydrogel allowed real-time activation of macrophages via $\alpha_v\beta_3$ integrins, which enhanced anti-inflammatory M2 polarization (Fig. 5f). In a different approach, Zheng *et al.* designed a photoresponsive hybrid biomaterial which dynamic surface topography for macrophage phenotype modulation [159]. The authors combined two- and four-branched polycaprolactone macromonomers with PEG-modified gold nanorods, casted them into a patterned mold and UV-cured them in the presence of a photoinitiator. The obtained microgrooved film was then compressed at high temperature with a flat mold and subsequently cooled to obtain a flat film. The obtained shape memory film rapidly recovers the original microgrooved shape under NIR irradiation. The dynamic surface topography can induce the elongation of bone marrow-derived macrophages adhered on the surface, which produces a phenotypic shift from pro-inflammatory (nitric oxide synthase positive, low interleukin-10) to anti-inflammatory, pro-healing (arginase-1 positive, high interleukin-10) [160]. The NIR-triggered dynamic surface topography also modulated macrophage phenotype in an *in vivo* rat subcutaneous implantation model. The use of photoresponsive immunomodulatory biomaterials may lead to optimization of healing outcomes.

3.2. Shape memory implants and tissue bonding

The ability of shape memory polymers (SMP) to change between a permanent and a temporary shape under certain conditions is promising in biomedical fields, such as tissue engineering and intravascular stents [161,162]. Different kind of stimulus such as temperature, light, solvents, ultrasound, electromagnetic fields, etc., can trigger the transition. Among photoresponsive SMP, two different groups can be considered [163]. The 'true' photoresponsive SMP which are based on reversible photochemical crosslinking or photoisomerizable chemical groups, and those SMP that take advantage of photothermal fillers and the heat generated by a light source to trigger a thermoresponsive polymer. Design and development of the first group of polymers is challenging but desired for biomedical applications in which a temperature change is not feasible. The photo-induced dimerization and cleavage at longer and shorter wavelengths, respectively, of cinnamoyl and anthracene functionalities has been used for developing photoresponsive SMP [164,165]. For instance, in reference Xie *et al.* developed a light induced shape-memory composite based on poly(L-lactide) (PLA) – PEG copolymer and anthracene groups selectively functionalizing the PEG soft segment [165]. Photoreversible cycloaddition of anthracene groups when illuminated with 365 nm UV light allowed for fixation of a temporary shape generated by an external force and further illumination with 254 nm UV light caused shape recovery due to crosslink cleavage (Fig. 6a). In a different approach, Zhang *et al.* made use of the photoswitchable glass transition temperature of an azobenzene-containing polymer network for developing a light-triggered athermal shape memory effect [166]. Sequential exposure to UV and visible-light illumination leads to glass transition temperatures below or above room temperature, inducing transition between permanent to temporary shapes (Fig. 6b). On the other hand, shape memory composites have been reported using photothermal fillers. In reference [167], Xie *et al.* added the natural and biocompatible photothermal substance melanin to polyurethane to obtain a NIR photoresponsive shape memory implant. Polyurethane owns its shape memory behavior to its two segments composition: a hard segment that determines the permanent shape and a soft segment that fixes the temporary shape below the shape memory transition temperature. The melanin/polyurethane composite presented no toxicity *in vitro* towards hMSCs and mouse fibroblast (L929) cells lines and *in vivo* in implanted mice. Moreover, a melanin/polyurethane column implanted in the vagina or back subcutis of mice rapidly recovered to its original state within 60 s under a very low NIR laser (Fig. 6c-e). Development of biodegradable SPM composites is crucial for reducing material time inside the body and deleterious effects. Piperazine-based polyurethane presents both thermoresponsivity and degradability. In reference [168], the authors incorporated NIR photothermal black-phosphorus sheets to piperazine-based polyurethane to obtain a SPM with controllable degradation. The composite presented no toxicity *in vitro* and *in vivo*, excellent *in vivo* shape memory capacity, and degrades naturally into non-toxic phosphate and carbon dioxide/water. In order to enhance tissue regeneration, Yang *et al.* combined cuprorivaite nanosheets into SMP poly (D, L-lactide-co-trimethylene carbonate) [169]. The resulting composites were biodegradable and presented excellent shape memory activity upon NIR irradiation. Sustained release of Cu^{2+} and SiO_4^{4-} ions stimulated the proliferation, migration, and tube formation of HUVECs *in vitro*. Moreover, the composite was tested as an 'smart' suture, NIR laser triggered self-knot in mice incisions and exhibited enhanced wound healing and angiogenesis *in vivo* in comparison to controls.

Sutures are often needed for wound closure and for the attachment of the increasing number of medical devices that are being implanted in the human body. However, due to drawbacks such as needle trauma, the requirement of skilled surgeons and unsuitability for certain tissues, such as eye or lung, there is an increasing need of new sutureless methods development [171]. In that vein, photochemical tissue bonding (PTB), *i.e.* the use of photosensitizing substances and light to crosslink proteins on tissue surfaces and form bonds, is receiving increasing attention. PTB can be simply applied by adding a photosensitizer such as rose Bengal and green light, as has been presented by Yao *et al.* in rat tendon injuries [172]. However, different materials are being developed to fill the wounds and enhance their healing, improve tissue bonding mechanical strength or change illumination parameters. In reference [173] the authors modified collagen, the most abundant protein in skin dermal ECM, with methacrylate moieties. The methacrylated collagen was combined with photosensitizer rose Bengal to obtain a light-activated biomimetic material for tissue sutureless bonding. Under green-light exposure, the activation and crosslinking of methacrylate moieties mediated by rose Bengal excited states leads to hydrogel assembly. By further incorporation of poly-L-lysine (PLL) to the mixture, reduced degradation rate and improved mechanical properties of the resulting bonded tissues was achieved. The performance of the photoactivable formulation was evaluated using an *in vivo* murine skin wound model. Traditional sutures were used as control. While the sutured wounds showed signs of inflammation, wounds treated with the tissue photobinding formulation showed a close resemble to non-wounded skin. As animal and recombinant proteins are difficult and expensive to isolate/produce, the use of synthetically prepared peptides is appealing as they can be prepared under stringent conditions in a cost-effective manner, they are easy to modify in comparison to full-length proteins and present decreased risks of xenogeneic response. In this vein, McTiernan *et al.* reported the obtention of adhesive hydrogels by light-triggered self-assembly of collagen-like peptides to acrylate functionalized PEG, with rose Bengal as visible light photoinitiator and PLL as electron donor. [174] By modifying the components concentration and irradiation times the mechanical properties of the obtained gels could be matched to different tissues. Moreover, *in vivo* experiments showed that the photocrosslinked collagen-biomimetic matrices were better at supporting epithelial growth and wound healing than conventional wound suture. PTB techniques can be combined with different strategies to promote tissue regeneration or achieve a certain functionality. In reference [175] Ruprai *et al.* developed biocompatible, biodegradable, photoactivated porous chitosan films able to support bone marrow derived hMSCs viability and multipotency. To mimic the porous structure of the natural ECM that allows cell and nutrients exchange, porous chitosan-based adhesive was obtained by freeze-drying. Furthermore, its degradability was tuned by making a blend of medium molecular weight and water-soluble low molecular weight chitosan. Rose Bengal was used as a photosensitizer. Tissue bonding of the film on sheep small intestine tissue *ex vitro* was achieved by green light illumination. The tissue bonding strength of the porous and erodible chitosan-based adhesive films could be further improved by incorporating L-3,4-dihydroxyphenylalanine (L-DOPA), a natural catechol [176]. PTB can be combined with soft bioelectronics for different bioapplications such as patches for damaged myocardium. In reference [177] Hoang *et al.* used laser ablation to introduce pores of different sizes and distances on chitosan films containing rose Bengal. The

film surface was further functionalized with conjugated polymer polyaniline. Both the conductivity and the mechanical properties of the obtained film varied as a function of porosity. The patches retained electronic properties under cyclic stretching mimicking the heart contraction cycles. The porous patch incorporated in chitosan adhesives containing rose Bengal could be bonded to samples of tissue cut from sheep small intestine by illumination with green light. To overcome the finite tissue penetration of green light, Han *et al.* developed a poly(allylamine)-modified UCNPs/Hyaluronate-rose Bengal conjugate complex for transdermal delivery and noninvasive PTB of deep tissue upon NIR light illumination [170]. HA was used as a transdermal delivery carrier due to its hygroscopic behavior that can hydrate skin and for the HA receptors expressed in skin tissues. Thus, conjugate complex could be delivered into a deep and wide area from the boundary of the wound (Fig. 6f). UCNPs were functionalized with poly(allylamine) to provide hydrophilicity and positive charge. Then, they were complexed with negatively charged HA-rose Bengal conjugate by electrostatic interactions. Upon noninvasive NIR light illumination, activation of rose Bengal induced collagen cross-linking and accelerated sutureless skin tissue bonding both *ex vivo* and *in vivo*, achieving higher tensile strengths than the sutured tissues (Fig. 6g and 6 h).

A brief summary of strategies for tissue engineering and wound healing reviewed in this section is presented in Table 4.

4. Photoresponsive soft materials for the delivery of therapeutics

The controlled delivery of therapeutics to a targeted site using nanotechnologies has received great attention in the past decades as an alternative that can enhance the therapeutics' efficacy and reduce nonspecific toxicity [178,179]. Stimuli-responsive therapeutic delivery systems that can be manipulated externally are highly desired. Light as external stimulus offers precise spatiotemporal control, it is relative safe, and it has minimal interaction with biological tissues [180,181]. Thus, photoresponsive materials have been extensively investigated to enable site-specific therapeutic release that is precisely controlled by light irradiation. Among the photoresponsive materials, polymeric and soft materials have gain attention for their tailorable chemical and physical properties [178]. Different approaches employing photoresponsive polymeric and soft materials for the delivery of drugs, genes, nanoparticles and other biologicals will be discussed in the following subsections.

4.1. Drug delivery

Different external stimuli approaches have been proposed to achieve control over the delivery of drugs such as magnetic, electric, pH, ultrasound, and light stimulation [182]. Light as external stimulus can trigger photoreactions with either the drug vehicle or the drug, as well as trigger photo-radiative phenomena (*i. e.*, photothermal or photoemissions) with light-responsive chemical structures [183,184]. A wide variety of polymeric and soft photoresponsive vehicles have been reported on literature, including nanoparticles, nanogels, micelles, nanofibers, etc. [178]. These photoresponsive systems often rely on different light-switch mechanisms to control drug release such as is photolysis triggered by oxidative stress [185-187], polyelectrolytes protonation/deprotonation in

acidic cellular environments [188-190], cleavage of disulfide linkers under reductive conditions [191-193], reduction of hypoxia-responsive moieties,[194,195] thermodynamic conformational changes, upconversion of light, etc. The field of light-triggered drug release using soft materials has been widely investigated, reported and reviewed. Thus, here we will only comment some of the most recent and relevant studies. For instance, Ghani *et al.* developed a reversible photoresponsive membrane for controlled drug delivery using the SP-MC switch [196]. The photo-responsive interpenetrating polymer network was demonstrated for the UV-light triggered release of dopamine, L-DOPA and prednisone, allowing to control the release of ~ 90–95 % of the payload. An image-guided drug delivery strategy for chemotherapy was designed by Wang *et al.* [197] Here, a photoresponsive membrane composed of poly (ethylene oxide)-*b*-poly(spiropyran) (PEO-*b*-PSPA) diblock copolymer was synthesized. The membrane switched its permeability upon UV and green light irradiation allowing the on-demand release of doxorubicin. Banerjee *et al.* developed a magnetic and photoresponsive drug delivery system based on functionalized electrospun nanofibers loaded with super-paramagnetic iron oxide nanoparticles [198]. The heat generated from the Nel relaxation effect of magnetic nanoparticles under applied magnetic fields and the laser illumination lead to conformational changes on the thermoresponsive polymer fibers, and consequently the release of therapeutics. A strategy for photoresponsive self-assembly nanocarriers was reported by Cheng *et al.* The carrier was composed by uracil end-capped PEG and the nucleobase adenine derivative methyl 3-(6-amino-9H-purin-9-yl) propanoate as a model drug. Upon light exposure, the polymeric micelles are disrupted and rapidly release the cargo [199]. Although less common due to challenging synthesis methods, photoresponsive nanocages have been also explored in controlled drug delivery. For instance, Huo *et al.* prepared polymersomes composed of amphiphilic block copolymers of poly (o-nitrobenzyl acrylate) and poly (*N,N*-dimethylacrylamide). Exposure to light irradiation at 365 nm triggered the photocleavage of o-nitrobenzyl groups, which resulted in dissociation of the polymersomes with simultaneous co-release of hydrophilic and hydrophobic cargoes [200]. Another example of photoresponsive nanocarriers are those based on donor-acceptor molecules. Enthilkumar *et al.*, developed a system consisting in photoresponsive conjugated polymer nanoparticles functionalized with donor–acceptor Stenhouse adduct (DASA) and folic acid units for controlled drug delivery and imaging. Upon visible light ($\lambda = 550$ nm) irradiation the delivery of both hydrophilic and hydrophobic drugs was triggered [201]. Gupta *et al.* reported a photodegradable polymeric nanoparticle system composed of an amphiphilic methoxy PEG-*b*-poly(*e*-caprolactone)–*co*-poly(azido-*e*-caprolactone-*g*-ortho nitrobenzyl retinoic ester) copolymer [202]. In this system retinoic acid was covalently grafted on the surface of the polymeric micelles through a photosensitive o-nitrobenzyl linker to investigate cardiac differentiation. The gradual light-triggered release of retinoic acid allowed a concurrent gradient-like pattern for cardiac differentiation.

Specific targeting of cells remains challenge in the design of drug delivery carriers. A useful approach to overcome the unspecificity of drugs is to modify drug carries with molecular messengers that allow for biorecognition. One of the most exploited specific ligands for cancer targeting is folic acid. In this context, Zhou *et al.* designed photoresponsive polymersomes electrostatically decorated with folic acid for doxorubicin release. The system

showed high cytotoxicity against HeLa cells [203]. Similarly, Gosh *et al.* designed a doxorubicin -controlled release system employing an amine-PEG wrapped on tetra carboxy zinc phthalocyanine metal–organic framework (ZIF-8) decorated with folic acid. This system showed increased cells death in LNCaP line [204]. Moreover, Yu *et al.* fabricated glutathione-responsive amphiphiles for specific tumor targeting and imaging-guided chemophotothermal combination therapy [205]. He *et al.* synthesized biomimetic polymersomes based on the self-assembling of amphiphilic diblock copolymers encapsulating the hypoxia-activated prodrug AQ4N and UCNPs for combined hypoxia therapy [206]. Biswass *et al.* reported the light-triggered dual anti-cancer drug delivery from a triblock co-polymer. Chlorambucil was conjugated to the polymer via 3-(3-(hydroxymethyl)-4-nitrophenoxy) propyl acrylate. The polymer prodrug formed spherical micellar nanoparticles that encapsulated a second drug (doxorubicin) in their hydrophobic core. Under UV irradiation both drugs were released [207].

One of the most popular soft nanocarriers for drug delivery are liposomes. Due to their easy fabrication, size control, cargo loading versatility and biocompatibility, liposomes represent a great option for photoresponsive drug delivery. For instance, Zheng *et al.* utilized the phospholipid 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine to fabricate thermosensitive liposomes loaded with the photosensitizer zinc phthalocyanine substituted by tetra-ethylene glycol for molecular imaging, chemo, photodynamic and photothermal therapy. *In vivo* experiments demonstrated that the doxorubicin loaded liposomes accumulated in the tumor, enhancing deleterious cancer effects and diminishing liver adsorption [208]. Along the same lines Shi *et al.*, introduced photo-activated nanoliposomes for light-controlled chemotherapy with doxorubicin [209]. Ilhami *et al.* also encapsulated doxorubicin and the pro-photosensitizer 5-aminolevulinic acid within adenine-functionalized supramolecular micelles to achieve effective photo-chemotherapy [210]. Multiresponsive drug delivery systems have been explored to enhance chemotherapy. In that vein, Bai *et al.* developed self-assembled supramolecular prodrug complexes with β -cyclodextrin–acylhydrazone–doxorubicin and the targeting of azobenzene-terminated poly[2-(dimethylamino) ethyl methacrylate] as a building block. The system displayed dual responsive behavior upon UV-light irradiation and pH changes [211]. Likewise Chen *et al.* reported a photo, pH, and redox responsive nanogel of poly(acrylic acid-*co*-spiropyran methacrylate) crosslinked by disulfide-containing *N,N*-bis(acryloyl)cystamine loaded with doxorubicin [212]. Liu *et al.* also demonstrated the suitability of a photo and pH-triggered liposome system for doxorubicin delivery [213].

Combination therapies with light-triggered drug release using soft materials is often targeted for synergistic therapeutic effects. Batta *et al.* reported chitosan-tripolyphosphate nanoparticles decorated with chlorin e6 and encapsulating doxorubicin [214]. The nanoformulation was prepared by ionotropic gelation and had significant anti-proliferative activity against MCF-7 breast cancer cells after NIR irradiation. A sequential strategy was successfully designed by He *et al.*, which consisted in a biodegradable backbone containing a photosensitizer ruthenium complex and the anti-cancer drug paclitaxel. Upon red light irradiation, the ruthenium complex is cleaved producing singlet oxygen molecules that triggered paclitaxel release (Fig. 7b).[215] The combined chemo-photodynamic therapy presented enhanced *in vivo* antitumor efficacy in 4T1 tumor-bearing mice (Fig. 7c). A

great advance was reported by Xu *et al.*, where they bioengineered living neutrophils as a novel type of “photoactive neutrophil”. The neutrophil system was loaded with the nanocomplex retinoic acid/chlorin e6. The irradiated neutrophils released the nanocomplex and after bypassing the tumor barrier, retinoic acid induced mitochondrial membrane disruption in combination with photodynamic therapy. The designed photoactive neutrophil produced tumor reduction without severe side effects [216]. Xu *et al.* developed a 3D pyramid-shaped RNA nanocage for light-controlled drug release using paclitaxel as a model drug. The RNA nanocage disintegration was achieved by introducing photocleavable spacers along the RNA chain. Exposure to UV-light triggered paclitaxel release showing high cytotoxicity against breast cancer cells [217]. In the same vein, Yang *et al.* used a nucleic acid to fabricate a new DNA aptamer-grafted photoresponsive hyperbranched polymer. The polymer self-assembled into nanoparticles. UV-light irradiation of the system allowed drug release due to nanoparticle disaggregation. The doxorubicin loaded DNA aptamer nanoparticles exhibited selective photo-triggered cytotoxicity towards cancer cells [218]. Guo *et al.* fabricated a multi-responsive PEG-based block copolymer through Cu(I)-catalyzed azide–alkyne cycloaddition click polymerization. Nile red was encapsulated as a model drug to study drug release in different environments. The system showed a photo, oxidative, and reductive response due to the o-nitrobenzyl groups, peroxalate ester bonds, disulfide bonds, and triazole units, which triggered the stimuli-specific responses [219]. Rafique *et al.* investigated a soft system coloaded with doxorubicin and chlorin e6 onto mesoporous-silica-coated UCNPs for antitumor combination therapy. On-demand controlled release was switched under NIR irradiation and the dual light-triggered release in a synergistic therapeutic effect that enhanced cell death [220]. Fan *et al.* developed a promising photoresponsive and degradable hollow mesoporous organosilica nanocarrier. The organosilica was bonded to organoalkoxysilanes and wrapped with graphene oxide quantum dots. Light irradiation leads to organosilica nanoparticles degradation, resulting in enhanced local doxorubicin release *in vivo* [221]. One more example of photoresponsive mesoporous silica drug delivery system was showed by Beová *et al.*, where p-coumaric acid derivatives were used as photo-switchable ligands for the delivery of the non-steroidal anti-inflammatory drug naproxen [222]. Another coumarin derivative light-triggered drug delivery system was proposed by Liu *et al.* This system consisted in a coumarin derivative hydrogelator which photocleavage at the C—N bond in 7-amino coumarin upon 365 nm light irradiation [223].

Hydrogels have been also used as drug carriers for phototriggered release. An approach for photoresponsive microneedle arrays was proposed by Amer *et al.* The system consist in the modification of the microneedle implant adherence upon light irradiation [225]. The microneedle arrays were fabricated with a photoresponsive polyvinyl alcohol and SP-conjugated *N*-isopropylacrylamide hydrogel. By phototriggering the deswelling of the microneedles, a significant decrease in extraction force was observed. In the same vein, Li *et al.* reported phototriggered implantable polymeric microneedles for transdermal analgesia delivery [226]. The system consisted in iron oxide nanoparticles coated with polydopamine, polyvinylpyrrolidone and polycaprolactone. The microneedles were loaded with lidocaine hydrochloride and administrated into porcine skin. NIR irradiation penetrated the skin and enhanced lidocaine hydrochloride release from the microneedles. Another photoresponsive

design was reported by Rastogi *et al.*, in which a hydrogel was prepared by the crosslinking of di-NHS ester of azo-benzoic acid with four-armed amine-terminated PEG. The hydrogel was loaded with the fluorescent dye Alexa Fluor 750 and its release was triggered by UV-light exposure. UV-light induced photoisomerization and the reduction of the hydrogel size as consequence. Hydrogel size reduction may be a result of the inherently smaller footprint of the *cis* azobenzene conformation, as well as dipole–dipole interactions between the polar *cis* azobenzene and the polymer network (Fig. 7a) [224].

4.2. Gene delivery

Gene therapy relies on the modification of the genome by delivering recombinant nucleic acids (DNA or RNA) that add, replace, or remove specific genetic sequences. Despite the recent advances in gene engineering, the safe and specific delivery of genes into targeted cells remains a challenge. Several approaches for the non-viral delivery of genes have been investigated, including the use of stimuli responsive materials as they provide options for on-demand gene release, targeting, and non-harmful immune or genotoxic off-target side effects, etc. [227].

In regard to photoresponsive gene delivery, Dang *et al.* designed gold nanoshells conjugated to methoxy-PEG-thiol and microRNA-34a, a tumor suppressor for triple-negative breast cancer that is degraded by nucleases and cannot passively enter cells [228]. The light-responsive nanocarrier enhanced the microRNA-34a stability and on-demand release following irradiation, resulting in a decrease on breast cancer cells viability, proliferation and migration. Lin *et al.* designed photoresponsive hollow silica nanoparticles loaded with chlorin e6 and a plasmid encoding caspase-8 gene attached to a polymer. Upon light irradiation at 405 nm, the system released the gene and generated ROS which showed antitumor effects both *in vitro* and *in vivo* [229]. A photo-responsive cationic block copolymer has shown potential in the development of robust approaches for gene therapy and regenerative medicine. The versatile system disassembles upon light irradiation facilitating the intracellular release of small interfering RNA (siRNA), messenger RNA, and proteins [230]. In this line, Greco *et al.* employed mPEG-*b*-poly(5-(3-(amino) propoxy)-2-nitrobenzyl methacrylate) polymers complexed with siRNA for photo-switching release. The nanocarrier exhibited good spatiotemporal control over cell-to-cell gene expression and low off-target effects [231]. Duan *et al.* reported the development of photodegradable, highly branched poly (β -amino ester) nanoparticles with strong nucleic acid binding capacity for DNA and siRNA delivery. The nanocarrier showed higher transfection efficiencies in multiple mammalian cells, and lower cytotoxicity compared to commercial available PEI 25 k and Lipofectamine 2000 reagents [232]. Vascular endothelial growth factor (VEGF) is the chief regulator in neovascular lesions. Li *et al.* proposed a strategy for the sequential light-triggered gene delivery of a CRISPR/dCas9 system. Poly(caprolactone)-PEG nanoparticles were loaded with a sgRNA that targeted the VEGF gene, and with arabidopsis flavoprotein cryptochrome 2-cib1 plasmids conjugated to CRISPR/dCas9. Upon light exposure the cib1 side of the plasmid fuses with CRISPR/dCas9, while the cryptochrome 2 side fuses with the histone of the sgRNA target. The linked plasmid construct acts on the VEGF gene triggering its transcriptional inhibition. Enhanced therapeutic efficiency was shown when the CRISPR nanosystem was designed as photoresponsive [233].

Often, photoresponsive gene delivery systems have been coupled to photothermal and/or photodynamic therapy to enhance therapeutic outcomes. Wang *et al.* developed a biomimetic gene delivery strategy to treat glioblastoma tumors. The team designed a lipoprotein-based system by fusing the tumor-penetrating lipoprotein tLyP-1 to the apolipoprotein A-I-mimicking peptide. Indocyanine green was encapsulated and the siRNA target HIF-1 α was anchored on the surface for targeting. The tLyP-1 facilitated blood brain barrier permeability, HIF-1 α siRNA induced hypoxia into the tumor, and indocyanine green acted as the photo-triggered molecule to release siRNA and produce ROS and local hyperthermia. The smart multi-stimuli nanocarrier was demonstrated as brain-cancer therapy [234]. Zhang *et al.* fabricated photosensitive nanocapsules comprised of core-shell UCNPs coated with a mesoporous silica layer and PEG was grafted using a photo-cleavable linker. The silica coating was loaded with the photosensitizer hypocrellin and a siRNA against polo-like kinase 1. Upon light exposure, PEG-siRNA was released and ROS were generated. Through this approach gene silencing efficiency was enhanced and cell proliferation was suppressed *in vitro* and *in vivo* [235]. Wu *et al.* reported poly (lactic-co-glycolic acid) nanoparticles surface modified with a disulfide-containing alkyl modified polyethylenimine. Doxorubicin was encapsulated through an o-nitrobenzyl ester linker, and siRNA of P-gp protein encapsulated onto the cationic polymeric shell. The polymer coating on the surface displayed reductive and photoresponsive behaviors. P-gp siRNA is released by enrichment of the reducing agent glutathione, and doxorubicin is released upon light exposure, demonstrating the sequential reduction/photo-triggered gene and chemotherapy strategy [236]. Lin *et al.* synthesized a photo-sensitive metal organic framework (MOF) for siRNA release accompanied by MOFs dissociation into protonatable 2-methylimidazole and osmotic rupturing Zn²⁺ ions. The release of siRNA and the dissociation products cooperatively contributed to endo/lysosomal rupture (~ 90 % efficiency). Photosensitive MOFs exhibited high control on siRNA [237]. DNAzyme is often used for gene silencing. To improve its efficiency Gong *et al.* proposed a nanocarrier to encapsulate DNAzyme and together with MnO₂ and indocyanine green. Upon light exposure DNAzyme is released and simultaneously MnO₂ is decomposed into Mn²⁺ ions, which supplemented with O₂ generation to enhance DNAzyme activity [238]. To overcome the challenges associated with light penetration into tissues and tumors, this being wavelengths ranging from the UV to NIR I region, novel material systems responsive to NIR II have been proposed [239-241]. Such photoresponsive materials include soft materials such as semiconducting polymers [242,243], or molybdenum polyoxometalate [244,245], and the combination of soft materials with D-A conjugated small molecular dyes [246], copper-based materials [247,248], or gold nanostructures [249,250], to name a few. In this vein, Lin *et al.* proposed a photothermal gene delivery system based on poly[2(dimethylamino) ethyl methacrylate] – copper sulfide – silicon dioxide nanoparticles loaded with a plasmid encoding IL-12 gene. This hybrid nanoformulation was demonstrated for simultaneous photothermal and immunotherapy *in vitro* and *in vivo* [251]. Moreover, photoresponsive systems for viral gene delivery have been also investigated. Wang *et al.* reported an unnatural azido-amino acid aided caging–uncaging strategy to control the transduction capability of a lentiviral vector *in vitro* and *in vivo* [252]. Horner *et al.* engineered a similar approach, using an adenoviral vector photoresponsive to red light [253].

4.3. Nanoparticle and biomacromolecules delivery

In the recent years, the FDA has been approving novel therapies that involve the use of biological macromolecules as therapeutic agents to treat different types of cancers, degenerative or inherited diseases. Some of those biomacromolecules are cytokines, antibodies, pro-apoptotic proteins, growth factors, and ribosomes [254-257]. Novel approaches for the delivery of biomacromolecules are focused on developing formulations highly stable, with good drug availability, and with targeting and on demand release capabilities. Additionally, non-biological nanoparticles made of polymers, metals, semiconductors, composites, and other materials, have shown effectiveness not only as carriers but as therapeutic agents themselves. Some drawbacks of the use of nanoparticles as therapeutic agents include the poor membrane permeability, cytotoxicity, and solubility in biological systems [258]. In this section we will summarize recent advances in photosensitive soft materials for the delivery of large therapeutics such as is the case of nanoparticles and biomacromolecules. For instance, Ballesteros *et al.* developed a system composed by a photoresponsive nanogel containing silver nanoparticles immobilized on the surface of electrospun polycaprolactone nanofibers mats. Silver nanoparticles are released when the nanofiber is irradiated with UV-light. Silver nanoparticles generate antibacterial activity against *S. aureus* and *E. coli* [259]. On the same line, a photoresponsive nanogel was fabricated based on aniline- and chitosan-containing silver nanoparticles with antibacterial properties to increase *E. coli* death [260]. Among the different light-responsive materials, conjugated polymers are emerging candidates with successful application in gene therapy. In this vein, Wang *et al.* reported photoresponsive conjugated polymer nanoparticles for remote control of gene expression. Upon irradiation the conjugated polymer dissipate heat, which serves as activation trigger for protein-70 promoter which begins transcription of downstream EGFP gene in the living cells [261].

In the case of biomacromolecule release Wang *et al.* synthesized protein-based photo-responsive hydrogels by covalently polymerizing the photoreceptor C-terminal adenosylcobalamin binding domain proteins using the genetically encoded SpyTagSpy-Catcher chemistry. The system was used for the release of bulky globular proteins, such as mCherry [262]. Song *et al.* designed a UV-light photoresponsive polypeptide-glycosylated poly(amidoamine) dendron amphiphiles for ovalbumin release. The polymersome was also pH sensitive self-assembling at pH 7.4 and disassembling at pH 5 [263]. Wang *et al.* designed nanoparticles for local light-triggered penetrating peptide release for choroidal neovascularization inhibition. After intravenous injection in mice and ocular light-irradiation, the nanosystem accumulated in the neovascular lesions [264]. In the same line, Peng *et al.* constructed a nanosystem with active tumor-targeting, enhanced penetration, and photoresponsive drug release behavior. The system encapsulated and delivered the programmed cell death-ligand 1 to enhance tumor immunotherapy. Tumor growth was inhibited by 97.5 % in the first 24, and total inhibition was achieved by the combinatorial release of a photosensitizer (IR820) for photothermal therapy [265]. Fujimoto *et al.* demonstrated the aggregation of liposomes using ultrafast DNA photocrosslinking with 3-cyanovinylcarbazole nucleoside. This technology has potential for biomacromolecules release [266]. Dai *et al.* reported a photoresponsive hydrogel by integrating 4arm-PEG and azobenzene into cellulose nanofibrils for the controlled release of bovine serum albumin.

Protein release in this system was reported to be 5-fold higher under UV light irradiation [267]. Yang *et al.* fabricated an enzyme and photoresponsive nanogel system through UV-light chemical cross-linking of cinnamyloxy groups with PEGylated HA. The CD44-targeted nanogels exhibited higher killing efficiency in CD44-positive A549 cells than to CD44-negative HepG2 cells [268]. Lim *et al.* engineered a nanosystem loaded with chlorin e6-conjugated di-block PEG-PLL copolymer and membrane disruptive D-(KLAKLAK)₂ peptide for photoresponsive combinational chemotherapy [269]. Kozaki *et al.* proposed a screening system for intracellular functional peptides. It combined a photocleavable peptide array system with cell-penetrating peptides (CPPs). A high capacity to induce cell death by the modified peptides was found [270]. Dong *et al.* fabricated nanoparticles based on the PA-C1b peptide labeled with sulfo-cyanine7 and loaded into mesoporous silica nanoparticles wrapped by graphene oxide and conjugated to folic acid. The light-mediated peptide release was tested for cancer therapy and for antimicrobial treatment [271]. Wan *et al.* developed a nucleus-targeting self-assembled nanoparticle system built on IR780 conjugated with TAT peptide and loaded with doxorubicin. The system showed both improved cellular internalization and enhanced photodynamic and photothermal efficacy. In a mice bearing breast cancer model, intratumoral injection of the nanoparticles with local laser irradiation achieved synergistic effects for breast tumor ablation and recurrence [263]. Designed a hybrid microparticles consisting of silk fibroin, gelatin, agarose, and NIR-responsive black phosphorus quantum dots were loaded with growth factors and antibacterial peptides. Upon NIR-irradiation the microparticles released in a controlled manner the growth factors and promoted neovascularization in *in vitro* and *in vivo* wound healing models [272]. Finally, cells can be also considered as particulate biomacromolecules. In that vein, Narayan *et al.* demonstrated the synthesis of genetically engineered Silk-Elastin-Like Protein photo-responsive hydrogels for the encapsulation and release of L929 murine fibroblasts from 3D cultures [273].

4.4. Photodynamic, photothermal and other light-based therapies

In previous sections we have introduced photodynamic therapy (PDT) and photothermal therapy (PTT) as synergistic approaches to aid photosensitive soft materials in the manipulation of cell functions, the regeneration of tissues, and the delivery of therapeutics. In most of the previously discussed combinatorial strategies, inorganic nanoparticles or molecules have been integrated into the soft systems to allow their combination with PDT and/or PTT. This section will be dedicated to review the scarce but highly relevant research done in the development of soft materials for PDT, PTT, and other light-based therapies.

PDT requires three basic components: a photosensitizer, light, and oxygen. These components are non-cytotoxic individually but when combined react to produce highly cytotoxic products, such as ROS, singlet oxygen or triplet oxygen [274]. Such cytotoxic products lead to cell apoptosis or necrosis, and to inflammatory responses that trigger the immunological activation of specialized cells [274]. For instance, Sánchez-Ramírez *et al.* synthesized poly (lactic-*co*-glycolic) nanoparticles loaded with carboplatin and indocyanine green. These nanoparticles were used against the ovarian cancer cell line SKOV-3, founding an enhanced cytotoxic effect upon light irradiation [275]. Pan *et al.* synthesized NH₂-terminated diethylene glycol ligands tethered to *cis*-silicon phthalocyanine

for the self-assembly of monodisperse nanospheres. These nanospheres exhibited enhanced red-shifted absorption and emission in the NIR range (750–850 nm), which resulted in an enhanced tumor inhibition effect against *in vitro* and *in vivo* models using A549 cells [276]. Liang *et al.* developed an oxygen self-supplemented PDT nanocarrier based on the ultrasonic dispersion of perfluorooctyl bromide liquid into porphyrin grafted lipid nanoparticles. Both *in vitro* and *in vivo* results demonstrated that the obtained lipid-based nanosystem could act as a prominent oxygen reservoir and effectively replenish oxygen into the hypoxic tumors with no need for external stimulation, and dramatically inhibited tumor growth and liver metastasis in an HT-29 colon cancer mouse model [277]. Similar to all medical treatments and therapies, PDT has its own limitations. Short lifetime and diffusion distance of ROS may weaken PDT efficiency [278]. Targeting mitochondria, which in tumor cells are particularly sensitive to redox reactions, may help overcome this limitation and increase tumor killing ability. For PDT to be effective, it is necessary to administer a relatively high dose of photosensitizer. Targeting strategies and physical forces (e.g., electric or magnetic field) can be used to increase drug accumulation in the tumor tissue, decreasing the necessary dose of photosensitizer. [279]. As patients undergoing PDT have to avoid direct sunlight until the drug is eliminated from the body to prevent skin and ocular lesions, developing activatable photosensitizer would be very beneficial. Photosensitizer quenching may hamper their performance, thus preventing their aggregation by dispersing them in functional materials is a viable option for enhancing PDT efficacy [278]. As photosensitizer accumulation in tumor cells may be hindered in some situations, electroporation can be used to increase the intracellular concentration of drug. The efficacy of PDT depends on the oxygen concentration and solid tumors tend to present hypoxic microenvironments [279]. To overcome this limitation, several strategies are being studied such as carrying oxygen to the tumor site or catalyzing hydrogen peroxide inside tumor tissue to generate oxygen.

On the other hand, PTT is based on the hyperthermia effect of certain materials when exposed to specific light wavelengths [280-285]. Although there is a wide variety of photosensitive materials investigated in PTT, here we focus on the soft materials. For example, Ko *et al.* developed a photoresponsive self-gelling hydrogel formed from HA and gallic acid coordination with ferric ions. The hydrogel could behave as an injectable and could also be adhered to the skin. In the injectable form, upon NIR irradiation the hydrogel was capable to suppress lung metastasis in 4T1-Luc orthotopic breast tumors. When adhere to the skin of mice bearing a xenograft of human epithelial carcinoma cells and NIR-light was applied, tumor ablation was achieved. The application of the hydrogel to skin A375 melanoma-xenografted tumor sites followed by NIR irradiation also resulted in complete tumor ablation [286]. Tang *et al.* reported a near-infrared (NIR) dye croconaine (CR780) engineered with RGD peptide and PEG, which self-assembled into uniform nanoparticles. These tumor-targeted multimodal nanotheranostic assembly was radiolabeled with ¹²⁵I to allow for tumor ablation and inhibition of tumor relapse [287]. Among the different light-responsive materials, conjugated polymers are emerging candidates with successful application in the PTT and gene therapy. Chen *et al.* demonstrated that the combination of mild hyperthermia with CAR T cells therapy can potentially increase the therapeutic index of solid tumors. In this work chondroitin sulfate proteoglycan-4-specific CAR T cells were administered along with poly(lactide-*co*-glycolide) nanoparticles carrying

indocyanine green into Nod scid gamma mice engrafted with the human melanoma cell line WM115. The combination therapy displayed superior antitumor activity after NIR exposure [288]. More recent research has been published supporting the potential in the combination of PTT and CAR T cell therapies for different tumor cancer models [289-291]. In a similar context, Jiang *et al.* fabricated red blood cell membrane-camouflaged melanin nanoparticles as a platform for *in vivo* antitumor PTT. These nanoparticles exhibited significantly higher PTT efficacy than that of bare melanin nanoparticles in A549 tumor-bearing mice [292]. Zhou *et al.* fabricated a dual peptide decorated melanin-like nanoparticle for tumor-targeted and autophagy-promoted PTT. *In vivo* experiments revealed that the tumor-targeted and autophagy promotion-associated PTT efficiently regressed tumors at temperatures around 43 °C [293]. PTT has been explored as an antibiotic-free strategy to treat bacterial infections. In this context, Han *et al.* reported hydrogels composed of quaternary ammonium and double-bond modified chitosan and metal-organic framework particles. The hydrogel was capable to inhibit 99.97 % and 99.93 % of bacterial growth for *Staphylococcus aureus* and *Escherichia coli*, respectively [294]. A critical factor limiting the use of PTT is thermal damage of normal tissues. To overcome this limitation, one alternative is to improve the tumor-specific targeting of photothermal reagents [278]. This can be done by using nanocarriers with tunable physicochemical properties or with targeting ligands. Another strategy involves the reduction of the heat resistance of tumor cells by inhibiting the synthesis of heat shock proteins in the tumor followed by low-temperature PTT. Both strategies aim to achieve tumor suppression while reducing thermal damage to normal tissues. Monotherapies, such as PTT or PDT, even in scenarios with high therapeutic effect, may not be enough to eliminate all tumor cells. This can lead to tumor recurrence and metastasis. Combining PTT and PDT with other treatment approaches such as immunotherapies or chemotherapies can provide synergistic therapeutical effects [295,296].

Photobiomodulation therapy (PBMT) emerges as utilitarian alternative for controlling and managing the interactions between light, biomolecules, photo-responsive materials and drugs. Several strategies have been proposed using PBMT for the treatment of diabetic ulcers, blood disorders, coronary artery disease, wound healing, inflammation, chronic pain, neurodegenerative disorders, etc. [297]. For instance, the association of Alzheimer disease with the aggregation of β -amyloid peptides is well known and a wide diversity of drugs and materials have been tested for to avoid amyloidosis with no success [298]. Recently, PBMT has been studied for Alzheimer disease treatment. Light exposure has been found to trigger numerous mechanism that led ultimately to amyloid aggregation obstruction. Specific light wavelengths are capable to trigger chemical and physical transformations in the cellular microenvironment such as oxygen reactive species production, heat release, chemical cleavage or peptide conjugative reactions. Those transformations interact with β -amyloid peptides provoking their degradation, crosslinking and other chemical alterations that knock out the aggregates and the oligomers [299-301]. The additional use of photosensitizers can improve the suppression of amyloidosis in a simple, non-toxic and cheap manner [302]. More recently, it has been explored the aiding use of fluorescent molecules and photo-responsive materials to block β -amyloid accumulation [303]. Other approaches based on PBMT have been emerged as prominent modalities to control and modulate the

immunological response of tumoral cells. In this case, the use of materials is critical to bridge the light action with immune activation. For instance, it has been reported that bacteria loaded into red blood cells membrane particles is able to release melanin. Melanin release triggers macrophage recruitment and accelerates the phenotype change of these cells to detonate an immune response. Simultaneously, melanin serves as photothermal agent for PTT. These combinatorial immunomodulatory and PTT approach inhibited melanoma and colon cancer using *in vivo* models [283]. Another interesting PBMT approach is for the photoinhibition of angiogenesis in tumors. In this case, polydopamine crosslinked collagen/silk fibroin composites were prepared to deliver thrombin for blocking blood vessels. The system showed a sustained effect to prevent the recurrence and metastasis of an *in vivo* model of triple negative breast cancer [304]. In the same line, NIR-II responsive hydrogels were constructed by the incorporation of nitric oxide precursors and 2D tungsten oxide nanosheets within a hydrogel. This hydrogel demonstrated angiogenesis inhibition and anti-recurrence tumor efficacy [305]. Finally, ana strategy for light controlled proteolysis targeting chimeras has been developed. Here, upon light irradiation targeted proteins promote proteasomes degradation with a high spatiotemporal control [306]. While PBMT and phototherapies in general present tremendous potential for minimally invasive topical or superficial treatments, poor tissue penetration of light represents a serious limitation for extending the application to deep tissues. While ultrasound can penetrate above 10 cm of soft tissues [307] and magnetic tissue penetration is only limited by the magnetic field generator's range [308], UV–vis light has a penetration depth of only a few millimeters or less in soft tissues and NIR just a few centimeters [309]. Several light delivery strategies are being developed to activate photoresponsive biomaterials *in vivo* such as optical waveguides and implanted micro-LEDs [310,311]. Though with these technologies is possible to overcome poor light penetration of tissues, it is worth noting that the implantation of these devices requires invasive interventions. A brief summary of phototherapies reviewed in this section is presented in Table 5.

5. Challenges, perspectives and conclusions

Here, we reviewed the different photomedicine approaches that have been developed using soft materials. Approaches to modulate cell functions, for tissue engineering and regenerative medicine, for controlled drug delivery and for phototherapy comment on the complexity of the photo-triggered effects on soft materials systems and on their therapeutic relevance. Photosensitive soft nano- and microstructures are capable to emulate nature's soft matter dynamic behavior offering multiple possibilities with high spatiotemporal control for the manipulation of cellular signaling and behavior, which has a clear potential as alternative treatments for various health conditions. All the soft materials systems discussed here rely on light-triggered mechanisms such as isomerization, cleavage, crosslinking, hyperthermia, activation reactions or electroconduction, that through different paths interfere with biological functioning at the cellular or tissue level. Photosensitive soft materials and biointerfaces have been explored to manipulate cellular responses such as adhesion, spreading, morphology, migration, and differentiation. These systems have been providing us with novel tools to interrogate cells and improve our understanding of basic cell biology including mechanics and signaling. Moreover, the ability to manipulate cell behaviors using

photosensitive soft materials and light as a trigger has allowed the investigation of alternative less invasive therapeutic solutions to modulate cell growth, differentiation, and migration. Synthetic soft material interfaces have been widely exploited to mimic the ECM because of their analogue physical and chemical properties. It is important to note that most of the materials and studies presented here used one stimulus to modulate cell behavior, whether it was mechanical, electrical or a change in wettability of the substrate. However, in physiological context, cells are under a complex and dynamic environment with several chemical and physical signals [129,312]. The design of future photoresponsive materials should aim to achieve precise control over multiple environmental properties and be able to provide multiple stimuli independently and with large spatiotemporal precision [21]. For instance, by combining a molecule exhibiting photoisomerization at a certain wavelength with other molecule exhibiting photovoltaic effect at a different wavelength, independent control over material structure and cell electrical stimulation could be achieved by using the appropriate light. Besides, photoresponsive materials could be combined with materials able to respond to other exogenous (ultrasound, electricity or magnetic fields) or endogenous (pH, reactive oxygen species, pressure) signals to obtain multiresponsiveness [313,314]. The integration of different functional units using engineering approaches will allow us to control multiple factors separately and to better mimic tissues' complex environments.

It is worth noting that light and photoresponsive soft materials offer tremendous opportunities as building blocks in modern bioengineering technologies. Photopolymerization, *i.e.*, light-induced chain-growth and crosslinking of functional monomers into polymers, can be used in light-based 3D-printing techniques to rapidly obtain complex, high resolution biomedical microdevices and photonics materials [315-318]. Moreover, light and photoresponsive materials offer great opportunities in the four-dimensional (4D) bioprinting technologies, in which the concept of time is integrated as a fourth dimension with traditional 3D bioprinting [319]. Due to light high spatial and temporal precision, it can act as a remote source of energy to induce rapid and localized transformation of material structure and chemistry. Photoresponsive polymers or polymer composites can be used as bioinks to print dynamic materials with light-triggered shape memory effect, self-healing or tunable biodegradability [320-323]. Another bioengineering technology in which photoresponsive materials could generate a large impact is the area of microfluidics, lab-on-a-chip and organ-on-a-chip. Light-based bioprinting of 3D structures with controlled shape and architecture may find interesting applications in hydrogel-based organ-on-a-chip devices [324,325]. Though microfluidic devices may be small, fluidic controllers are often large, inaccurate, or expensive. The integration of microscale photoresponsive soft polymer actuators within microfluidic devices may serve as an inexpensive and highly accurate alternative [326-328]. The micromanipulation offered by these light-controlled actuators may be useful in fluid handling and circulation of culture media in organ-on-a-chip devices [329]. Photonic hydrogels has been proposed for non-invasive real-time control and investigation of the extracellular stiffness in cell incubation systems such as organ-on-a-chip devices [98]. Finally, photoresponsive soft materials are being used for the development of autonomous and highly controlled light-driven soft robots [330]. For instance, light responsiveness and molecular anisotropy have been used to create soft robots able to crawl and jump or elicit complex underwater locomotion [331,332].

Photoresponsive soft scaffolds have provided a unique approach for remote-triggered restoration and replacement of different biological tissues. These photosensitive soft microstructures have been investigated also when combined with drugs, other photosensitive molecules, or nanoparticles to endow light-triggered multifunctionalities and improve tissue engineering and regenerative medicine outcomes. Photosensitive soft nanomaterials have been developed for the wireless on-demand delivery of therapeutics. Photosensitive soft drug delivery systems can be surface engineered to target specific organs/tissues and can be loaded with multiple therapeutics. In these systems, NIR light provides a unique contact less option that can reach few centimeters into the body with high precision to control the delivery of drugs, genes, nanoparticles, or energy. The combination of multiple therapeutic delivery approaches has resulted in enhanced effects. Although with less incidence, photoresponsive soft materials have been explored as mediators of PDT, PTT, and other light-based therapies. The overall goal for the development of photoresponsive soft biointerfaces and materials is to provide minimally invasive therapeutic options that can be externally controlled with high precision.

Nevertheless, the most critical drawback of all photomedicines relies on the light and the biological tissues wavelength-dependent optical properties. Short wavelength light is less desired because it penetrates only 0.5–2.5 mm into biological tissues with up to a 40 % of light scattering. NIR light can penetrate 8–10 mm into biological tissues without scattering [333], still being insufficient to pass into deep tissues or through bone and cartilage tissues. Moreover, the majority of the light responsive motifs have low sensitivity to NIR light which results in high optical power density requirements for their activation [179]. Although light stimulation provides high spatial control, the micrometer incident light can trigger nonspecific and undesired photoreactions in surrounding healthy cells and tissues. Other impairments on the clinical translation of photomedicines are the design of biodegradable and biocompatible photosensitive materials and their controlled large-scale production.

To overcome light penetration and specificity limitations, UCNPs have been proposed. Specifically, UCNPs systems for transforming NIR light into UV/visible light to enhance the effect of PTT and PDT. However, UCNPs biocompatibility, biodegradability, and safety remains to be addressed [334]. The evident need of external stimuli with higher penetration into biological tissues has led to the development of NIR II-triggered strategies. NIR II approaches are in their earlier stages of development, but the limited knowledge in the field suggests their great potential to be utilized in photomedicines when combined with NIR II photosensitive materials [335]. It is clear that there is a big gap between fundamental and translational research that needs to be addressed to improve our understanding of photosensitive soft material's cytotoxicity, biodegradability, and long-term effects. It is expected that the interactive collaboration between material scientists and chemists, biologists, and clinicians will unlock photomedicines future clinical translation.

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Data availability

No data was used for the research described in the article.

Abbreviations:

BMP	Bone Morphogenetic Protein
BSA	Bovine Serum Albumin
β-CD	β-cyclodextrin
CSFD	Critical Size Femoral Defect
ECM	Extracellular Matrix
ECs	Endothelial Cells
EGF	Epidermal Growth Factor
GF	Growth Factor
HA	Hyaluronic Acid
HUVECs	Human Umbilical Vein Endothelial Cells
LED	Light-Emitting Diode
MC	Merocyanine
MMP	Matrix Metalloproteinase
MSC	Mesenchymal Stem Cell
NIR	Near-Infrared
PBMT	Photobiomodulation therapy
pDR1m	poly-Disperse Red1-methacrylate
PEG	Polyethylene Glycol
PBS	Phosphate Buffered Saline
PLA	Poly(L-Lactide)
PLL	Poly-L-Lysine
PMMA	Poly(methyl methacrylate)
PTB	Photochemical Tissue Bonding
RGD	Arg-Gly-Asp, arginine-glycine-aspartate

SAMs	Self-Assembled Monolayers
SEM	Scanning electron microscopy
SM	Stem Cell
SMP	Shape Memory Polymer
SP	Spiropyran
UCNPs	Upconversion Nanoparticles
UV	Ultraviolet
VEGF	Vascular Endothelial Growth Factor

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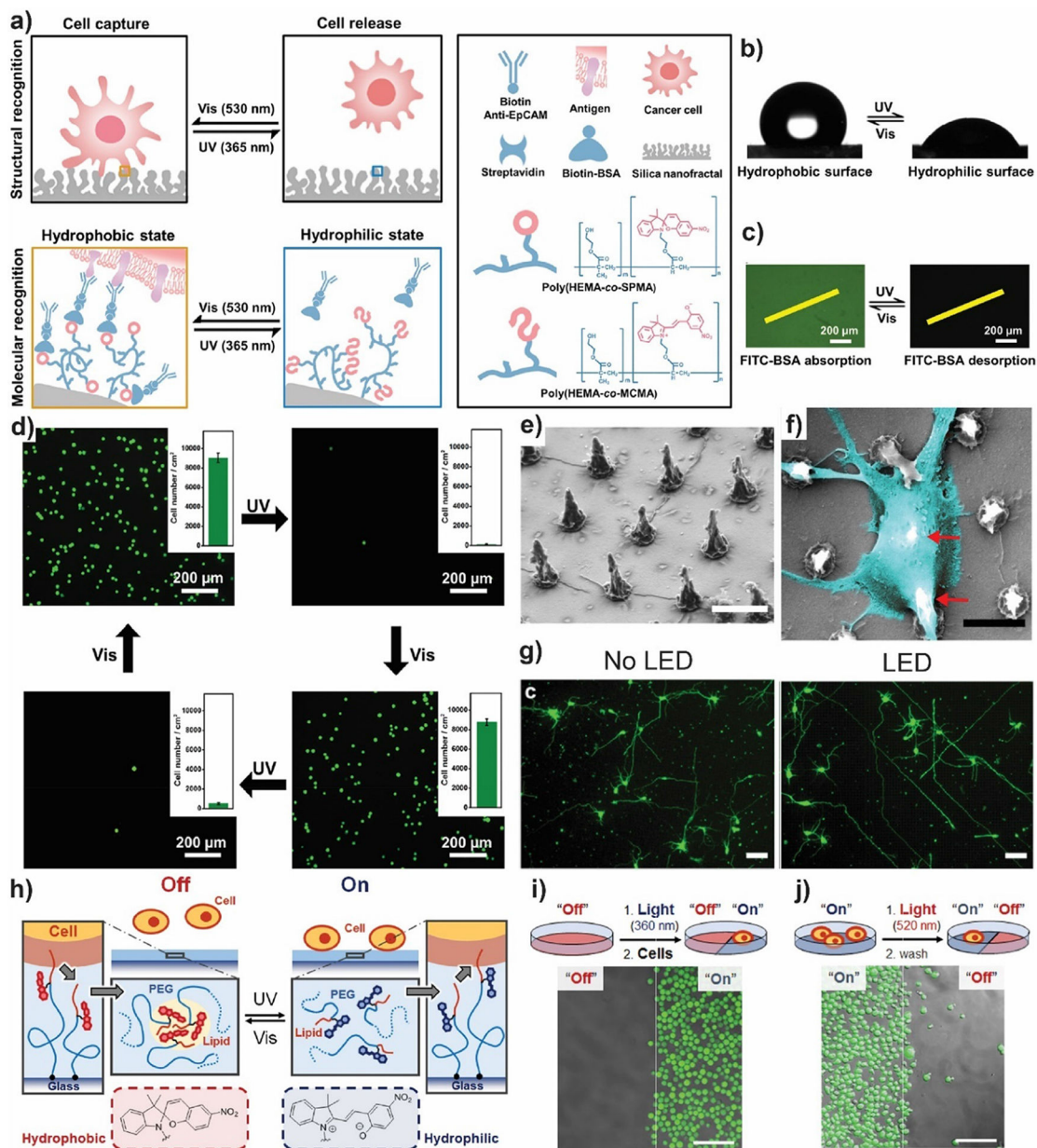


Fig. 1. a) Scheme of the photo-irresponsive molecule-enhanced wettability switch on photoresponsive nanostructured surfaces toward targeted cancer cells reversible capture. Yellow and blue color in the nanostructured surfaces represent the hydrophobic and hydrophilic properties of photoresponsive components, respectively. b) Evaluation of the surface wettability of the modified silica nanofractal under UV and visible light irradiation. c) Adsorption/desorption of green fluorescent BSA under UV and visible light irradiation. d) Reversible capture and release of target breast cancer cell line (MCF-7) on the photoresponsive nanostructured surface by alternately changing UV and vis light irradiation and employing epithelial cell adhesion molecule antibody as a cell capture agent. Insets show the number of cells adhered on the surface during the reversible capture and release

process. e) Scanning electron microscopy (SEM) images of P3HT micropillar array. Scale bar: 5 μm . f) Focused ion beam/SEM characterization of a rat primary cortical neuron soma suspended over two pillars (red arrows). Scale bar: 5 μm . g) Growth of neuronal cells on P3HT micropillars after 3 days *in vitro* with and without photostimulation (green: β -III-tubulin). Scale bar: 50 μm . h) Scheme of the working hypothesis of reversible cell immobilization with spiropyran-functionalized PEG-lipids conjugates. In the hydrophobic 'closed' form, the lipid moiety may be localized in hydrophobic assemblies inside the PEG layer, thus preventing their interaction with cells. In the hydrophilic 'open' form, the PEG-lipid may be dispersed in solution facilitating interaction between lipid moiety and the lipid bilayer of cells. Confocal microscopy images of partial cell immobilization (i) and release (j) of murine pro-B non-adherent cell line expressing green fluorescent protein. Merged fluorescence and phase contrast image is shown. Scale bar: 100 μm . a)-d) Adapted with permission from [61]. Copyright 2019 American Chemical Society. e)-g) Adapted with permission from [64], 2020 American Chemical Society. h)-j) Adapted with permission from [65]. Copyright 2019 American Chemical Society.

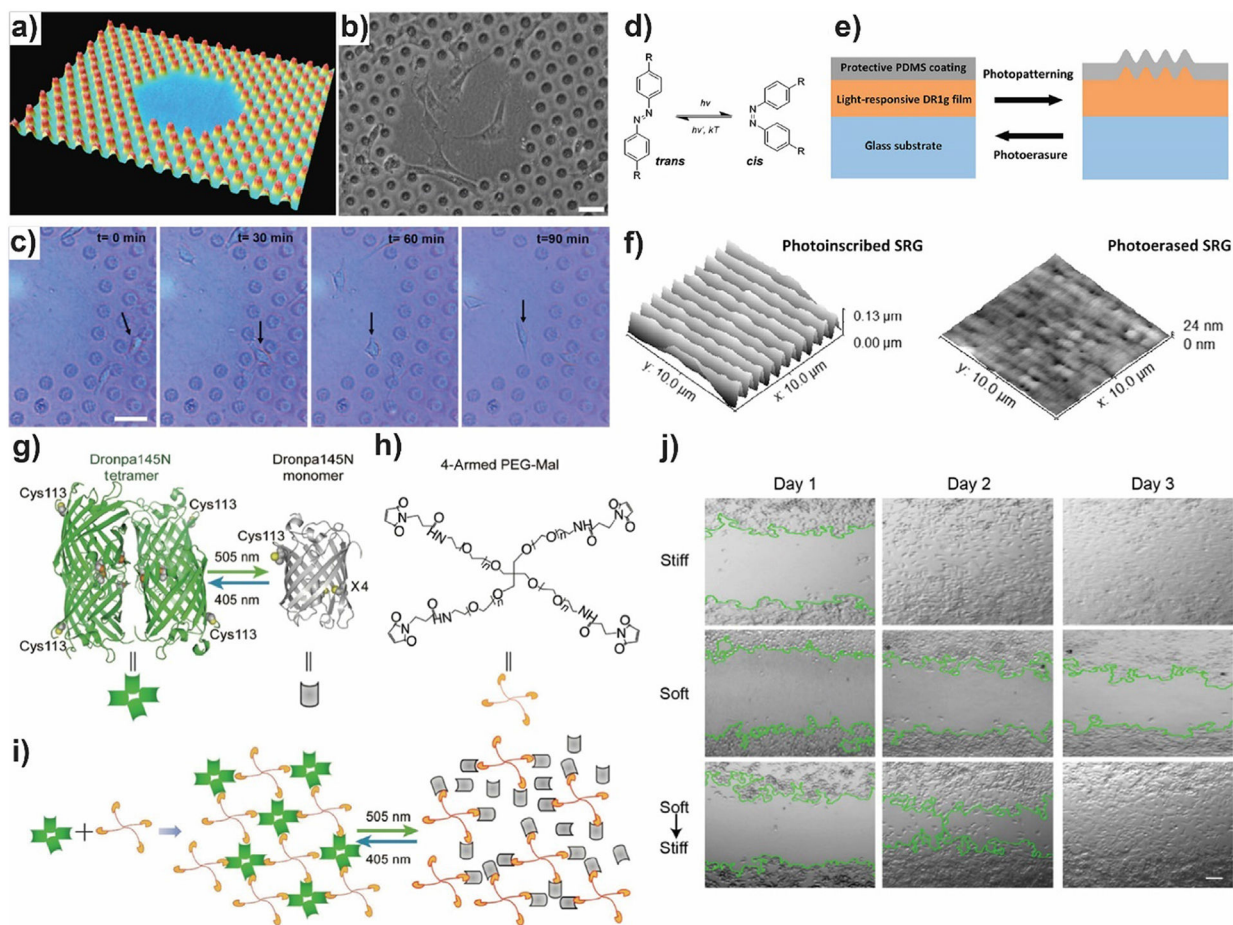


Fig. 2.

a) Three-dimensional representation of the mixed flat not entirely illuminated surface surrounded by hexagonally arranged pillars with a height of 1.1 μm . b) Phase contrast image of NIH3T3 fibroblasts on liquid crystal polymer network (LCN) surface after 3 days of culture. c) Live cell imaging of a representative cell going from the pillar area to the flat area. Scale bar: 50 μm . d) Photoisomerization of azobenzene between the thermodynamically stable *trans* isomer and the metastable *cis* isomer. e) Scheme of the bilayer structure and the azobenzene-driven surface relief gratings (SRG) formation and erasure (DR1g: disperse Red 1-containing molecular glass; PDMS, polydimethylsiloxane). f) AFM images of the surface topography of DR1g-PDMS1 after inscription (left) and erasure (right). g-j) Scheme of the photoresponsive hydrogel made of four-armed PEG crosslinked by Dronpa145N. g) Dronpa145N oligomerization states can be switched by irradiation with cyan and violet light. In both states, only one thiol group is exposed. h) Four-armed PEG- maleimide chemical structure. Maleimide end of each arm can react with thiol exposed from Dronpa145N. i) Illustration of the gel (left), sol (right) and photocontrolled sol-gel transition. j) Controlling cell migration in a wound closure experiment by tuning hydrogel stiffness. Representative pictures taken at different time points. The green line shows the colony interface. Scale bar 50 μm . a)-c) Adapted with permission from [85]. Copyright 2017 Wiley. d)-f) Adapted from [86]. g)-j) Reprinted by permission from [88], Copyright 2018 Springer Nature.

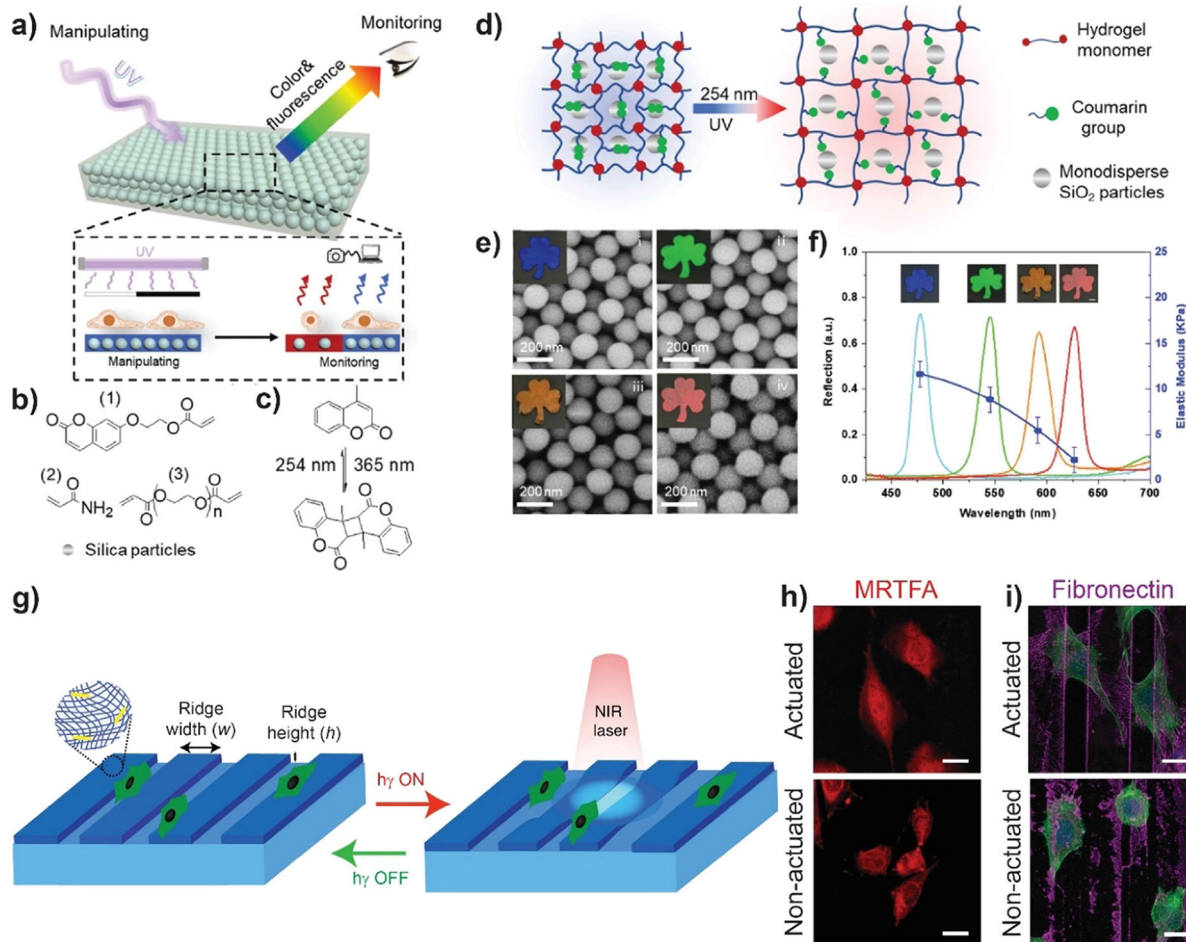


Fig. 3.

a) Scheme of the principle of *in situ* manipulation and monitoring of mechanical properties using photonic hydrogel. b) The hydrogel is synthesized by copolymerization of acrylate monomers in the presence of coumarin-containing acrylate and silica nanoparticles. c) Reversible photo-induced dimerization and cleavage of methyl coumarin group. d) Scheme of the reconfiguration and self-reporting of the photonic hydrogel. e) SEM and optical (inset) images of the generated hydrogel before and after reconfiguration. i) original hydrogel and after 2 (ii), 4 (iii) and 5 (iv) min illumination. As the hydrogels were freeze dried before SEM visualization, polymer networks were not visible from a top view. The center-to-center distance between the particles increases and the color of the hydrogel gradually changed from blue to red. f) Reflection spectra and the corresponding stiffness of the reconfigured hydrogels. g) Scheme of the soft and patterned light-triggered hydrogels composed of thermoresponsive polymer and gold nanorods. Gold nanorods convert NIR light-illumination into heat, leading to gel collapse. Pulsing laser results in actuating (beating) hydrogels. h-i) Immunofluorescent images showing the effect of actuation on mechanosensitive protein myocardin related transcription factor A (MRTFA) localization and fibronectin distribution. Cells in the actuating area show nuclear localization of MRTFA, whereas for cells in the non-actuating area MRTFA is in the cytoplasm (h). When cells are actuated, fibronectin secretion is more aligned (i). a-f) Republished with permission of

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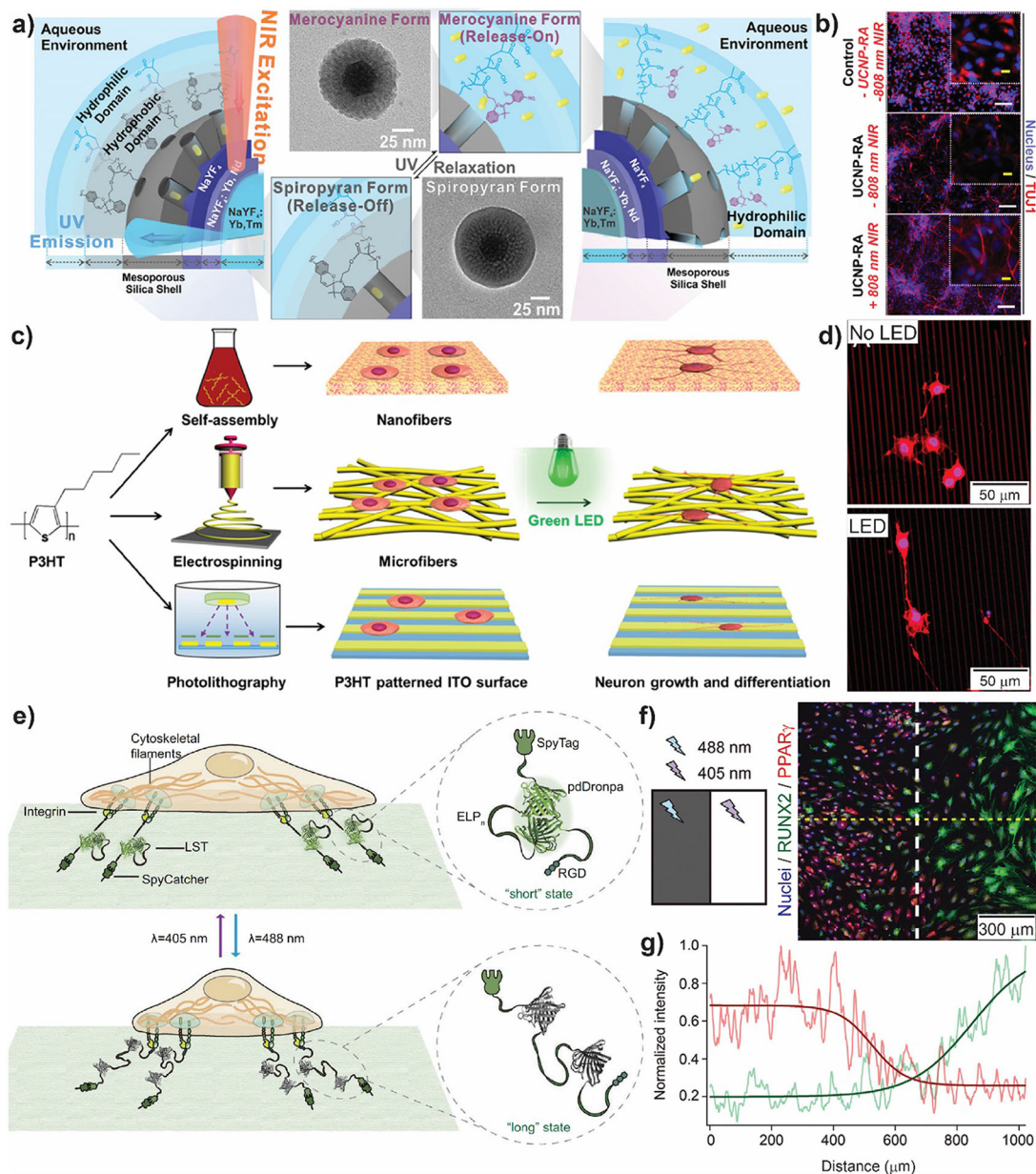


Fig. 4.

a) Scheme of the NIR-mediated photoswitching of the spiropyran polymer and subsequent hydrophobic-hydrophilic transition on the designed UCNP nanoconstructs to induce on-demand small-molecule release. b) Early neuronal markers expression in control human-induced pluripotent stem cell-derived neural stem cells, and cells exposed to retinoic acid loaded nanoparticles (UCNO-RA) without (–808 nm NIR) and with (808 nm NIR) light stimulation. Blue: nucleus; Red: *TUL1* neuronal marker. Scale bar = 100 μm; inset scale bar = 25 μm. c) Scheme of the preparation of P3HT micro/nanofibers and P3HT-patterned surface for PC12 cell culture. d) Laser scanning confocal microscopy images of neuron-like pheochromocytoma (PC12) cells stained for actin cytoskeleton and cultured on ITO-coated glass surfaces patterned with 3 μm wide stripes of P3HT with and without LED

illumination. e) Light-switchable tether (LST) scheme. The LST consists of *N*-terminal SpyTag to covalently link to SpyCatcher immobilized on glass and C-terminal RGD to bind to integrin. When pdDronpa dimer is formed, repeats of elastin-like peptide (ELPn) are sequestered. Length of LST can be switched between long and short states upon 488 and 405 nm illumination and pdDronpa dissociation and association. f) Spatially control of human MSCs differentiation with light. Scheme of the photomask used to spatially regulate adhesion and differentiation of human MSCs and immunofluorescent images after 10 days differentiation. Nuclei, osteogenic differentiation marker RNX2 and adipogenic differentiation marker PPAR γ are shown in blue, green and red respectively. g) Normalized average fluorescent intensities of RNX2 (green) and PPAR γ (red) along the horizontal path (yellow dotted line) shown in (f). a)-c) Adapted with permission from [106]. Copyright 2020 American Chemical Society. c)-d) Adapted with permission from [109]. Copyright 2019 American Chemical Society. e)-g) Adapted with permission from [114]. Copyright 2021 Wiley.

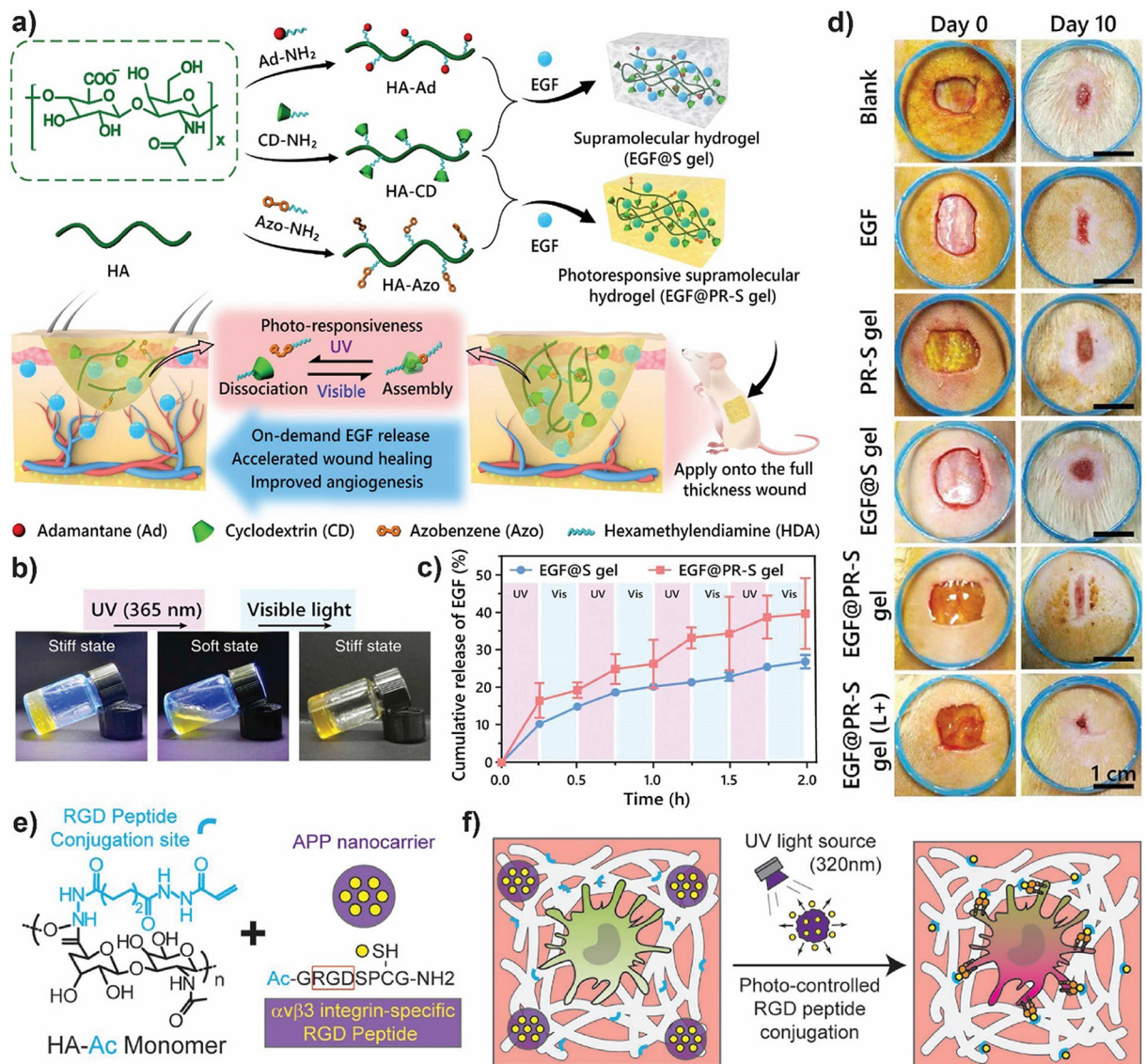


Fig. 5. a) Scheme of supramolecular hydrogels' synthetic route and their application as controlled delivery systems for accelerated wound healing. Adamantane, which also complexes with CD but it is not photoresponsive, was used for the obtention of non-responsive control supramolecular hydrogels (EGF@S gel). b) Photographs of the reversible stiff-soft and soft-stiff state transitions of photoresponsive supramolecular hydrogels (EGF@PR-S) upon exposure to UV and visible light, respectively. c) EGF release profile of EGF@S and EGF@PR-S gels upon alternating UV and ambient visible light irradiation. d) Photographs of full thickness wounds (day 0) and further healing with different treatments (day 10). Blank; non-treated control; EGF: EGF solution; L+: UV irradiated for 15 min. e) Schematics of acrylate-HA macromers and RGD-loaded photodegradable alkoxyphenacyl-based polycarbonate (APP) nanocarriers (purple). f) Upon UV exposure, RGD peptides (yellow) are released and covalently conjugate to acrylate groups (blue) in crosslinked HA hydrogels (white) to temporally activate $\alpha\beta3$ integrins (orange) macrophage expressions,

leading to macrophage polarization. a)-d) Adapted from [147], Copyright 2020, with permission from Elsevier. e)-f) Adapted with permission from [150]. Copyright 2018 Wiley.

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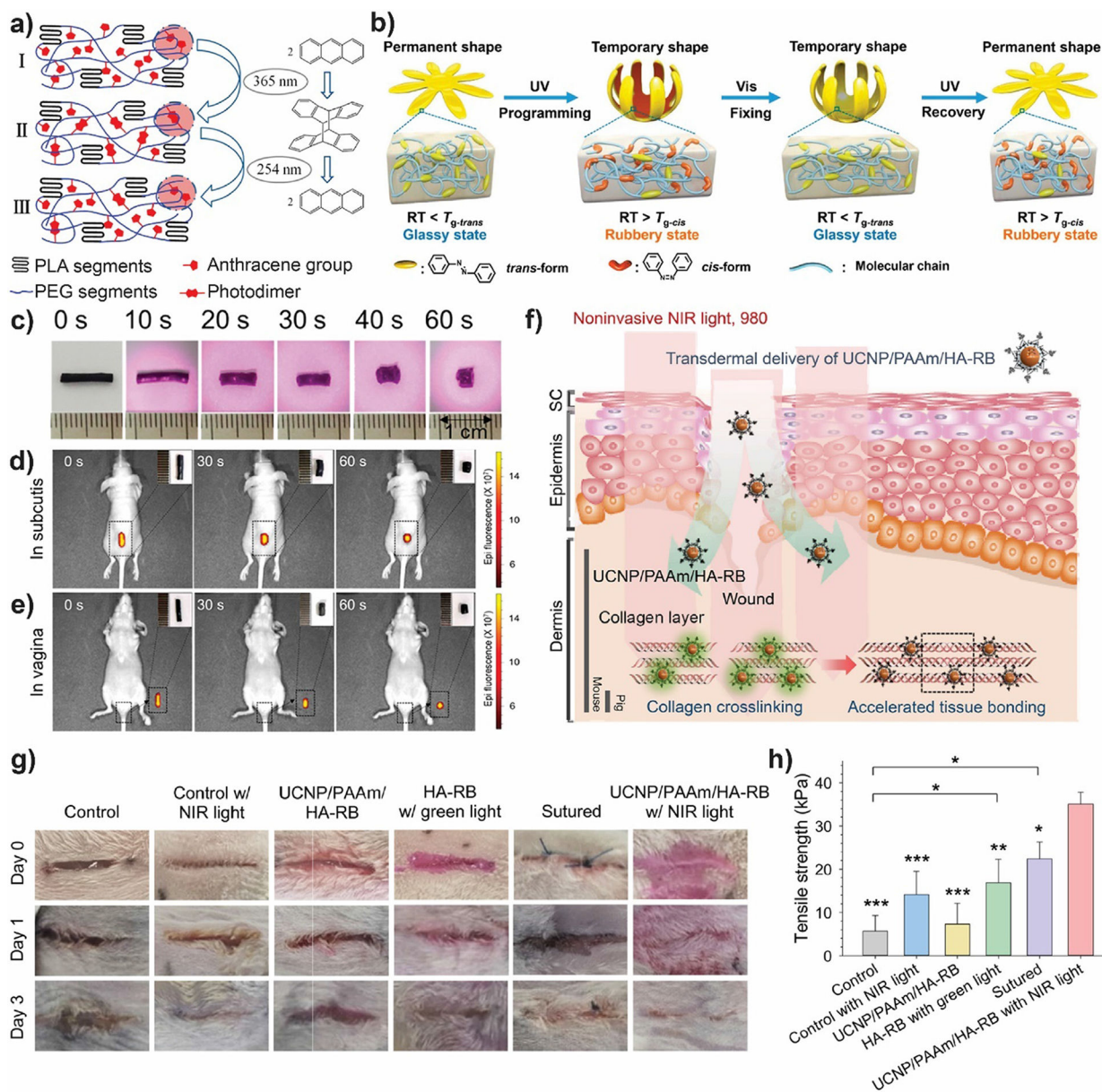


Fig. 6.

a) Scheme representing the mechanism of light-induced shape-memory effect of PLA-PEG-anthracene composite. PLA crystalline and PEG amorphous regions are represented. b) Shape memory effect of a modeling flower and the mechanism of azobenzene-containing polymer network shape transition. In the permanent shape, azobenzene units are in the *trans* form and glass transition temperature of the polymer network is above room temperature. After UV irradiation the azobenzene-containing polymer isomerizes to *cis* form, whose glass temperature is below room temperature and a transition to a temporary shape occurs. This shape can be fixated with visible-light and can be reverted when exposed to UV-light again. c) *In vitro* shape memory behavior of Cy5.5-labeled melanin/polyurethane (YM/PU) column under the NIR laser. Photographs and fluorescence images displaying the *in vivo* shape memory behavior of the Cy5.5-labeled YM/PU column in the mouse subcutis

(d) and vagina (e) under NIR laser. f) Scheme of the photochemical tissue bonding of injured collagen matrix. Polyallylamine modified UCNP/hyaluronate-rose Bengal conjugate (UCNP/PAAm/HA-RB) complex is delivery transdermally and NIR light is applied for wound healing (gray scale bars = 100 μm , SC: stratum corneum). Images of *in vivo* photochemical tissue bonding of incised dorsal skin mice (g) and the resulting tensile strength at day 3 (h). Control: phosphate buffered saline (PBS). a) Reprinted with permission from [165]. Copyright 2016 American Chemical Society. b) Reprinted with permission from [166]. Copyright 2019 American Chemical Society. c)-e) Reprinted with permission from [167]. Copyright 2020 American Chemical Society. f)-h) Adapted with permission from [170]. Copyright 2017 American Chemical Society.

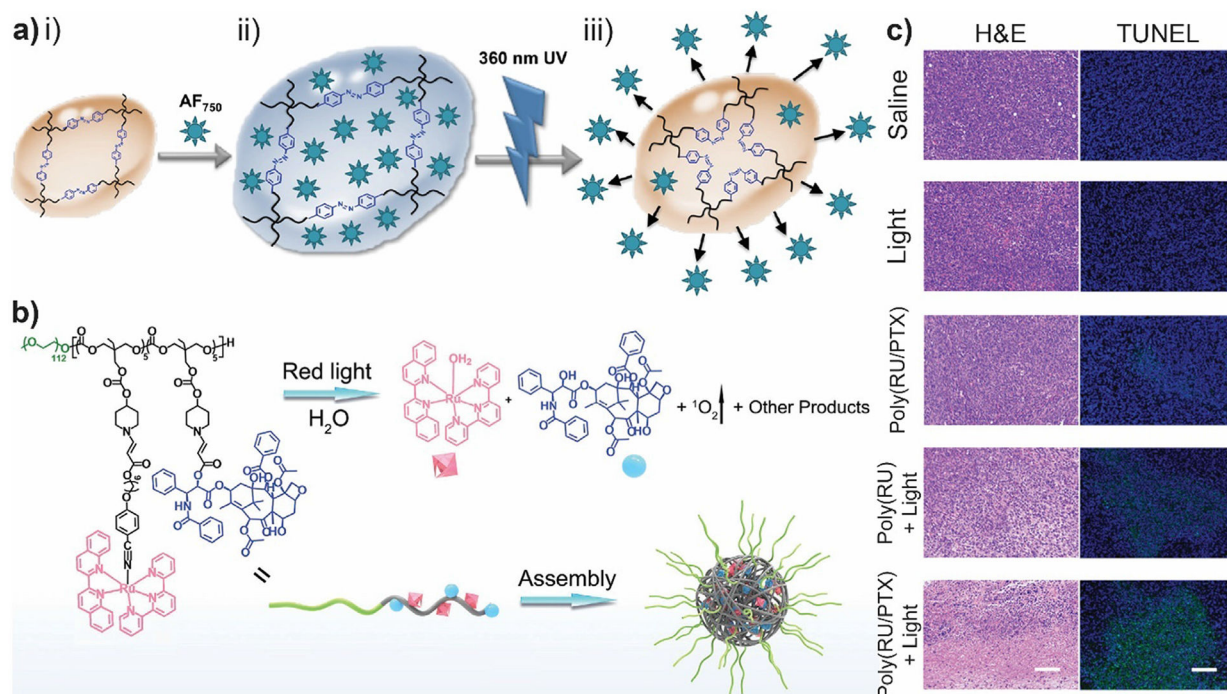
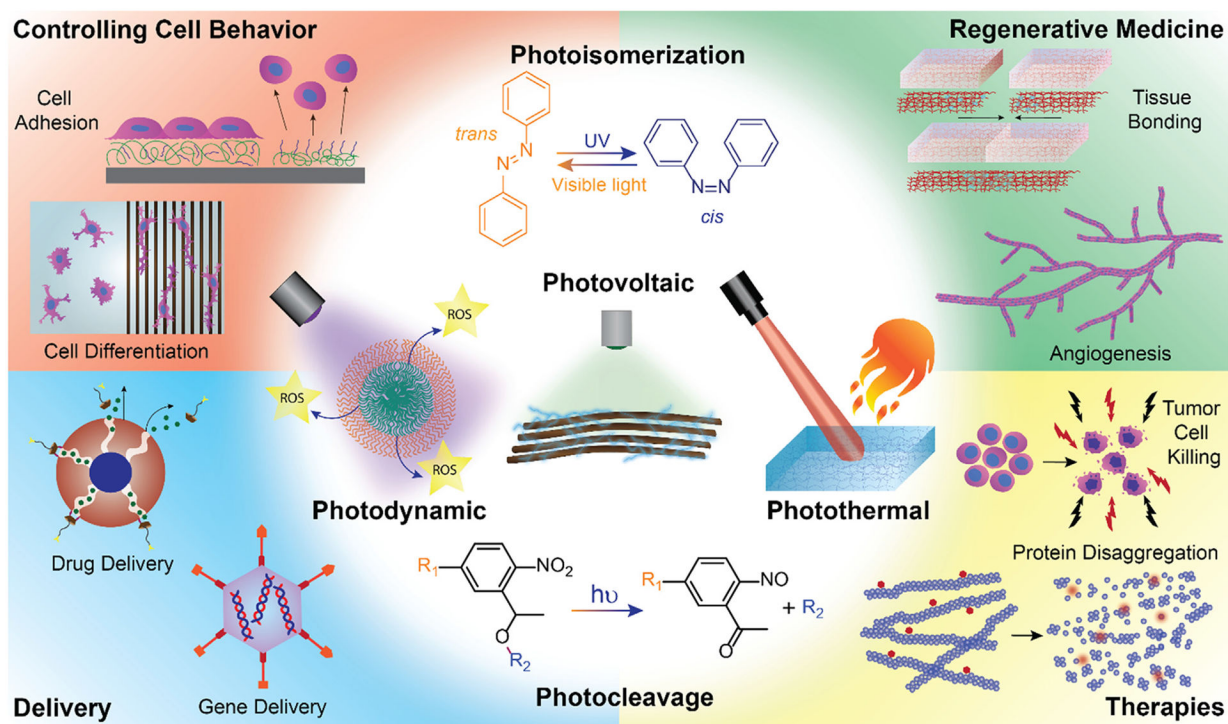


Fig. 7.

a) Swelling and contraction of photoresponsive hydrogel composed of azobenzoic acid and four-armed PEG. i) Dry hydrogel with *trans*-azobenzene. ii) Swollen hydrogel loaded with Alexa Fluor 750. iii) After UV illumination, photoisomerization leads to hydrogel contraction and Alexa Fluor 750 release. b) Chemical structure of the biodegradable, biocompatible, amphiphilic block copolymer with paclitaxel (PTX) and Ru complexes (poly (Ru/PTX)). Cleavage of the Ru complex, generation of $^1\text{O}_2$ and release of anticancer drug PTX can be induced with red light irradiation. c) Ex vivo histological analyses of tumor sections after different treatments by hematoxylin and eosin (H&E) and (TUNEL) terminal deoxynucleotidyl transferase mediated UTP end labeling staining. Scale bar: 100 μm . Significant tumor cell nuclear ablation and higher level of apoptosis (green) in tumor tissues from mice in the poly (Ru/PTX) can be observed in H&E and TUNEL staining, respectively. Adapted with permission from [224]. Copyright 2018 American Chemical Society. Adapted from [215]

**Scheme 1.**

Schematic representation of different photo-triggered effects and the use of photo-responsive materials for controlling cell behavior, for delivery and regenerative medicine strategies and for phototherapies.

Table 1

Summary of strategies for controlling cell adhesion reviewed in this article.

Phototunable Property	Material	Phototriggered effect	Observed Properties and Effects	Ref
Stiffness	Thiolated HA polymers	Photocrosslinking and photodegradation	Photoinduced healing, patterned stiffness, and control of hMSCs adhesion	[57]
Wettability	SP based acrylic nanofibers	Photoisomerization	Dynamic control of cell adhesion and detachment	[58]
Wettability	Amphiphilic diblock copolymer with SP moieties in the hydrophobic block	Photoisomerization	Opposite polarity changes to the expected for photoisomerization of SP, switchable cell-repellent cell-adhesive surface	[59]
Ligand presentation	Sugar-modified azobenzene derivatives	Photoisomerization	Switchable and selective protein/cell adhesion	[60]
Wettability	Copolymer of SP derivatives and photoresponsive molecule. Molecular recognition system	Photoisomerization	Amplified wettability transition, reversible capture and release of targeted cells	[61]
Stiffness and ligand presentation	O-nitrobenzylphosphate ester photoprotected nucleic acid-based polyacrylamide hydrogel	Photocleavage	Patterned and selective HeLa cell adhesion using specific aptamers	[63]
Wettability	Core-sheath fiber scaffold, the sheath being a SP containing copolymer	Photoisomerization	3D scaffold with controllable cell adhesion	[66]
Ligand presentation	Hydrogel microspheres with β -CD moieties and RGD-functionalized azobenzene	Photoisomerization	3D scaffold with controllable cell detachment	[67]
Ligand presentation	β -sheet forming peptide connected to RGD motif using a nitrobenzyl linker	Photocleavage	Gradient of RGD on the fibrils and gradient of cell adhesion	[71]
Electrical stimulation	P3HT micropillars	Photovoltaic	Alignment and length increase of neurons axons	[64]
Ligand presentation	PGG connected to an oleyl group by a photocleavable linker	Photocleavage	Patterned nonadherent cell trapping and controllable release	[75]
Ligand presentation	SP-conjugated PEG – lipids	Photoisomerization	Spatially, switchable non-adherent and adherent cells immobilization	[65]
Ligand presentation	Photocleavable RGD-PEG conjugate surface	Photocleavage	Patterning of cell adhesive and non-adhesive regions and further release	[76]
Substrate topography	Vertical micropillars of pDR1m	Photoisomerization and mass migration	Pillar to ellipsoidal bar shape transition and changes in cell actin dynamics	[78]
Substrate topography	pDR1m substrate	Photoisomerization and mass migration	Generation of dynamic concentric rings patterns led to changes in fibroblasts' shape	[79]

Summary of strategies for controlling cell migration and for performing mechanobiology studies reviewed in this article.

Table 2

Phototunable Property	Material	Phototriggered effect	Observed Properties and Effects	Ref
Substrate topography	Azobenzene containing liquid crystal networks	Photoisomerization and mass migration	Nanoroughness increase upon illumination leading to decreased cell speed	[85]
Substrate topography	Azobenzene-based molecular glass surface coated with PDMS layer	Photoisomerization and mass migration	Grating photo-inscription and photo-erasure that control cell orientation and migration	[86]
Stiffness	Thermo responsive copolymer hydrogel and gold nanorods	Photothermal	Optomechanical stimulation increases cell motility	[87]
Stiffness	Four-armed PEG-Dronpal45N hydrogel	Photoisomerization	Real-time modulation of substrate stiffness and collective cell migration	[88]
Stiffness	HA modified with methacrylate and coumarin moieties	Photocleavage	Increased endothelial cells migration into the softer hydrogels	[93]
Stiffness	Azobenzene crosslinker containing hydrogel	Photoisomerization	<i>In situ</i> tuning of substrate stiffness affecting MSCs adhesion and morphology	[95]
Stiffness	Azadibenzocyclooctyne containing click hydrogel	Photocrosslinking	Encapsulation of myoblast in 3D hydrogels and change in cellular localization of mechanoregulatory protein	[96]
Stiffness	Azobenzene-bearing hydrogel	Photoisomerization and phase transition	Reversible softening-stiffening affecting gene expression levels of E-cadherin	[97]
Stiffness and color	PEG diacrylate hydrogel containing coumarin and mono-dispersed silica NPs	Dimerization and cleavage	<i>In situ</i> manipulation of substrate stiffness and monitoring. Applicable in microfluidics and cell culture microarrays	[98]
Stiffness	Patterned thermoresponsive hydrogel containing gold nanorods	Photothermal	Mechanical actuation induces changes in cell migration, localization of mechanosensory protein and secretion and alignment of FN	[99]
Stiffness	Hydrogels containing crosslinkers with stimuli-dependent intramolecular association	Reversible association-dissociation	Myoblasts transdifferentiation under cyclic mechanical stimulation	[100]

Table 3

Summary of strategies for controlling cell differentiation and for cell stimulation reviewed in this article.

Mechanism	Material	Phototriggered effect	Observed Properties and Effects	Ref
Bioactive molecule release	UCNPs with multishell structure containing SP	Upconversion and photoisomerization	Remotely controlled retinoic acid release promoted neuronal differentiation	[106]
Electrical stimulation	Polycaprolactone, P3HT and polypyrrole tricomponent platform	Photovoltaic	Enhanced neuronal differentiation	[108]
Topography and electrical stimulation	Different micro/nanoscale structures of P3HT	Photovoltaic	Directed cell growth and enhanced neuronal differentiation	[109]
Stiffness	Biorthogonal SPAAC synthesized hydrogels containing photocleavable <i>ortho</i> -nitrobenzyl	Photocleavage	Control over skeletal muscle stem cells fate	[111]
Topography	pDR 1m substrate	Photoisomerization and mass migration	Rerouting SCs' fate by dynamic modulation of morphological signals	[112]
Mechanical signals	UCNPs substrate functionalized with photocleavable PEG and RGD-PEG	Upconversion and photocleavage	Differentiation of MSCs towards adipocytes or osteoblasts	[113]
Mechanical signals	Light switchable tethers containing pdDronpa	Dimerization and cleavage	Expression of osteogenic or adipogenic markers depending on illumination	[114]
ROS generation	P3HT NPs	Photocatalysis	Trigger of intracellular calcium ion flux	[124]
Electrical stimulation	Interface composed of chemically modified organic materials	Photovoltaic	Stimulation of explanted degenerated mice retinas	[125]

Table 4

Summary of strategies for tissue engineering and wound healing reviewed in this article.

Mechanism	Material	Phototriggered effect	Observed Properties and Effects	Ref
EGF release	HA hydrogel containing azobenzene and β -CD	Photoisomerization	Dynamic controllable stiffness, enhanced wound healing and angiogenesis <i>in vivo</i>	[147]
Cells and neuroprotective protein delivery	Hydrogels synthesized via metal-directed assembly of His6-tagged proteins	Photocleavage	Injectable, self-healing hydrogel, enhanced axonal regeneration in mouse optic nerve injury model	[148]
Electrical stimulation	P3HT films	Photovoltaic	Enhanced proliferation and tubulogenesis of endothelial colony-forming cells	[152]
VEGF peptidomimetic release	Hydrogel containing a VEGF peptidomimetic with a photoremovable protecting group	Photocleavage	Spatio-temporal control of new blood vessel formation in the 3D hydrogel	[153]
Topography	pDR1m substrate	Photoisomerization and mass migration	Sprouts followed the direction of the generated pattern	[154]
Ca ²⁺ regulators delivery	UCNPs coated with mesoporous silica shell and peptide-bearing molecular cap	Upconversion and photocleavage	Control of macrophage polarization towards pro-inflammatory or pro-healing	[157]
RGD presentation	Acrylate-HA hydrogel and photodegradative RGD-loaded nanocarriers	Photocleavage	Enhanced anti-inflammatory M2 polarization	[150]
Topography	Gold nanorod-containing shape memory polycaprolactone film	Photothermal	Induce elongation and pro-healing polarization of macrophages <i>in vivo</i>	[159]
Shape memory implant	Copolymer of PLA and anthracene-functionalized PEG	Dimerization and cleavage	Tunable stiffness and athermal shape memory effect	[165]
Shape memory implant	Azobenzene-containing polymer network	Photoisomerization	Athermal shape memory effect by photoswitching of glass transition temperature	[166]
Shape memory implant	Melanin/polyurethane Composites	Photothermal	Biocompatible and shape memory effect <i>in vivo</i> using NIR light	[167]
Shape memory implant	Piperazine-based polyurethane and black-phosphorus sheets	Photothermal	Biodegradable, biocompatible and shape memory effect <i>in vivo</i> using NIR light	[168]
Shape memory implant	Cuprorivaite nanosheets into SMP	Photothermal	Biodegradable, ions release enhances wound healing and angiogenesis <i>in vivo</i>	[169]
Tissue bonding	Methacrylated collagen combined with rose Bengal and PLL	Photocrosslinking	Improved mechanical properties and no inflammation signs in skin wound model	[173]
Tissue bonding	Collagen-like peptides, acrylate functionalized multi-armed PEG, rose Bengal and PLL	Photocrosslinking	Tunable mechanical properties, improved wound healing in comparison to conventional suture	[174]
Tissue bonding and cell delivery	Porous chitosan film with rose Bengal	Photocrosslinking	Cultured hMSCs maintained viability and multipotency	[175]
Adhesive bioelectronic patch	Porous chitosan functionalized with polyamine and containing rose Bengal	Photocrosslinking	Stable mechanical and electronic properties under cyclic stretching	[177]
Tissue bonding	Poly(allylamine)-modified UCNPs/Hyaluronate rose Bengal conjugate complex	Upconversion and photocrosslinking	<i>In vivo</i> tissue bonding with higher tensile strengths than sutured tissues	[170]

Table 5

Summary of phototherapies reviewed in this article.

Therapy	Material	Observed Properties and Effects	Ref
PDT, PTT and chemotherapy	Poly(lactic- <i>co</i> -glycolic)/chitosan NPs loaded with carboplatin and indocyanine green	Biodegradable and biocompatible NPs for multimodal cancer therapy	[275]
PDT and PTT	NH ₂ -terminated diethylene glycol ligands tethered to <i>cis</i> -silicon phthalocyanine forming nanospheres	Multimodal therapy and phototheranostic agent, tumor-sensitive system due to pH-dependent response	[276]
Oxygen self-supplemented PDT	Ultrasonic dispersion of perfluorooctyl bromide liquid into porphyrin grafted lipid nanoparticles	Oxygen replenish into hypoxic tumors, can act as phototheranostic agent, inhibits tumor growth and metastasis	[277]
PTT	Hydrogel based on HA and gallic acid coordinated with ferric ions	Tumor ablation <i>in vivo</i> both in injectable and skin adherable forms	[286]
PTT	Croconaine dye and RGD engineered radiolabeled PEG self-assembled into NPs	Multimodal nanotheranostic assembly, tumor ablation and inhibition of tumor relapse	[287]
PTT and cell therapy	CAR T cells administered along with indocyanine green-loaded poly (lactide- <i>co</i> -glycolide) NPs	Combination therapy presents superior antitumor activity	[288]
PTT	Red blood cell membrane-camouflaged melanin nanoparticles	Enhanced blood retention and tumor accumulation. Higher PTT efficacy than bare melanin NPs	[292]
PTT	Dual peptide decorated melanin-like NPs	Tumor-targeting and autophagy-promotion synergistically enhances tumor regression	[293]
PTT	Prussian blue and modified chitosan hydrogel	Bacteria capture and kill	[294]
PTT and immunotherapy	Melanin-releasing bacteria loaded into red blood cells membrane	Recruitment and anti-tumor polarization of macrophages along with PTT inhibit tumor growth	[283]
PTT and anti-angiogenic therapy	Polydopamine crosslinked collagen/silk fibroin composites loaded with thrombin	Thrombin blocking blood vessels and PTT prevention of angiogenesis synergistically inhibits tumor relapse	[304]
Anti-angiogenic therapy	Hydrogel containing nitric oxide precursors and 2D tungsten oxide nanosheets	Tumor growth and recurrence inhibition	[305]