

Self-Healing Injectable Hydrogels for Tissue Regeneration

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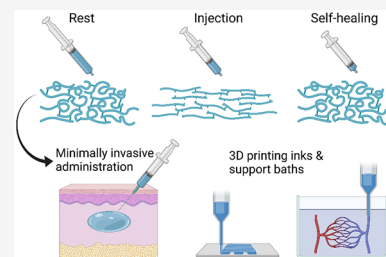
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ABSTRACT: Biomaterials with the ability to self-heal and recover their structural integrity offer many advantages for applications in biomedicine. The past decade has witnessed the rapid emergence of a new class of self-healing biomaterials commonly termed injectable, or printable in the context of 3D printing. These self-healing injectable biomaterials, mostly hydrogels and other soft condensed matter based on reversible chemistry, are able to temporarily fluidize under shear stress and subsequently recover their original mechanical properties. Self-healing injectable hydrogels offer distinct advantages compared to traditional biomaterials. Most notably, they can be administered in a locally targeted and minimally invasive manner through a narrow syringe without the need for invasive surgery. Their moldability allows for a patient-specific intervention and shows great prospects for personalized medicine. Injected hydrogels can facilitate tissue regeneration in multiple ways owing to their viscoelastic and diffusive nature, ranging from simple mechanical support, spatiotemporally controlled delivery of cells or therapeutics, to local recruitment and modulation of host cells to promote tissue regeneration. Consequently, self-healing injectable hydrogels have been at the forefront of many cutting-edge tissue regeneration strategies. This study provides a critical review of the current state of self-healing injectable hydrogels for tissue regeneration. As key challenges toward further maturation of this exciting research field, we identify (i) the trade-off between the self-healing and injectability of hydrogels vs their physical stability, (ii) the lack of consensus on rheological characterization and quantitative benchmarks for self-healing injectable hydrogels, particularly regarding the capillary flow in syringes, and (iii) practical limitations regarding translation toward therapeutically effective formulations for regeneration of specific tissues. Hence, here we (i) review chemical and physical design strategies for self-healing injectable hydrogels, (ii) provide a practical guide for their rheological analysis, and (iii) showcase their applicability for regeneration of various tissues and 3D printing of complex tissues and organoids.



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1. INTRODUCTION

Biomaterials are designed to support, treat, augment, repair, or replace a part of body tissue or its function. Over the past decades, the steady rise and optimization of biomaterials has revolutionized many fields of medicine.^{1,2} Biomaterials are subjected to continuous mechanical load or biochemical degradation which can impair their structural integrity and ultimately their functionality. Hence, extensive research efforts have been dedicated to the design of biomaterials that are self-healing, i.e., can halt or even reverse damages induced by mechanical or biochemical stresses. While self-healing may refer to the recovery of any biomaterial function, it most commonly describes the recovery of a material's structural integrity and associated mechanical properties.^{3–8} This review provides an overview of self-healing injectable hydrogels, a particular class of self-healing biomaterials that can fluidize under shear stress followed by recovery of their mechanical properties, and show exciting prospects for applications in tissue regeneration and 3D (bio)printing.

In context of self-healing, hydrogels are a promising class of biomaterials because of their dynamic and diffusive nature compared to traditional polymers, ceramics, or cements. Hydrogels with self-healing capacity can be assembled from a large toolbox of biocompatible materials exploiting noncovalent or dynamic covalent interactions.^{9–13} Hydrogels have long been recognized as promising biomaterial platforms with various applications in biomedicine.^{14–16} Hydrogels can be engineered to closely resemble the natural 3D environment, distribution of cell ligands and nutrients, and viscoelasticity of the extracellular matrix (ECM) of various tissues.^{17–19} They are common scaffold materials for the ex situ cultivation of tissue or organoids, commonly known as tissue engineering.^{20–22} Hydrogels are also increasingly used in cell culture, particularly in 3D, which has resolved many issues such as abnormal cell shaping or differentiation observed for cells cultured in 2D monolayers or on hard substrates.^{23–25} Hydrogel-based cell culture is still in its infancy, and several groups have provided practical guides on the use of hydrogels for cell culture to promote its implementation in biomedical research.^{26–29}

One particularly interesting class of self-healing hydrogels involves injectable or printable (in context of 3D printing) hydrogels. These self-healing injectable hydrogels are able to temporarily fluidize under shear stress and recover their original structure and mechanical properties after release of the applied stress, as schematically illustrated in Figure 1. This unique feature of self-healing injectable hydrogels has paved the way for several exciting applications in biomedicine, as summarized in Box 1. Most importantly, self-healing injectable hydrogels can be administered in a minimally invasive manner at the target

site.^{30–32} The hydrogels can be structurally and mechanically fine-tuned to mimic various tissues and aid regeneration by providing mechanical tissue support.^{33,34} Because of their rapid self-healing, these hydrogels can be administered with high spatial control and mold into patient-specific tissue defects without undesired off-target leakage. This opens many avenues for personalized interventions, in particular in combination with noninvasive imaging techniques.^{35–38} Self-healing injectable hydrogels can be exploited for locally targeted and sustained delivery of therapeutics,^{39–42} and their shear-thinning plug flow in syringes facilitates administration of live cells.^{43–45} Ultimately, self-healing injectable hydrogels are increasingly used as inks in 3D (bio)printing or support matrices in freeform 3D printing, and facilitate printing of complex tissue models and organoids with spatial control over material composition and distribution of cells or biomolecules.^{46–49}

Box 1: Potential advantages of self-healing injectable hydrogels for tissue regeneration

- Minimally invasive administration through narrow syringes
- Moldability to patient-specific irregular tissue defects
- High spatial control of hydrogels without off-target leakage
- Spatiotemporally controlled delivery of cells and therapeutics
- Increased cell survival and function compared to suspension-based delivery
- Suitability as 3D (bio)printing inks and support baths in freeform 3D printing

Accordingly, there has been an increasing number of studies reporting novel tissue regeneration strategies exploiting self-healing injectable hydrogels. Nevertheless, there are still several bottlenecks that currently impede their development and translation. First of all, the nomenclature and definitions in literature are often inconsistent, wherefore we summarized the relevant terms related to self-healing injectable hydrogels in section 2. The design of self-healing injectable hydrogels requires precise control over hydrogel properties that allow for injectability, self-healing, as well as desired tissue interactions. Hence, we provide an overview of chemical and physical design strategies in section 3. There is currently no clear consensus which rheological protocols and benchmarks are most suitable for the characterization of self-healing injectable hydrogels. In section 4, we provide a practical guide for their rheological analysis. The translation of self-healing injectable hydrogels toward biomedical applications requires hydrogels designed specifically for the target tissue and mode of regeneration. Consequently, section 5 elaborates hydrogel requisites and regeneration strategies for specific tissues. Ultimately, self-healing injectable hydrogels are widely used as 3D (bio)printing

inks, but the lack of quantitative parameters associated with printability often impedes their translation from the rheometer to the printer. In section 6, we discuss the requirements for hydrogels as 3D (bio)printing inks and their potential for printing complex tissues and organoids.

2. THE SELF-HEALING DICTIONARY

The field of self-healing biomaterials is still in its infancy with first reports dating from the late 1990s^{50,51} but has evolved very rapidly, particularly during the past decade. Upon emergence of self-healing biomaterials as a research field, various terms and nomenclatures have been introduced which are not always well-defined and sometimes used inconsistently in literature. In 2011, Brochu et al.³ introduced a classification of biomaterials depending on their self-healing capacity. *Zeroth generation* materials are thereafter able to merely retard deterioration, mostly by tailored composite mixtures that reduce wear or crack propagation.⁵² *First generation* materials are able to irreversibly repair defects without restoring the original structure, mostly by healing agents incorporated in capsules or tubes that are released upon breakage, referred to as **extrinsic** self-healing.^{53,54} *Second generation* materials are able to fully restore their original structure due to noncovalent or reversible covalent chemistry, also called **intrinsic** self-healing.^{4,9} This may occur spontaneously under ambient conditions (**autonomous**) or rely on an external trigger such as heat or UV-light (**stimulus**).^{15,55} This traditional classification of self-healing focuses on the avoidance and repair of small defects induced by physicochemical deterioration of biomaterials in situ. However, there has been an increasing demand for biomaterials that are able to fully fluidize temporarily, i.e., exhibit a shear-induced viscosity decrease by the order of decades, followed by self-healing and recovery of their original mechanical properties.^{12,30} This self-healing injectable behavior is almost exclusively observed for viscoelastic soft matter such as hydrogels with reversible chemistry, along with certain dense suspensions, colloidal glasses and gels, and emulsions.^{56–62} The driving force for this development has been the ambition to administer biomaterials in a minimally invasive manner, along with the rapid emergence of 3D printing. Because of their ability to fully fluidize during capillary extrusion in a syringe or 3D printing nozzle, these hydrogels are commonly termed **injectable**, or in context of 3D printing, **printable**. Hence, self-healing injectable hydrogels unite two seemingly contradictory properties, flowability and mechanical stability, depending on the experienced shear stress. Compared to other self-healing biomaterials, they experience much higher stresses, span much wider ranges of viscosity and need to recover at much shorter time scales. In continuation of the classification introduced by Brochu et al.,³ we propose that self-healing injectable biomaterials represent the *third generation* of self-healing biomaterials. The relevant terms used for self-healing biomaterials are summarized in Box 2. An extensive compilation of terminology used for biomaterials is provided by Vert et al.⁶³

Box 2: Definitions of self-healing biomaterials

Self-healing biomaterial. A biomaterial with the ability to halt or repair structural damages and thereby maintain or recover its functionality.

Extrinsic. The biomaterial contains structural elements, e.g. capsules or tubes, filled with a chemical healing-agent that is released upon breakage of the element.

Intrinsic. The biomaterial is able to recover its structure without any specialized healing-agent due to reversible interactions, i.e. noncovalent or reversible covalent.

Autonomous. The self-healing process occurs spontaneously under ambient conditions (temperature, pH, ionic strength) of material use.

Stimulus. The self-healing process is triggered by an external input of energy (heat, UV, electric field) or a change in the physicochemical environment (temperature, pH, ionic strength).

Injectable/printable. The biomaterial is able to temporarily fluidize upon mechanical load or during capillary extrusion followed by recovery of its original structure and mechanical properties.

3. DESIGN STRATEGIES FOR SELF-HEALING INJECTABLE HYDROGELS

Hydrogel formation requires the establishment of cross-links between molecular and/or particulate building blocks in an aqueous environment, resulting in assembly of these units into a 3D interconnected hydrogel network. A wide range of material types have been used as building blocks for the formation of self-healing injectable hydrogels. Early work on reversible hydrogels has focused particularly on the reaction of boric acid with charged polysaccharides.^{64–67} Natural polymers commonly used for the formation of such hydrogels include gelatin, collagen, hyaluronic acid, alginate, and chitosan, while synthetic polymers include poly(ethylene glycol) (PEG) and poly(*N*-isopropylacrylamide). These different material systems can be functionalized with various reversible cross-linking strategies. Evidently, hydrogels and cross-linking strategies envisioned for biomedical applications should be biocompatible, i.e., (i) should not trigger an excessive inflammatory response, (ii) be biodegradable within a desired time frame (unless envisioned as permanent implant), and (iii) be cleared from the body without the production of toxic byproducts. Also, it is important to bear in mind that hydrogels may be affected by swelling, hysteresis, or aging in situ, which can affect their mechanical and self-healing properties.^{68–70}

The design of hydrogels that can temporarily fluidize during extrusion and exhibit rapid self-healing requires in-depth understanding of chemical mechanisms involved in hydrogel

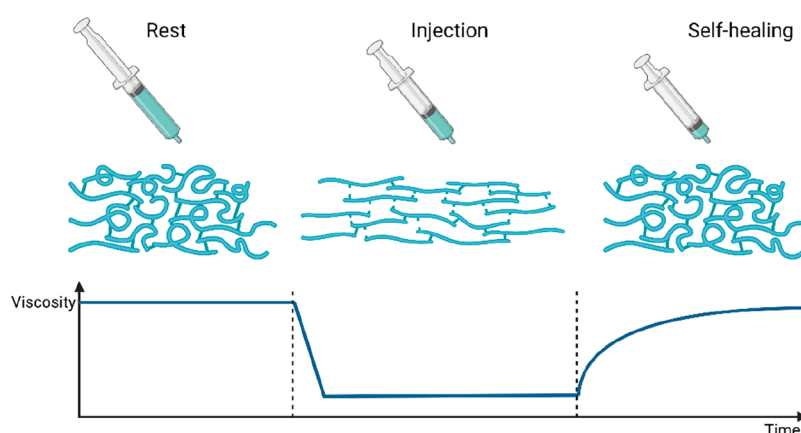


Figure 1. Schematic behavior of a self-healing injectable hydrogel with (i) gel-like properties at rest, (ii) fluidization under shear due to reversible chemistry and/or alignment in the flow field, and (iii) self-healing of the original structure and mechanical properties after flow.

Table 1. Overview of Equilibrium Binding Constants K_{eq} of Reversible Interactions Commonly Employed for Self-Healing Injectable Hydrogels

noncovalent interactions					
type	metal coordination	metal coordination	metal coordination	hydrophobic	hydrogen bonding
motif	catechol-Fe ³⁺	bisphosphonate-Ca ²⁺	histidine-Zn ²⁺	β -cyclodextrin-adamantane host–guest complexation	ureidopyrimidinone
K_{eq} (M ⁻¹)	10 ⁴⁰ –10 ⁴⁵	10 ^{17.25}	10 ^{6.5}	10 ⁵	6 × 10 ⁷
conditions	in aqueous media	in aqueous media at 25 °C	in aqueous media at 25 °C	in aqueous media	in chloroform at 25 °C
refs	72,79	72,80	72,81	82,83	84
dynamic covalent bonds					
reaction	Diels–Alder			Schiff base	
K_{eq} (M ⁻¹)	~10 ⁶			10 ⁴ –10 ⁶	
conditions	for furan and maleimide motifs; In aqueous media at ~92.5 °C			for hydrazone linkages	
refs	71,85			86,87	

formation. A fundamental prerequisite for chemical design of such material systems is the reversibility of bonds responsible for cross-linking of the hydrogel network. The reversibility of interactions is a key design criteria that allows for injectability as well as *intrinsic* self-healing (see section 2). Additionally, the physical form and network structure of hydrogels can strongly impact their properties, including injectability and self-healing performance. Therefore, in this section, we discuss key strategies for the design of self-healing injectable hydrogels both in terms of chemical mechanism (section 3.1) as well as physical form (section 3.2).

3.1. Chemical Design of Self-Healing Injectable Hydrogels

The design of hydrogels that are self-healing and injectable but also physically stable is a complex trade-off that needs to be carefully balanced. On one hand, the strength and density of cross-links is crucial for the formation of mechanically stable hydrogels. On the other hand, the self-healing and injection capacity of hydrogels largely depend on the reversible nature of the cross-links. Consequently, the chemical design of self-healing injectable hydrogels is achieved by exploiting non-covalent interactions, dynamic covalent bonds, or combinations thereof. The dynamic behavior of these reversible cross-links is regulated by their association rate constant (k_a), dissociation rate constant (k_d), and equilibrium binding constant ($K_{eq} = k_a/k_d$).⁷¹ k_a determines the rate of cross-link formation, and higher k_a values translate to faster gelation kinetics and self-healing, e.g., after shear-induced damage during injection.^{72,73} k_d on the other

hand indicates the rate of rupture of these cross-links. Higher k_d values can translate to higher molecular mobility in the gel network and therefore favor injectability and a larger degree of self-healing after mechanical damage. K_{eq} , which is determined by the ratio between k_a and k_d , is consequently related to all these factors (i.e., gelation kinetics, injectability, and self-healing).^{71,72,74} An overview of K_{eq} of interactions commonly employed for self-healing injectable hydrogels is provided in Table 1. Generally, excessively large K_{eq} values result in hydrogels that are not self-healing nor injectable due to a low dynamicity of the cross-links. Lower k_{eq} values favor injectability and self-healing but may result in hydrogels with lack of integrity and rapid dissolution.^{72,73}

Hence, it is important to tune the dynamics of self-healing hydrogels to the relevant processing time scales. Thereto, the cross-link lifetime ($\tau_b = 1/k_d$), which is the average time that a bond is at its associated state, can be a useful measure.^{71,75,76} Previous reports indicate that hydrogels with τ_b values in a range of 1 μ s to 1 min exhibit self-healing at relevant time scales.^{77,78} However, a purely chemical approach at self-healing via binding constants may not be sufficient to characterize self-healing hydrogels, which also involves many aspects of polymer physics. In practice, rheology provides a useful tool to determine self-healing kinetics of hydrogels. For ideal Maxwell fluids, relating the material relaxation time τ_R to the relevant observation time τ_{obs} of a specific process, i.e., the Deborah number $De = \tau_R/\tau_{obs}$, provides a good measure.⁷¹ As many hydrogels behave as elastic

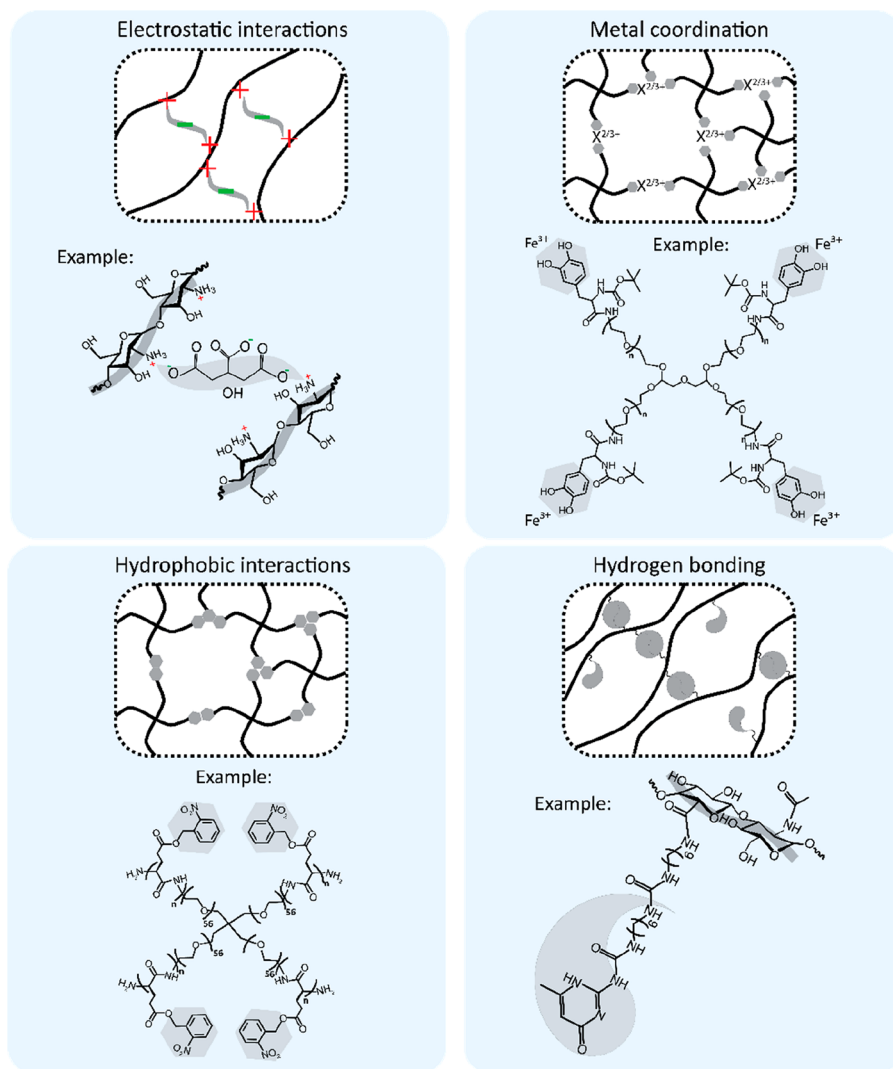


Figure 2. Overview of common noncovalent chemical interactions used for the design of self-healing injectable hydrogels. Examples for electrostatic, metal coordination, hydrophobic, and hydrogen bonding are based on refs 91, 92, 32, and 93, respectively. Adapted with permission from ref 4. Copyright 2018 Wiley.

solids before injection and no relaxation time can be determined, measuring their transient self-healing kinetics is a viable alternative. The rheological characterization of hydrogels will be discussed in detail in section 4.

Consequently, there is no “one-size-fits-all” chemical design strategy for self-healing injectable hydrogel systems, and the selected strategy requires various interrelated considerations that depend on the specific hydrogel application. In the following sections, we discuss key chemical strategies for the design of self-healing injectable hydrogels for tissue regeneration.

3.1.1. Noncovalent Interactions. Noncovalent interactions are widespread in nature, as their versatility allows for unique material behavior, ranging from soft and short-lived hagfish slime to the strong adhesive capacity of marine mussels.^{88–90} Thanks to their reversibility and possibility to be employed in aqueous environments, various noncovalent interaction strategies have been used for the design of self-healing injectable hydrogels, as summarized in Figure 2.

3.1.1.1. Electrostatic Interactions. Electrostatic attractive forces between oppositely charged chemical groups have been exploited in a wide range of strategies for the design of self-

healing hydrogels. One common route for this design is the use of intrinsic attractive forces between anionic and cationic polymers. Examples for such strategies include combinations of anionic (bovine) and cationic (porcine) gelatin.⁶² Alternatively, an ionic monomer such as negatively charged citrate can be added as a cross-linker to a cationic polymer such as chitosan to form self-healing injectable hydrogels.⁹¹ Various natural polymers like proteins are polyampholytes, and both anionic and cationic groups exist along their chains. Consequently, “anionic” or “cationic” designations only refer to the net charge of such macromolecules. Synthetic zwitterionic polymers can be developed by copolymerization of anionic and cationic building blocks, which can assemble into self-healing hydrogels based on intermolecular electrostatic attractive forces.^{94,95} Importantly, electrostatic interactions are highly susceptible to the ionic strength and pH of their environment. Under conditions of high ionic strength electrostatic forces are screened and might not be sufficiently strong to form hydrogels or maintain their physical integrity.⁹⁶ Similarly, changes in pH can alter the net charge of polymers, potentially reverting electrostatic attractive forces to repulsive interactions.⁹¹ In spite of the potential negative impact of these environmental factors, they can also provide unique

opportunities for stimulus-responsive control of in situ assembly and tuning of hydrogel properties.^{61,97–99}

3.1.1.2. Metal Coordination Interactions. Metal–ligand coordination interactions are widely employed in nature for structural support. These interactions typically take place through a chelation process by sequestration of metallic ions by multiple organic ligands. As such, multiple coordination bonds form between a ligand motif and the sequestered ion.¹⁰⁰ The strength of metal coordination interactions varies significantly depending on the involved ligand–ion pair, with k_{eq} values ranging from $10^{6.5} \text{ M}^{-1}$ for histidine– Zn^{2+} to 10^{45} M^{-1} for catechol– Fe^{3+} .^{72,79,81} A widely known example of metal–coordination interactions is the complexation between catechol groups of the dihydroxyphenylalanine (DOPA) amino acids and Fe^{3+} cations in the cuticle of mussel byssal threads.¹⁰¹ Numerous studies described such mussel-inspired self-healing hydrogels based on reversible catechol– Fe^{3+} coordination. In the earliest report, self-healing hydrogels were developed by combining 4-arm PEG polymers with Fe^{3+} cations.⁹² Although this study did not investigate the injectability of the hydrogels, this strategy has been successfully employed by other groups to develop self-healing injectable hydrogels.^{72,102,103} An alternative mussel-inspired strategy involves the use of histidine–metal ion coordination for hydrogel cross-linking. However, the injectability of such hydrogel systems has only been demonstrated prior to complete gelation.^{104,105}

Bisphosphonate-containing drugs, such as alendronate, are often employed as medication to treat osteoporosis. The bisphosphonate groups in these drugs exhibit a high binding affinity toward the calcium within the inorganic phase of bone. Accordingly, the strong yet reversible ($k_{\text{eq}} \sim 10^{17.25} \text{ M}^{-1}$)^{72,80} nature of these coordination interactions offers a great opportunity for the design of self-healing injectable hydrogels. Because Ca^{2+} ions are abundantly present in the mineral phase of bone, this strategy has been particularly successful for the development of bone regenerative systems.^{106–111}

A common coordination-based strategy involving Ca^{2+} ions is the use of alginate biopolymers. The hydroxyl and carboxylate groups within alginate chains can form complexations with Ca^{2+} ions, leading to hydrogel formation. The viscoelastic properties of such hydrogels can be easily tuned by various factors such as molecular weight of alginate chains and concentration of Ca^{2+} ions used.^{29,112–114} Although injectable systems based on alginate– Ca^{2+} coordination have been successfully developed for tissue regeneration,^{115–118} the self-healing capacity of this system from shear-induced damage has not been extensively demonstrated in literature.⁷² Nevertheless, previous work has shown that alginate hydrogels can self-heal after network disruption caused by ultrasonication employed for on-demand drug release.¹¹⁹ Similar to alginate, carrageenans exhibit a rapid and strong ion-sensitive gelation that can be exploited for self-healing hydrogel design.^{120,121} Interestingly, the coordination of carrageenans with different ions can be exploited to induce secondary, tertiary, and quaternary structures in carrageenans, yielding hydrogels with tunable properties.¹²²

3.1.1.3. Hydrophobic Interactions. Hydrophobic interactions play a central role in various biological processes such as protein folding.¹²³ These reversible interactions are driven by nonpolar moieties or hydrophobic sections of polymer chains, which tend to minimize contact with water molecules through their aggregation. Hydrogels based on hydrophobic interactions can be formed by modification of hydrophilic polymers with hydrophobic units such as alkyl chains.¹²⁴ Alternatively,

hydrogel building blocks can be modified with hydrophobic peptides, as exploited for elastin-like polypeptides with glycine-rich and proline-rich hydrophobic domains,^{125,126} as well as by conjugation of poly(γ -*o*-nitrobenzyl-L-glutamate) to 4-arm PEG.⁹³

Host–guest interactions involving hydrophobic interactions with cyclodextrin (CD) motifs as the host molecule have also been frequently exploited to construct self-healing injectable hydrogels. CD molecules are cyclic oligosaccharides which contain an interior hydrophobic cavity. Several studies have functionalized polymers (e.g., hyaluronic acid) with CD motifs as host and complementary hydrophobic moieties such as adamantane (Ad) molecules as guest motifs.^{32,127–131} This reaction has a k_{eq} of $\sim 10^5 \text{ M}^{-1}$.^{82,83} Such two-component systems can self-assemble into self-healing injectable hydrogels thanks to reversible CD–Ad complexation.^{32,129} Interestingly, other studies have exploited the intrinsic aromatic groups of gelatin (e.g., phenylalanine) to form reversible host–guest cross-links with CD-functionalized polymers for self-healing hydrogel design.^{132,133}

3.1.1.4. Hydrogen Bonding Interactions. Hydrogen bonds are dipole–dipole interactions that are responsible for a wide range of biological processes such as DNA base-pairing. A hydrogen bond involves a donor and acceptor, which are typically a hydrogen-bonded electronegative atom and another electronegative atom in its vicinity. Several strategies have been developed for the design of self-healing injectable hydrogels that rely on hydrogen bonds.^{134–143} A prominent example is the linking of ureido-pyrimidinone (UPy) units to a polymer chain via alkyl-urea spacers.^{135,136} This reaction has a k_{eq} of $6 \times 10^7 \text{ M}^{-1}$ (measured in chloroform at 25 °C).⁸⁴ In water, hydrogen bonds need to be shielded from competing hydrogen-bonding water molecules to be effective cross-linkers for hydrogels. In UPy-based hydrogels, the alkyl spacers can create a hydrophobic pocket, shielding the hydrogen-bonding UPy or urea moieties from the water molecules. This strategy has been successful for the development of self-healing hydrogels with different polymeric backbones.^{137–141} An emerging strategy for the design of self-healing injectable hydrogels is based on catechol-mediated hydrogen bonding. While catechols have traditionally been employed for hydrogel design via metal coordination interactions or quinone-based covalent bonding upon their oxidation, recent studies have demonstrated that catechol motifs can also be employed for the formation of self-healing injectable hydrogels based on hydrogen bonding.^{142,143} The complementary pairing of DNA strands is another avenue for hydrogel formation based on reversible hydrogen bonding. Although injectable¹⁴⁴ or self-healing¹⁴⁵ systems have been developed using this strategy, this approach has not yet been extensively employed for self-healing injectable hydrogels. These designs rely on the intrinsic capacity of DNA strands for complementary pairing between adenine (A) and thymine (T), as well as guanine (G) and cytosine (C) nucleotides. The high specificity of DNA base pairing exhibits a great potential to precisely define, at the nanoscale, the assembly of self-healing injectable hydrogels and their resulting properties.

3.1.2. Dynamic Covalent Interactions. Chemical cross-linking of polymers by covalent bonds is the conventional strategy for hydrogel formation. However, these cross-links are typically static and do not exhibit the reversibility required for the design of self-healing injectable hydrogels. Therefore, dynamic covalent interactions have emerged for the formation of self-healing systems. Figure 3 provides an overview of

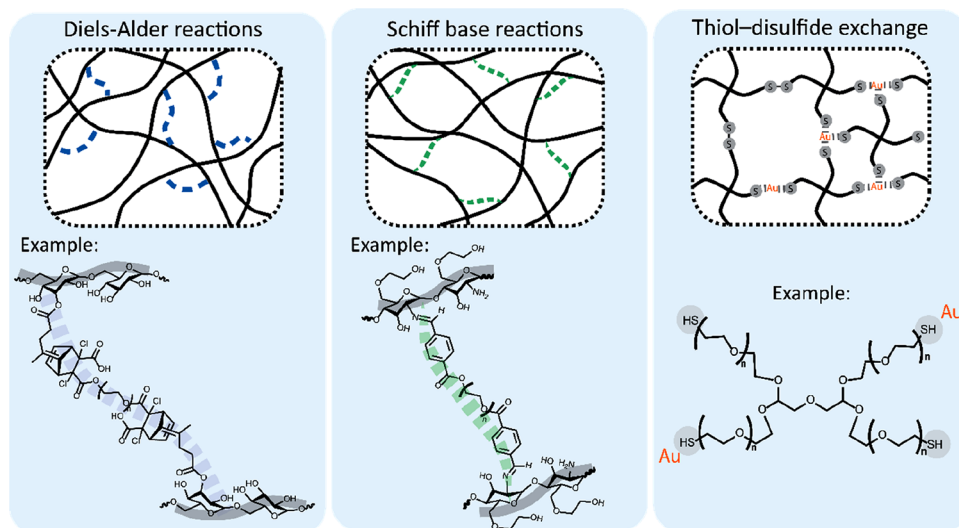


Figure 3. Overview of common strategies for the design of self-healing injectable hydrogels based on dynamic covalent interactions. Examples, from left to right, are based on refs 146, 147 and 148, respectively. Adapted with permission from ref 4. Copyright 2018 Wiley.

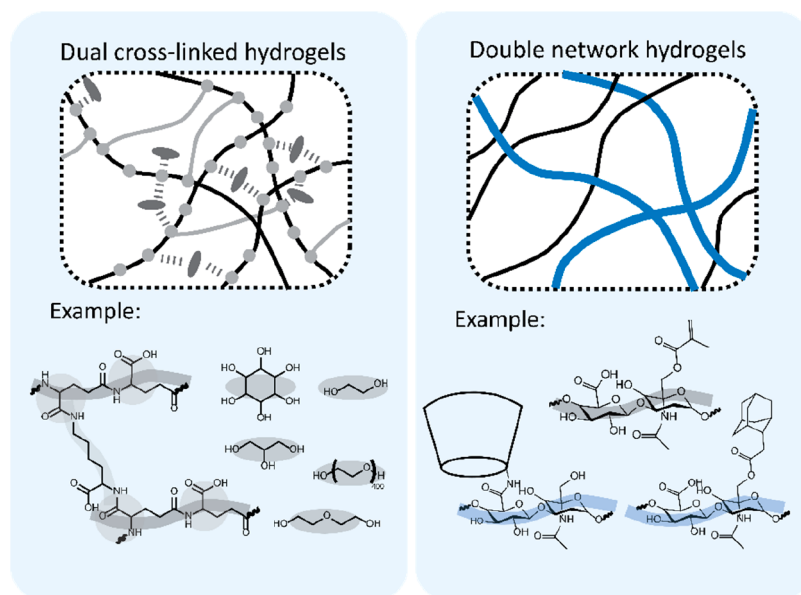


Figure 4. Overview of common strategies for the design of self-healing injectable hydrogels based on multiple interactions (dual cross-linked) or multiple materials (double network). Examples, from left to right, are based on refs 165 and 166, respectively. Adapted with permission from ref 4. Copyright 2018 Wiley.

common reactions that can be used for the design of self-healing injectable hydrogels based on dynamic covalent interactions.

3.1.2.1. Diels–Alder Reactions. Diels–Alder (DA) reactions take place between a diene and a dienophile. DA reactions are described as “click-type” reactions because they are selective and catalyst-free without forming byproducts.¹⁴⁹ For tissue engineering applications, the most common DA-based strategy involves combination of a polymer containing maleimide groups (as dienophile) and a polymer with furan groups (as diene).^{150,151} The reversibility of the resulting bonds relies on their ability to undergo a reverse reaction (retro-Diels–Alder reaction). This reversibility, however, is usually achieved at high temperatures,¹⁵² limiting the applicability of DA chemistry for the design of self-healing injectable hydrogels for tissue regeneration. The k_{eq} of furan and maleimide is $\sim 1 \text{ M}^{-1}$ at $92.5 \text{ }^{\circ}\text{C}$.^{71,85} This limitation has been overcome by employing

fulvene-modified hydrophilic dextran and dichloromaleic-acid-modified PEG, as dienes and dienophiles, respectively.¹⁴⁶ Thanks to the reversibility of their dynamic covalent cross-links, the hydrogels formed based on the DA reaction of these two components were able to self-heal at room temperature after shear or cutting-induced damage.

3.1.2.2. Schiff Base Reactions. Schiff base reactions are the reaction of a nucleophilic group (e.g., amine or hydrazine) and the electrophilic carbon of aldehydes or ketones and result in the formation of reversible quasicovalent imine or hydrazone bonds. These selective reactions have been widely employed as dynamic covalent bonds to form self-healing hydrogels through mixing of two-component systems containing the reactive motifs.¹⁵³ Their rate and capacity of self-healing is determined by the involved chemical groups and their specific k_{eq} .¹⁵⁴ For instance, for hydrazone linkages k_{eq} values between 10^4 and 10^6

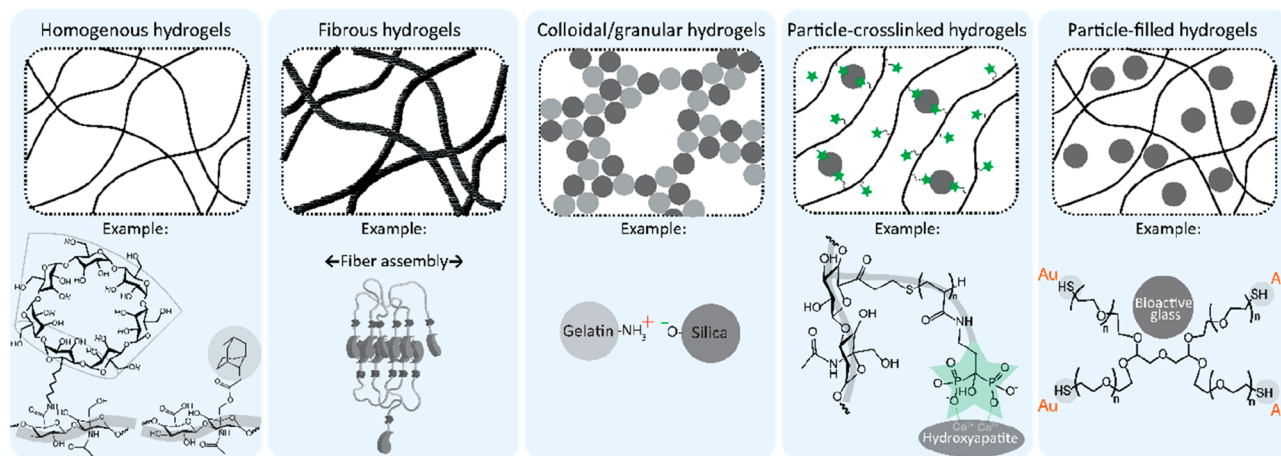


Figure 5. Overview of common physical forms of self-healing injectable hydrogels. Examples, from left to right, are based on refs 32, 136, 61, 110, and 192, respectively. Adapted with permission from ref 4. Copyright 2018 Wiley.

M^{-1} have been reported.^{86,87} The most commonly employed Schiff base approach is the reaction between an aldehyde-functionalized polymer with the amine groups of another component. This strategy for self-healing hydrogel formation has been realized in various material systems such as hyaluronic acid–cystamine,¹⁵⁵ dextran–chitosan,¹⁵⁶ glucosaminan–chitosan,¹⁵⁷ and chitosan–cellulose–polydopamine.¹⁵⁸ Owing to the fast gelation kinetics of certain Schiff base reactions, recent investigations have employed dual-barrel syringe systems to facilitate injectability followed by in situ gelation.^{157,158}

3.1.2.3. Thiol–Disulfide Exchange Reactions. Thiol–disulfide exchange reactions exploit the dynamic behavior of disulfide bonds in the presence of nucleophilic thiols under neutral or alkaline pH conditions, enabling the formation of reversible cross-links for self-healing hydrogels. During thiol–disulfide exchange, a sulfur atom of a disulfide bond is attacked by a thiolate anion, which is an effective nucleophile. As a result, a new disulfide bond is formed, while a new thiolate becomes available.¹⁵⁹ The thiolation of polymeric building blocks can be achieved by functionalization of polymer chains with thiol groups^{160–162} as well as the reduction of disulfide bonds of proteins into thiols.¹⁶³ Thiol–disulfide exchange reactions lose their dynamic and reversible nature upon aerial oxidation of thiolate groups, which can impede the self-healing of hydrogels. This problem can be solved by protection of reactive thiolates from aerial oxidation through capping with Au(I) or Ag(I) ions.^{148,164}

3.1.3. Combination of Interactions. Self-healing injectable hydrogels are increasingly designed by combining multiple cross-linking strategies. As shown in Figure 4, this can be achieved by (i) using different types of interactions to cross-link a single polymer network (dual cross-linked hydrogels) and/or (ii) combining two interpenetrating polymer networks which are independently cross-linked (double network hydrogels). The use of multiple interaction types or polymers can be exploited to fine-tune the mechanical properties of hydrogels and balance the trade-off between self-healing capacity and physical stability.

Noncovalent interactions are rather weak and might be sensitive to certain environmental factors (e.g., pH or ionic strength). Hence, several studies have combined multiple noncovalent interactions, typically involving electrostatic, hydrophobic, and hydrogen bonds, for the design of self-healing injectable hydrogels.^{167–170} Among the various types of

dynamic covalent interactions that have been combined with noncovalent cross-links^{158,171–174} or with other dynamic covalent cross-links,¹⁷⁵ significant research interest has been focused on the use of Schiff base reactions. Accordingly, imine bonds arising from these reactions have been combined with metal coordination interactions,^{171–173} hydrogen bonds,¹⁷⁶ and electrostatic interactions.¹⁷⁴ Interestingly, the co-utilization of metal coordination bonds involving catechol groups has been successful to endow hydrogels with tissue-adhesives functionalities.^{158,173}

Another class of self-healing injectable hydrogels that benefit from multiple cross-linking modalities are double network hydrogels. These materials are composed of two interpenetrating polymer networks which are independently cross-linked. The mechanical response and stability of these materials do not solely depend on a single hydrogel network, and each network can make a distinctive contribution to the properties of the resulting double network hydrogel. A typical design of these materials exploits “weaker” noncovalent cross-links to form one network that is readily reversible to facilitate injection and rapid self-healing. The second network is cross-linked based on “stronger” covalent bonds that can provide further mechanical support. Entanglement of the interpenetrating networks can additionally contribute to the mechanical response of these materials.^{177–179} Double network hydrogels that solely rely on noncovalent cross-links can offer new possibilities for specific applications. For instance, hybrid double network hydrogels composed of synthetic and natural polymers have been synthesized using catechol-based coordination and UPy-based hydrogen bonding, which exhibit photothermal properties that are responsive to near-infrared light and pH stimuli.¹⁸⁰

Naturally, the reinforcement of self-healing hydrogels with additional cross-links can be also achieved using static covalent bonds. Although static covalent cross-links based on Michael-addition reaction have been employed for the formation of self-healing injectable double network hydrogels,¹⁶⁶ static covalent cross-links are not reversible and typically render hydrogels noninjectable and nonself-healing. Therefore, static covalent cross-links are commonly formed postinjection (e.g., via photocross-linking) for in situ stabilization of extruded materials.^{181–186}

Finally, it is important to point out that many interaction types, particularly noncovalent interactions, are inherent to most materials. For example, self-assembling peptides or proteins

form supramolecular hydrogels typically based on a combination of interactions such as hydrogen bonding, hydrophobic, and electrostatic forces.^{187–190} Moreover, although one interaction type might be the driving force behind hydrogel formation, engineering the properties of these systems requires holistic understanding of other interactions involved. For instance, attractive electrostatic forces between anionic and cationic gelatin have been employed for hydrogel formation. Nevertheless, at high ionic concentrations, electrostatic interactions are screened, and other interactions such as hydrophobic and van der Waals forces might play a more significant role in determining properties of such gelatin-based hydrogels.^{62,191}

3.2. Physical Design of Self-Healing Injectable Hydrogels

In addition to the type of chemical cross-links employed for hydrogel design, the physical form and spatial architecture of the hydrogel network largely impact the properties of the final hydrogel system. While monolithic hydrogels composed of a homogeneous 3D polymer network is the traditional strategy for the physical design of hydrogels, an increasing number of investigations employ alternative physical design approaches for structurally heterogeneous hydrogels to overcome challenges and/or endow hydrogels with unprecedented properties. An overview of physical hydrogel design strategies is provided in Figure 5. In the following sections, we discuss key strategies concerning the physical design of hydrogel networks for self-healing injectable systems.

3.2.1. Monolithic Hydrogels. The most common approach for the design of hydrogels involves the use of one polymer and formation of cross-links among polymer chains. At sufficiently high polymer concentration and cross-linking (number) density, a cross-linked network of polymer chains can span the 3D space resulting in the formation of a monolithic hydrogel with homogeneous structure and gel-like behavior ($G' > G''$, frequency-independent moduli). Following this approach, various types of monolithic self-healing injectable hydrogels have been developed.^{32,93,102,126,127,129,143,146,155} In these systems, factors such as network mesh size, cross-linking density, as well as molecular weight and shape of polymeric building blocks, impact the network topology of resulting hydrogels, which in turn influence the bulk properties of hydrogels.^{14,193}

3.2.2. Fibrous Hydrogels. In contrast to conventional monolithic hydrogels, natural ECM in tissues is formed hierarchically from molecular building blocks commonly resulting in fibrous structures. A well-known example for this phenomenon involves fibrous collagen structures that are assembled hierarchically from molecular building blocks into fibrils, fibrils into fibers, and fibers into a 3D fibrous networks.¹⁹⁴ The fibrous nature of these structures has been shown to impact mechanical (e.g., strain stiffening¹⁹⁵) and biological (e.g., directional cell migration¹⁹⁶) properties of these materials. Hence, research on hydrogels with a fibrous structure has gained considerable interest. Fibrous hydrogel scaffolds can be obtained by decellularizing ECM followed by reinjection.^{197–201} Alternatively, fibrous hydrogels can be assembled from collagen^{202,203} or by the bottom-up assembly of proteins into amyloids and, ultimately, fibrous hydrogels.^{188,204} A synthetic strategy comprises tuning electrostatic interactions between poly-L-lysine and self-assembling dipeptides, resulting in fibrous self-healing injectable hydrogels.^{205,206} PEG-based supramolecular hydrogels that utilize UPy motifs (discussed as hydrogen bonding groups in section 3.1.1) for dimerization and lateral

stacking result in fibers, which form an entangled 3D fibrous network that is self-healing and injectable.¹³⁶ Importantly, the properties of these fibrous hydrogel networks not only depend on the supramolecular interactions between molecular building blocks for fiber assembly but also on interfiber interactions that enable cross-link formation between the fibers.

3.2.3. Colloidal and Granular Hydrogels. An emerging approach for the design of self-healing injectable hydrogels is based on the use of particles as building blocks. In this strategy, hydrogels are formed through 3D assembly or jamming of colloidal (nano)particles (nanometers to a few micrometers)^{61,184,207–214} or larger microgels (few to several micrometers).^{134,215–220} Generally, hydrogels made of colloidal particles are referred to as colloidal hydrogels, whereas those assembled from larger microgels are termed granular hydrogels. Hydrogels based on colloidal/granular building blocks have the potential to be more dynamic compared to monolithic hydrogels, which can be favorable for dynamic biological phenomena such as cell ingrowth.^{207,221} Although inorganic and/or nonswollen polymeric particles can also be employed to form colloidal hydrogels,^{109,222–225} the particulate building blocks utilized in both colloidal and granular hydrogels are usually of organic nature. Colloidal hydrogels can be obtained by the aggregation of natural organic nanoparticles. In particular, polysaccharide nanoparticles such as nanocellulose have been extensively studied in the past years for the formulation of self-healing injectable hydrogels^{226–229} or 3D printing inks.^{230–234}

Another route is based on hierarchical bottom-up assembly of polymer building blocks into hydrogel particles, and assembly of these hydrogel particles into bulk colloidal/granular hydrogels. This hierarchical network design offers flexibility in terms of types of interactions and materials that can be used for the formation of self-healing injectable hydrogels. For instance, highly cross-linked hydrogels are generally not self-healing and injectable. However, smaller microgel particles made from the same material and type of cross-links may very well be self-healing and injectable.¹³⁴ Following this approach, several self-healing injectable colloidal hydrogels have been developed based on colloidal hydrogel particles. By employing reversible noncovalent interparticle interactions, gelatin nanoparticles have been assembled, with or without other particle types, into dynamic colloidal gel networks.^{61,62,109,191,207,212,218,223,235} Covalently cross-linked hyaluronic acid-based microgels were fabricated and jammed to form self-healing injectable granular hydrogels based on reversible interparticle host–guest,²¹⁷ hydrazone,²³⁶ or metal coordination interactions.²¹⁶ Chitosan can also be aggregated into spherical microgels or nanogels to form granular hydrogels, which have been used as injectable tissue scaffolds and drug delivery vehicles.^{237–240} Recent findings suggest that altering the morphology of the microgel building blocks allows tuning of the properties of resulting granular hydrogels.^{215,219}

3.2.4. Particle Cross-Linked Hydrogels. In addition to their use for the formation of colloidal and granular hydrogels, particulate building blocks can also be employed for the formation of mixed polymer–particle hydrogels. To this end, attractive interactions can be exploited to enable polymer chains to bridge (nano)particles and form a percolated hydrogel network (bridging flocculation). Incorporated (nano)particles can act as fillers in polymer hydrogels to enhance their mechanical properties, as well as providing a more dynamic network structure associated with enhanced self-healing. Importantly, the mechanical response of these hydrogel

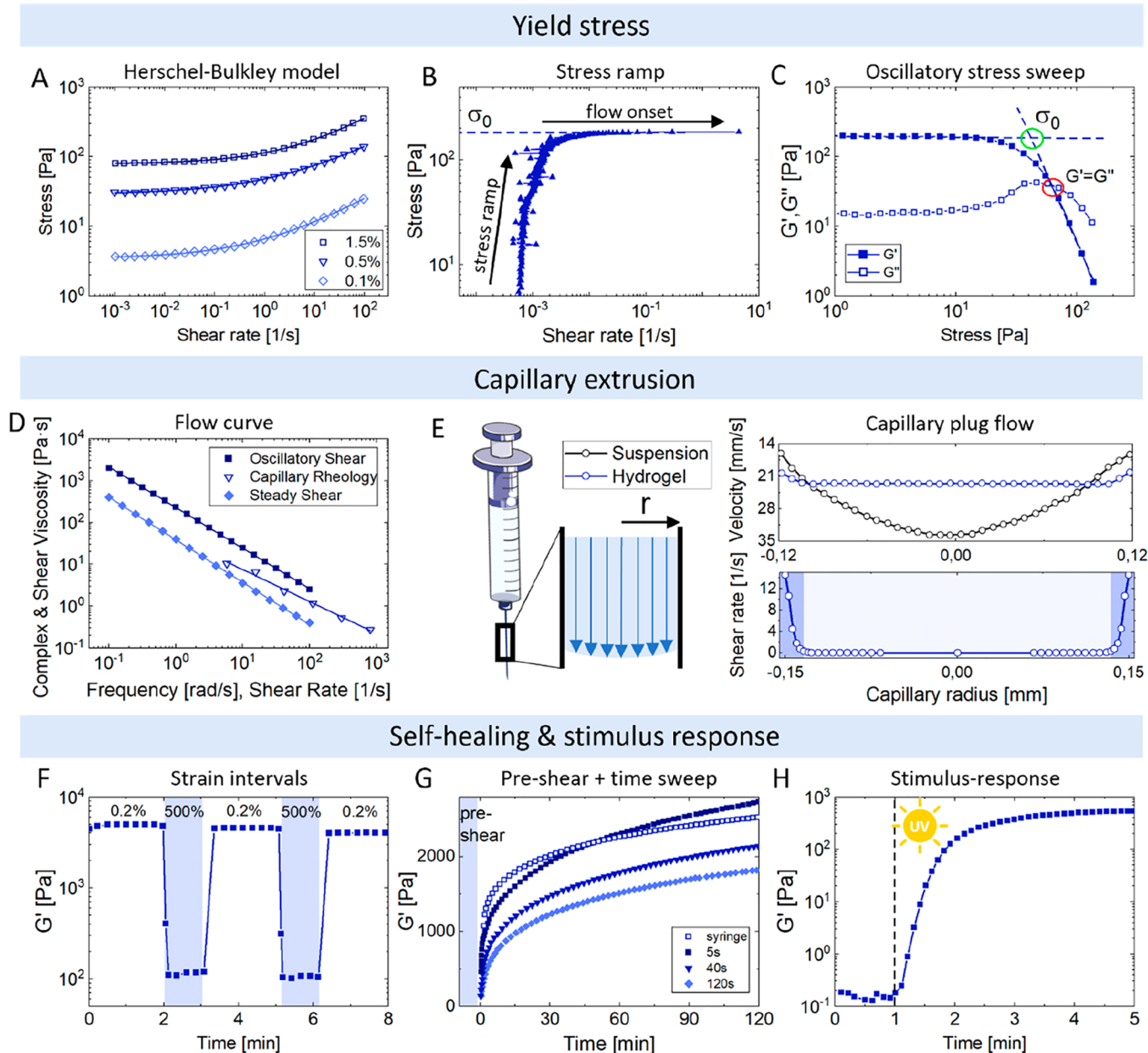


Figure 6. Overview of rheological protocols for the quantification of apparent yield stress, capillary extrusion, and self-healing capacity of self-healing injectable hydrogels. (A) Flow curves down to low shear rates with Herschel–Bulkley model fit. (B) Stress ramp to detect onset of material flow. (C) Oscillatory stress sweeps with apparent yield stress extraction at crossover of G' tangents of the linear and nonlinear regime. (D) Flow curves of the same hydrogel obtained by oscillatory, capillary, and steady shear rheology. (E) (left) Schematic of hydrogel plug flow in a syringe needle. (right) Experimental data on hydrogel velocity and shear rate profile as a function of capillary radius compared to cell suspension. (F) Self-healing test using alternating low-high strain cycles. (G) Self-healing determined by oscillatory time sweep following preshear at a shear rate of 1000 1/s for varying periods or upon deposition of the hydrogel through a 26-gauge needle. (H) Example of stimulus-induced hydrogel strengthening to enhance mechanical hydrogel properties after extrusion. Note: Graphs show different materials. (A,C) Replotted with permission from ref 265. Copyright 2016 Elsevier. (B,D) Replotted with permission from ref 227. Copyright 2019 American Chemical Society. (E) Replotted with permission from refs 44 and 234. Copyright 2012 and 2018 American Chemical Society. (F) Replotted with permission from ref 31. Copyright 2017 American Chemical Society. (G) Replotted with permission from ref 261. Copyright 2010 Royal Society of Chemistry, (H) Replotted with permission from ref 270. Copyright 2020 Wiley.

materials is highly determined by their cross-linking density, as particles act as cross-linking nodes. To tune the polymer–particle interactions, polymers and/or particles can be functionalized with motifs capable of forming dynamic covalent and/or noncovalent interactions. These polymer–particle hydrogel networks have been assembled using electrostatic,^{241,242} hydrophobic,^{243,244} and coordination interactions,^{106,108,110,245} as well as molecular recognition motifs.²⁴⁶ Moreover, dynamic covalent

bonds based on Schiff base,^{247–250} thiol–disulfide,^{251,252} and boronic ester²⁵³ have recently been employed to form these hydrogels.

3.2.5. Particle-Filled Hydrogels. (Nano)particles can be included in hydrogel formulations without actively contributing to the cross-linked network. The particles can be exploited to modify hydrogel mechanical properties and often act as fillers to reinforce hydrogels. In context of self-healing injectable

hydrogels, the incorporation of particles is attractive, as they can provide increased mechanical stability at rest while remaining dynamic which facilitates injection and self-healing. Besides mechanical aspects, many hydrogels for tissue regeneration are loaded with functional (nano)particles, either as drug carriers or due to their inherent antibacterial, anticancer, or pro-angiogenic action, which therefore also fall in this category. Several examples are discussed in section 5. A critical factor is a balanced distribution of particles within the hydrogel matrix to achieve uniform mechanical properties.²⁵⁴ This criterion is typically achieved by dispersing the particles within the hydrogel precursor solutions prior to gelation.^{192,255} The colloidal self-ordering of charged particles can be exploited to obtain uniform crystalline particle arrays.²⁵⁴ Alternatively, chemical strategies have been employed to allow for in situ formation of particles within the hydrogel matrix.^{256,257}

4. RHEOLOGY GUIDE TO SELF-HEALING INJECTABLE HYDROGELS

While self-healing may generally refer to the recovery of any material functionality, in the context of injectable hydrogels, it mostly refers to the recovery of mechanical properties after partial fluidization. To qualify as self-healing injectable hydrogel or 3D printing ink, a hydrogel should exhibit three key criteria: (1) A yield stress, (2) extrudability, and (3) fast recovery of the mechanical properties, e.g., viscoelasticity or yield stress after flow.^{30,31,258–260} Rotational rheology is commonly applied to characterize self-healing injectable hydrogels, however, there is currently no clear consensus which protocols are most suitable to assess these characteristics. On the other hand, certain rheological procedures are well established but may not be suitable for the intended purpose. Most notably, it should be emphasized that rotational rheology is not able to mimic the breakup and capillary flow of hydrogels during injection.^{44,227,234,261} Furthermore, there is a lack of clear rheological benchmarks that render a hydrogel injectable or printable. Here, we provide a practical guide for the characterization of self-healing injectable hydrogels using rheology and suggest which protocols and experimental setups are most suitable to assess the three individual characteristics of self-healing injectable hydrogels (a summary is provided in Box 3). For a general overview on avoiding misinterpretations in shear rheology caused by torque limits, inertia effects, surface tension, or wall slip, the reader is referred to the overview provided by Ewoldt et al.²⁶²

Box 3: Rheology guide for self-healing injectable hydrogels

1) Determination of yield stress

- From Herschel–Bulkley fit of flow curves (from low to high shear rates)
- Stress ramp (critical: avoid slip)
- From tangent cross-over in oscillatory stress sweeps

2) Capillary extrusion flow

- Ideally: Capillary or in-line rheology
- Alternative 1: Oscillatory frequency sweep or steady shear flow curve (over- or underestimation of viscosity due to different flow fields)
- Alternative 2: Measure extrusion pressure on syringe plunger (results depend on used syringes/needles)

3) Self-healing and stimuli-response

- Strain intervals
- Oscillatory time sweep following disruptive shear or stimulus

4.1. Yield Stress Measurement

A yield stress before and after extrusion is considered a critical factor for the mechanical stability and integrity of injectable hydrogels, as well as the shape fidelity of 3D printing inks.^{30,31,258–260} The concept and measurement of yield stresses is one of the biggest controversies in soft material rheology. Most soft materials do not have a true yield stress and will flow at sufficiently long time scales. In this case, the concept of a yield stress is an idealization trying to define the stress required to induce flow at more relevant time scales and is therefore termed apparent yield stress.²⁶³ As a consequence, “The” yield stress σ_0 can be determined by several rheological protocols which may produce considerably diverging values.^{264,265} One approach involves performing rate-controlled flow curves and fitting of the Herschel–Bulkley constitutive equation (Figure 6A):²⁶⁶ $\sigma = \sigma_0 + k\dot{\gamma}^n$, where σ is the measured stress, $\dot{\gamma}$ the shear rate, and k and n adjustable model parameters. To obtain ideal flow curves, this procedure is usually performed from high to low shear rates. However, structural recovery of self-healing hydrogels may interfere with the data obtained at decreasing shear rate. Therefore, it is recommended to measure from low to high shear rates and ensure full material recovery after loading, which may be guaranteed by performing an oscillatory time sweep at low strain (e.g., 0.01%) until the hydrogels have reached their equilibrium state again. Nevertheless, it may be difficult to obtain data at low enough shear rates for a good fit. Alternatively, a stress ramp experiment may be performed, where the stress is continuously increased to detect at which stress the material yields, as shown in Figure 6B. Stress ramps can be found in literature plotted as a function of shear rate, deformation, or viscosity.^{227,234,267} As these experiments are prone to wall slip they should ideally be performed using a vane or rough geometry.^{268,269} Apparent yield stresses can also be determined from oscillatory stress sweeps as shown in Figure 6C. However,

there is a controversy regarding the derivation of the apparent yield stress from such strain sweeps. The crossover of G' and G'' is a common benchmark, which however is usually beyond material yield and overestimates the apparent yield stress. A better approximation is based on the intersection of the tangents of the linear and nonlinear regime of G' (see Figure 6C), which provides values close to those obtained from Herschel–Buckley fitting.²⁶⁵ Other possibilities to determine apparent yield stresses such as stress growth or creep experiments were found impractical.²⁶⁵

4.2. Capillary Extrusion Flow

The assessment of hydrogel extrudability requires a major methodological optimization because the currently applied protocols are often not suitable to assess rheological characteristics of hydrogels during extrusion through a capillary. On one hand, it is common practice to claim suitability of hydrogels for injection or 3D printing based on confirmation of their shear-thinning behavior, where the terms “shear-thinning” and “injectable” are occasionally used synonymously. Shear-thinning indeed facilitates injectability through small needles as a lower pressure is required for their extrusion. However, hydrogels are almost exclusively shear-thinning, which does not automatically render them suitable for injection or printing. On the other hand, a material with an apparent yield stress and Newtonian flow, i.e., a Bingham plastic, may be injectable if it can be extruded at a reasonable pressure.²⁷¹ Furthermore, the injectability of hydrogels is most commonly determined using rotational rheometers, which are not able to reproduce the flow profile of hydrogels during syringe or dye extrusion. Figure 6D shows flow curves of the same hydrogel obtained from three different rheological setups, namely oscillatory, capillary, and steady shear rheology, revealing considerable discrepancies regarding the measured viscosity of 1 order of magnitude. This deviation is attributed to the fact that hydrogels are structured soft materials which typically do not follow the Cox–Merz rule,²⁷² i.e., the measured viscosity depends on the applied flow profile and degree of destructive shear.^{273,274} The highest viscosity was measured using oscillatory frequency sweeps in the linear viscoelastic regime where no structural breakup occurs. A medium viscosity was measured using a capillary rheology setup which most closely resembles the flow profile during extrusion. The lowest viscosity was measured using steady shear rheology, indicating destructive shear. Hence, both oscillatory and steady shear rotational rheology fail to capture the flow profile and rheology of hydrogels during capillary extrusion and result in an over- or underestimation of their viscosity, respectively.²²⁷ The flow profile of hydrogels during capillary extrusion was investigated by tracking incorporated fluorescent beads,^{44,275} small-angle X-ray or neutron scattering,^{138,261,276} or polarization microscopy exploiting the alignment of anisotropic particles.^{234,277} The reports all indicate that hydrogels exhibit a wide central plug flow region where the material experiences minimum shear rates, and a narrow shear zone near the capillary wall, as visualized in Figure 6E. In contrast, more liquid samples such as cell suspensions exhibit a parabolic flow profile with relative shear over the whole syringe radius, which is detrimental for cell survival.⁴⁴ Such a plug flow cannot be accurately reproduced using rotational rheology. Hence, to truly capture the flow profile of injectable hydrogels during extrusion, the use of a capillary extrusion setup is essential.

A straightforward approach to this end involves force measurement directly at the syringe plunger upon hydrogel

extrusion, allowing easy assessment and comparison of different hydrogel formulations.³¹ The disadvantage of this technique is that the force measured at the syringe plunger strongly depends on the employed syringe and needles which limits its reproducibility. In a capillary rheology setup, the pressure is measured inside the syringe before the contraction, which allows calculation of the material viscosity independent of the setup. Capillary rheology is considered the most suitable technique to determine hydrogel viscosity during injection. There are several commercial benchtop capillary rheometers available, which however are usually designed for relatively high volumes and pressures and have rarely been employed for biomedical hydrogels.²⁷⁸ Nevertheless, several viable alternatives have been proposed in literature. Lopez-Hernandez et al.²⁷⁹ combined a syringe pump with a load cell to control extrusion pressure and measure the corresponding flow rate. Bertsch et al.²²⁷ described a straightforward capillary rheometer setup based on inexpensive and readily available equipment, namely a syringe pump and a 3D printed syringe attachment that houses a pressure sensor and can mount different capillaries. One problem of these setups can be the relatively high sample volumes required compared to rheometers. As alternatives that require lower volumes, setups based on a micropipette modified with a stepper motor and microcontroller²⁸⁰ or microfluidics²⁸¹ have been proposed. For 3D printing applications, Coogan and Kazmer²⁸² described an elegant 3D printing nozzle containing a pressure transducer and a thermocouple, essentially upgrading the nozzle to an in-line rheometer. As an alternative to capillary rheology, Allmendinger et al.²⁸³ proposed a mathematical model to translate rheological data obtained by rotational rheology to extrusion flow.

Another bottleneck that may impede translation of hydrogel formulations from the rheometer to specific applications is the lack of quantitative rheological benchmarks that render a hydrogel injectable or printable. There have recently been efforts to quantify the range of the consistency index k and flow behavior index n of power law fluids.^{279,284} An interesting insight from these studies is that hydrogels require different flow behavior for administration via short syringes compared to longer catheters.²⁷⁹ We consider the establishment of such quantitative rheological benchmarks an important step to foster the future translation of self-healing injectable hydrogels.

To conclude, the commonly applied oscillatory and steady shear rheology protocols are not able to reproduce the flow profile of hydrogels during capillary extrusion. Along with the lack of quantitative benchmarks, this can strongly impede the translation of hydrogels toward biomedical applications. Assessment of injectability using rotational rheometers will probably remain the standard approach for the foreseeable future due to their widespread availability and usability. However, it should be stressed again that capillary rheology setups are more relevant to mimic injection and capture the true material behavior during extrusion flow.

4.3. Measuring Self-Healing and Stimulus-Response

Fast self-healing, here defined as the recovery of mechanical properties, is crucial for spatial in situ confinement of injectable hydrogels and shape fidelity of 3D printing inks.^{30,31,38,258–260} The kinetics of self-healing should be in a relevant range for the envisioned application. For ideal Maxwell fluids, relating the material relaxation τ_R time to the relevant observation time τ_{obs} (Deborah number $De = \tau_R / \tau_{obs}$) provides a useful measure.⁷¹ However, most hydrogels exhibit a purely elastic response at

small strains (frequency-independent moduli), and no relaxation time can be extracted from frequency sweeps. Instead, rheological protocols aim at measuring the transient recovery of viscosity/elasticity after breakup. The transient self-healing of injectable hydrogels can be determined by oscillatory time sweeps following destructive shear, either by short periods of high strains (e.g., 1000%), sometimes called the three interval-time-thixotropy (3ITT) test, or a preshear at high shear rates.^{31,260,261} Multiple consecutive high–low strain cycles are often performed to confirm that self-healing properties are maintained, as visualized in Figure 6F. Reported protocols for the high strain phase vary considerably in literature regarding strain values and periods, which impedes the comparability of hydrogel breakup and self-healing. Furthermore, while oscillatory time sweeps are suitable to capture the self-healing of hydrogels, oscillatory strain or shear is not able to mimic the destructive shear experienced by hydrogels during extrusion, as discussed in detail in section 4.2. Hydrogels are transported in a plug flow through capillaries and only experience structural breakup near the outer wall.^{44,234,261,275} Yan et al.²⁶¹ convincingly demonstrated that the rate of self-healing strongly depends on the time and shear rate of the applied preshear, as shown in Figure 6G. Moreover, the authors tried to mimic the recovery following extrusion by injecting the hydrogel through a syringe directly on the rheometer, quickly lowering the geometry, and measure self-healing. While this approach is not ideal due to the lowering of the plate, it exemplifies the problem of mimicking hydrogel breakup in capillary shear because the observed self-healing kinetics differed from those observed for any rotational preshear (Figure 6G). As a consequence, self-healing kinetics reported in literature are difficult to compare as different strains or preshear treatments are employed. Furthermore, the term self-healing is used rather qualitatively and sometimes ambiguously, as there is no defined recovery threshold to justify its use. Nevertheless, measuring G'/G'' or viscosity in oscillatory time sweeps is certainly suitable to capture the transient self-healing of injectable hydrogels following destructive shear. The destructive shear during the 3ITT test or preshear are rather exaggerated compared to the plug flow in capillaries and should therefore not impede the translation of injectable hydrogels. While many hydrogels may exhibit transient self-healing for minutes to even hours after shear, a sufficiently fast recovery within the first few seconds is probably most relevant for applications as injectable hydrogels or 3D printing inks.

There is a great interest to design hydrogels that can be mechanically reinforced after injection beyond their intrinsic self-healing capacity. Such stimuli-responsiveness can also be captured by oscillatory time sweeps while applying the stimulus, as shown in Figure 6H. For injectable hydrogels, the change in ambient temperature^{285–292} or pH^{61,98,99} in the body may be exploited to mechanically strengthen hydrogels. While the temperature can be readily adapted in most rheological setups, the variation of pH or ionic strength may require specialized geometries that allow for subphase exchange,²⁹³ controlled setting of hydrogels,²⁹⁴ or the use of slow-dissolving salts or acids.⁶¹ Magnetic hydrogels have been developed and investigated using specialized rheological setups, allowing the local heating or stiffening upon application of a magnetic or electrical field.^{295,296} A common stimulus-responsive reinforcement strategy that is particularly useful for 3D printing inks involves the application of photo-cross-linking after extrusion,

which requires a transparent UV-rheology setup to capture the increase in mechanical properties.^{270,297}

5. APPLICATIONS OF SELF-HEALING INJECTABLE HYDROGELS FOR TISSUE REGENERATION

Self-healing injectable hydrogels are at the forefront of many emerging strategies for tissue regeneration. Their main advantage is their ability to be injected locally in a minimally invasive manner followed by self-healing and recovery of their mechanical properties to guarantee in situ hydrogel confinement. In several applications, the mechanical support of self-healing hydrogels may already be sufficient to aid tissue regeneration, e.g., after myocardial infarction.^{33,298,299} spinal cord injuries,^{300,301} or vitrectomy.³⁰² It is important to note that rheological requirements for injectable hydrogels may be different for delivery by a short syringe compared to a long percutaneous catheter.^{279,303} Lopez Hernandez et al.²⁷⁹ provided an insightful analysis of hydrogel administration in syringes vs catheters, including quantitative boundary limits for the consistency index k and flow behavior index n for both administration routes. Another key advantage of self-healing injectable hydrogels is their moldability to patient-specific tissue defects, which allows for personalized interventions. Particularly in combination with noninvasive imaging techniques, the volume, location, and even stiffness of administered hydrogels can be adapted to the patient-specific injury.^{35,304–307} Self-healing hydrogels may be loaded with bioactives to further promote tissue regeneration or therapeutics to combat diseases. The fast self-healing allows local confinement of hydrogels and incorporated compounds, resulting in a higher and more sustained effective dose and reduced off-target side effects.^{38,41,42,308} The retention at the injection site and biodistribution of injected hydrogels is an aspect that is often neglected. Schotman and Dankers³⁸ recently provided an insightful review on this issue, pointing out the importance of hydrogel mechanical properties and degradation, administered volume, as well as biological factors such as tissue contractions and hydrogel-tissue affinity. Drug release kinetics of therapeutics from hydrogels depend on the hydrogel pore size, drug size, and solubility, and drug–matrix interactions.^{14,42,309,310} Drug release mechanisms can range from simple Fickian diffusion^{310,311} to sophisticated stimuli-responsive or on-demand release systems.^{312–315} Hydrogels equipped with complementary oligonucleotide sequences or antibodies have been proposed as reloadable depots that can actively capture systemically administered drugs from the bloodstream.^{316–319} The longevity of hydrogels is also exploited for the local delivery of excitable particles for repeated photothermal or brachytherapy against cancer.^{320–322}

Hydrogels for tissue regeneration are often designed to provide an ideal physicochemical environment for cell ingrowth and subsequent tissue regeneration in terms of, e.g. porosity, cell adhesion ligands, and viscoelasticity.^{18,323–325} Because of the plug flow in capillaries (Figure 6E) hydrogels are suitable for the delivery of live cells, as embedded cells experience a reduced shear stress compared to suspensions.^{43,44,326–328} Cell survival rates are also maintained in longer catheters.^{329,330} Hydrogels can thus be used as carriers for live stem or progenitor cells to stimulate tissue regeneration^{326,328,331–337} or cell encapsulation therapy, i.e., the administration of genetically engineered cells which release regenerative growth factors.^{338,339} The mechanical properties of hydrogels significantly affect the recruitment and differentiation local cells. For instance, soft hydrogels have been

found to promote adipogenesis, while stiffer hydrogels induce osteogenesis of stem cells.^{112,340} Hydrogels are also increasingly designed to specifically recruit local immune cells and exert immunomodulatory effects, e.g., for cancer immunotherapy.^{341–344} There are many self-healing injectable hydrogel formulations currently at a preclinical or clinical stage. Interesting perspectives how to foster their translation are provided by Correa et al.¹⁶ and Øvrebø et al.³⁴⁵

To conclude, self-healing injectable hydrogels may be exploited for several tissue regeneration strategies, either as “empty” hydrogels for mechanical support, for controlled delivery of drugs or cells, for repeated localized radiation therapy, or for local cell recruitment. A schematic overview of tissue regeneration strategies using self-healing injectable hydrogels is provided in Figure 7. Tissue regeneration strategies for specific tissues are discussed in more detail in the following subsections.

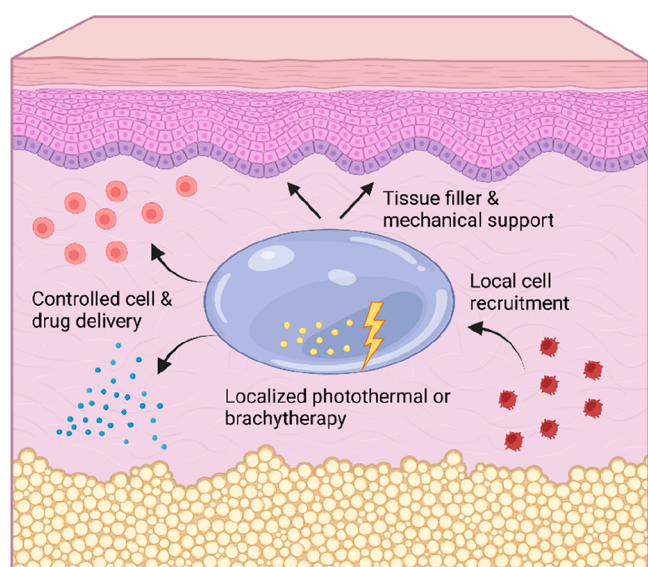


Figure 7. Schematic overview of tissue regeneration strategies employing self-healing injectable hydrogels.

5.1. Cardiac Tissue Regeneration

Myocardial infarction, i.e., heart attack, is a leading cause of death and morbidity in modern society. More specifically, left ventricular remodeling after myocardial infarction is the main cause of heart failure.³⁴⁶ Myocardial infarction and ischemia result in an acute loss of myocardium and mechanical stability, which leads to dilation, hypertrophy, and tissue scarring, particularly around the left anterior descending coronary artery.^{347,348} Early postinfarction restraint and mechanical support can greatly reduce infarct expansion and pathological remodeling.³⁴⁹ Self-healing injectable hydrogels hold great promise to prevent such left ventricular remodeling, as they can be administered rapidly by minimally invasive surgery and provide mechanical tissue support, as visualized in Figure 8A. The potential of self-healing injectable hydrogels to mechanically support infarcted myocardium and prevent pathological ventricular remodeling has already been demonstrated in rodent, ovine, and porcine models.^{37,200,358,350–357} Stiffer hydrogels show greater efficiency in preventing ventricular remodeling, stressing the need for hydrogels that remain injectable but achieve high stiffness in situ, e.g., by secondary cross-linking strategies.³⁵⁹ Besides mechanical support, self-

healing injectable hydrogels can be functionalized in various ways to support cardiac tissue regeneration. Hydrogels with antioxidative properties can reduce the oxidative stress in ischemic myocardium,^{360–363} while hydrogels loaded with growth factors, pro-angiogenic cytokines, miRNA, stem, or progenitor cells can stimulate cardiac repair.^{364–373} Hydrogels with immunomodulatory efficacy were shown to reduce postinfarct inflammatory response.³⁷⁴ Infarct type and extent of damage may vary considerably within patients. Self-healing injectable hydrogels offer the possibility to precisely tune the volume, placement, and stiffness of the used hydrogels to the patient-specific infarct. The combination of noninvasive magnetic resonance imaging and finite element simulations have proven particularly useful to visualize the affected region and predict the required tissue support, allowing for fast and personalized treatment of heart attacks.^{35,304–307} The spatial retention of injected hydrogels at the target site is often insufficiently considered. Schotman and Dankers³⁸ recently addressed this issue specifically for hydrogels used to treat myocardial infarction and identified hydrogel formulation (mechanical properties, degradation, tissue affinity), therapy strategy (injection timing and volume), and cardiac pulsation as important factors determining the retention of injected hydrogels and contained therapeutics. An elegant approach toward enhanced spatial control exploits the pericardial cavity as natural mold for hydrogel delivery.^{375,376} First clinical trials confirmed that injectable hydrogels based on alginate can prevent pathological left ventricular remodeling and improve exercise capacity after myocardial infarction. However, while these hydrogels were well tolerated without severe side effects in one study,³⁷⁷ another study reported a 30-day mortality of 8.6%,³⁷⁸ underlining the need for further investigations toward safe and effective clinical applications.

5.2. Spinal Cord Injuries and Ischemic Stroke

The central nervous system comprises some of the body's most fragile and surgically least accessible tissues, with still limited treatment options to date. Self-healing injectable hydrogels have the potential to overcome many issues associated with the clinical use of conventional biomaterials. In spinal cord injuries, viable axons are often left at the injury site that may allow partial axonal rewiring. Bridging of the lesion with a supportive structure considerably favors recovery, but invasive surgery or implants may be detrimental at this stage.³⁰⁰ Furthermore, implants are often not versatile enough for the wide variety of spinal cord injuries. Self-healing injectable hydrogels provide a new prospect, as they allow for minimally invasive administration and filling of patient specific spinal cord injuries. Self-healing injectable hydrogels have been successfully applied to bridge spinal cord lesions and promote neovascularization and axonal ingrowth in rodent and porcine models.^{301,384,385–393} Incorporated growth or trophic factors as well as progenitor or Schwann cells can further enhance tissue regeneration and axonal rewiring.^{392,394–401} Biomaterials for spinal cord injuries should ideally provide directional guidance to promote axonal rewiring. There are several possibilities to introduce structural anisotropy in injectable hydrogels, e.g., exploiting the flow field in the syringe or magnetic alignment.^{228,234,402–405} Rose et al.⁴⁰² demonstrated that dorsal root ganglions show directed growth in a hydrogel with magnetically aligned anisotropic microgels. An interesting alternative is the design of electroconductive hydrogels that facilitate transmission of electrical signals between nerve cells and promote their rewiring.^{249,406,407}

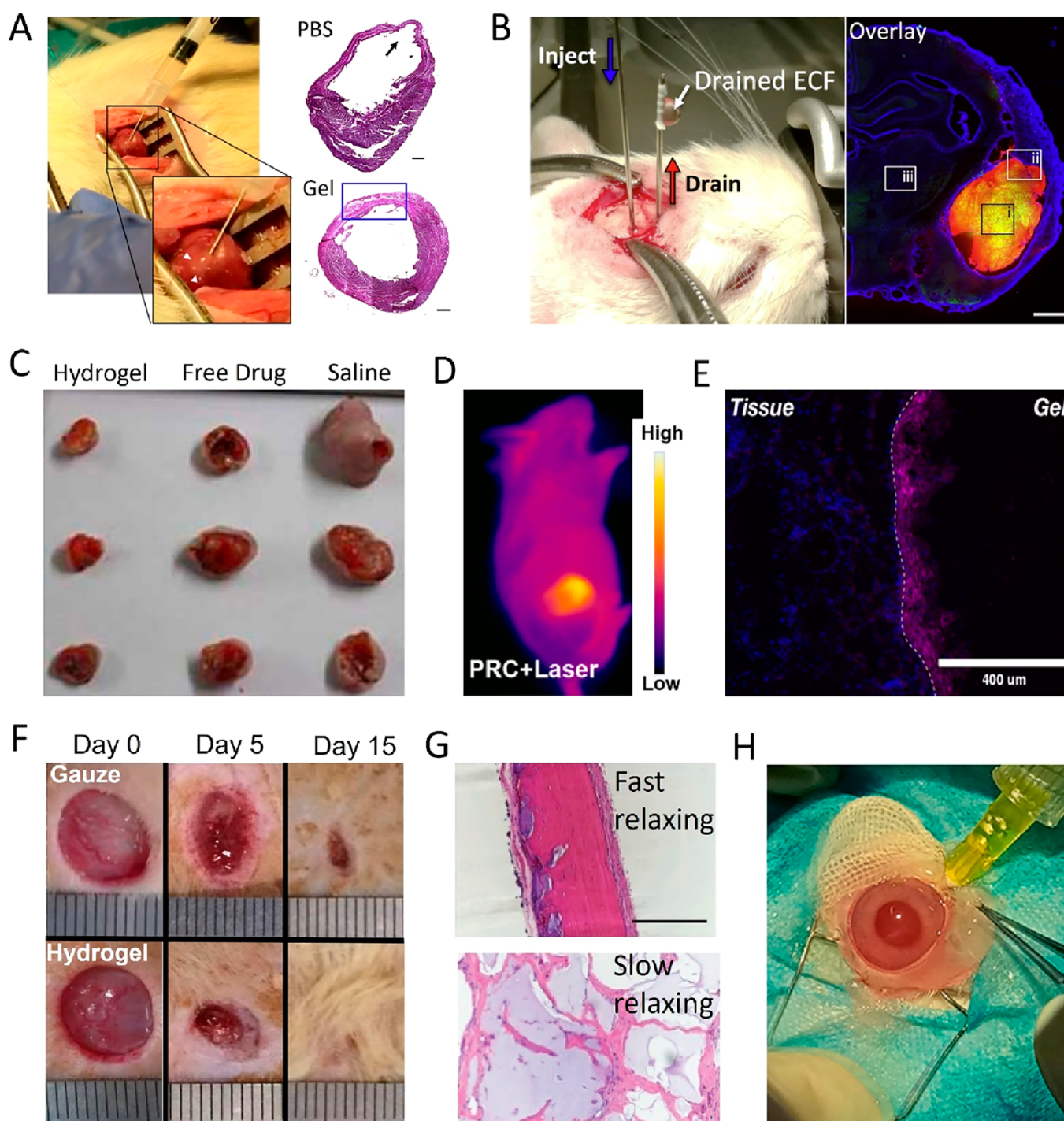


Figure 8. Overview of applications of self-healing injectable hydrogels for regeneration of different tissues. (A) Cardiac hydrogel injection to provide mechanical support and prevent left ventricular remodeling after myocardial infarction compared to injection of phosphate buffered saline (PBS, scale bar = 0.5 mm). Reproduced with permission from ref 31. Copyright 2017 American Chemical Society. Reproduced with permission from ref 352. Copyright 2009 Elsevier. (B) (left) Hydrogel injection into stroke cavity with simultaneous drainage of extracellular fluid (ECF) to maintain intracerebral pressure. (right) Histological image showing the injected hydrogel in the stroke cavity (orange, scale bar = 1 mm). Reproduced with permission from ref 36. Copyright 2015 Elsevier. (C) Images of excised fibrosarcomas 20 days after intratumoral injection of doxorubicin in a hydrogel matrix, free doxorubicin, or saline. Reproduced with permission from ref 379. Copyright 2015 American Chemical Society. (D) Infrared image of an intratumorally administered injectable hydrogel containing excitable nanoparticles for photothermal therapy of hypoxia-resistant breast tumors. Reproduced with permission from ref 321. Copyright 2021 Elsevier. (E) Histological image showing the recruitment of dendritic cells (purple) by cytokine-loaded hydrogels from subcutaneous tissue. Reproduced with permission from ref 380. Copyright 2019 American Chemical Society. (F) Closure of *Pseudomonas aeruginosa* infected wounds dressed with gauze or antibacterial hydrogels. Reproduced with permission from ref 381. Copyright 2019 Elsevier. (G) Histological image of calvarial bone with hematoxylin and eosin staining three months postinjury showing mature collagen-rich bone for fast relaxing hydrogels and sparse disorganized collagen without mature bone for slow relaxing hydrogels. Scale bar corresponds to 180 μ m. Reproduced with permission from ref 382. Copyright 2017 Wiley. (H) Injection of a hydrogel as vitreous substitute during vitrectomy. Reproduced with permission from ref 383. Copyright 2021 Elsevier.

Besides spinal cord injuries, self-healing injectable hydrogels are also being investigated to prevent intervertebral disc degeneration^{201,408–412} or to deliver neuroprotective therapeutics to counteract neurodegenerative diseases such as Parkinson's or Huntington's disease.^{413–417} Hydrogels for spinal cord injection should not swell in situ, as this may increase the intraspinal pressure and lead to secondary injuries.⁴¹⁸

Ischemic stroke is a major cause of death and disability with very limited treatment options to date. A stroke not only causes ischemic necrosis at the site of the infarct but also the release of ECM-degrading enzymes and reactive oxygen species which induce secondary ischemic injury and tissue scarring that impedes regeneration.^{34,419} Self-healing injectable hydrogels are considered promising candidates to limit secondary ischemic injury as they may be injected rapidly and minimally invasively across the blood–brain barrier into the stroke cavity (Figure 8B), provided that intracerebral fluid is drained at the same time to keep the intracranial pressure constant.³⁶ Promising reports have already been published on the injection of hydrogels loaded with growth factors, neural progenitor cells, or erythropoietin directly in the stroke cavity to reduce secondary ischemic injury or promote angiogenesis and neurogenesis after stroke.^{420–425}

5.3. Anticancer Strategies and Immunomodulation

Chemotherapy remains one of the major treatment strategies for cancer. However, chemotherapy relies on systemic delivery of multiple cytotoxic and cytostatic chemotherapeutics, which typically cause severe side effects.⁴²⁶ Other anticancer strategies are based on delivery of drug-loaded nanoparticles into tumor blood vessels^{427,428} or cancer immunotherapy, i.e., the targeted programming of immune cells to detect and kill cancer cells.^{341–343} All of these strategies potentially benefit from locally targeted peri- or intratumoral delivery via self-healing injectable hydrogels. Self-healing injectable hydrogels are able to spatially confine therapeutics and release them locally in a sustained manner, thereby maximizing therapeutic effects and minimizing off-target side effects. The use of injectable hydrogels for delivery of chemotherapeutics^{429–438} or nanoparticles^{439–446} has been investigated for various types of cancer. Intratumoral administration of chemotherapeutics using a hydrogel matrix prolongs their therapeutic efficacy compared to free drug administration and allows sustained tumor growth suppression, as shown in Figure 8C. Many self-healing hydrogels for intratumoral injection are designed for pH-responsive release, exploiting the acidic extracellular pH in tumors.^{379,447–454} Cancer cells are often more susceptible to short-term high-dose drug bursts than long-term constant doses. Hence, hydrogels with magnetic, ultrasound, or photosensitive release mechanisms have been designed to induce burst-type drug release triggered by external stimuli.^{119,295,321,455,456} Injectable hydrogels loaded with magnetic or excitable nanoparticles are employed to induce intratumoral magnetic hyperthermia or facilitate photothermal therapy,^{295,321,457–461} as shown in Figure 8D. Injectable hydrogels loaded with radioactive iodine-131 have been investigated for intratumoral radiotherapy (brachytherapy),^{322,462,463} while radiopaque hydrogels are used as injectable tissue markers^{464–466} or spacers to protect nearby tissues and organs.^{467–470} A key advantage is that hydrogels can be designed to remain intact over several weeks and can therefore be used for repeated periodic treatments. Because of their longevity, hydrogels modified with oligonucleotides that can actively capture chemotherapeutics with

complementary sequences from the bloodstream have been proposed as reloadable depots for chemotherapeutics.³¹⁶

Cancer immunotherapy is a fast-evolving treatment strategy triggering a patient's own immune system to fight cancer. In checkpoint blockade therapy, immune checkpoint inhibitors are administered to block checkpoint proteins on tumor or T-cells that refrain T-cells from killing tumor cells.⁴⁷¹ In chimeric antigen receptor (CAR) T-cell therapy, a patient's own T-cells are genetically modified ex vivo and reinfused to specifically recognize and kill tumor cells.⁴⁷² Both therapies have shown promising results against a variety of cancers but are still limited by low response rates and side effects. Self-healing injectable hydrogels can be exploited for a more targeted delivery of immune checkpoint inhibitors^{473–477} or CAR T-cells^{478–482} to achieve higher local effective doses and increase cell survival while reducing off-target side effects. The effectiveness of cancer therapies is often impeded by the immunosuppressive tumor microenvironment. Accordingly, injectable hydrogels have been designed for the delivery of immune-adjuvants^{320,483–486} or reprogramming of tumor-associated macrophages from pro-tumor (M2) to antitumor (M1) phenotype.^{487–489} Dendritic cell therapy is an immunotherapy approach wherein dendritic cells are activated in the presence of tumor antigens, whereafter the antigen-presenting dendritic cells migrate to lymph nodes to prime T-cells.^{490,491} Dendritic cells can be activated ex vivo followed by reinjection in a hydrogel matrix or may be administered in a hydrogel that contains a combination of immature dendritic cells, tumor antigens, and adjuvants.^{492,493} The efficacy of administered dendritic cells is often limited by poor cell survival and limited migration and homing to lymph nodes. This has triggered the approach to design biomaterials that recruit and home local dendritic cells (see Figure 8E), present tumor antigens, and trigger dendritic cell migration to lymph nodes to induce T-cell priming.^{341,494–496} Self-healing injectable hydrogels have been successfully designed for the enrichment and activation of dendritic cells and induction of specific and protective antitumor immunity.^{205,380,489,497–502}

5.4. Wound Healing and Soft Tissue Regeneration

Impaired wound healing, wound infections, or development of chronic wounds are a major cause for complications following surgery or injury. Wound healing involves multiple hemostatic, inflammatory, catabolic, and anabolic processes that occur at time scales from minutes to months.⁵⁰³ Because of their ability to reside at the place of injury, multifunctional hydrogels with hemostatic, antioxidative, antibacterial, pro-angiogenic, and epithelializing effect have been developed that support wound healing over several healing stages.^{381,504–512} Thereby, wound closure can be accelerated compared to traditional gauze, as shown in Figure 8F. Ma et al.⁵¹³ described an elegant multilayered injectable hydrogel able to sequentially deliver different bioactive substances in three different stages of wound healing. Czuban et al.³¹⁹ designed a reloadable hydrogel that is able to capture and activate antibiotic prodrugs.³¹⁹ A common approach to promote wound healing is the incorporation of functional ions or ion nanoparticles with antibacterial^{514–520} or pro-angiogenic effects.^{520–524} Recent studies have investigated the ability to modulate the inflammation processes using self-healing injectable hydrogels. For instance, fibroblast migration to the wound site can be promoted by increased hydrogel stiffness,⁵²⁵ while macrophage polarization may be modulated by high molecular weight hyaluronic acid⁵²³ or delivery of exosomes.⁵²⁶

Articular cartilage has a poor healing capacity due to its avascular, aneural, and nonlymphatic nature and inherently low density of chondrocytes.⁵²⁷ Accordingly, self-healing injectable hydrogels are designed to mimic native cartilage and deliver stem or progenitor cells or mature chondrocytes to promote cartilage regeneration.^{197,290,528–532} More recently, hydrogels with immunomodulatory function are investigated to enhance local stem cell recruitment and chondrogenesis.^{533–535} The chondrogenic differentiation of stem cells as well as collagen synthesis by chondrocytes is strongly affected by the presence of cell-binding ligands^{536,537} and hydrogel stiffness, with an optimum reported around 1000 Pa.^{538–540} Hydrogels loaded with anti-inflammatory drugs and cartilage regenerative properties have also been investigated for the treatment of osteoarthritis and osteoarthrosis.^{541–543}

Regarding muscle regeneration, most studies addressed the regeneration of ischemic myocardium as discussed in section 5.1. For skeletal muscles, only a few studies have been dedicated to the design of self-healing injectable hydrogels as cell carriers or scavenging of reactive oxygen species to support muscle regeneration,^{156,544,545} particularly in context of avoiding muscle loss following limb ischemia.^{546–548} Wu et al.³¹⁷ proposed a reloadable hydrogel depot that is able to capture PEG-modified growth factors from the bloodstream to treat limb ischemia. Chang et al.⁵⁴⁹ demonstrated the use of a magnetic injectable hydrogel that can be exogenously actuated to stimulate muscles and avoid muscle degeneration.

Soft tissue defects may arise following surgical resections, severe trauma, or lumpectomy and require soft tissue fillers for adipose tissue regeneration. Adipose tissue regeneration recently gained particular interest due to the increased number of cosmetic adipose tissue reconstructions. Autogenous lipofilling is still the gold standard, but this procedure is often impeded by low adipocyte survival and fast fat resorption.⁵⁵⁰ Furthermore, currently used soft tissue fillers often show side effects like inflammation, fat necrosis, or fibrosis and show poor adipocyte differentiation and survival.^{550–552} Currently, hydrogels from novel biomaterials^{553–555} or decellularized adipose tissue^{198,199} are considered as self-healing injectable soft tissue fillers with enhanced biocompatibility, improved fat retention, and promoted adipocyte differentiation and survival. Regarding hydrogel design for adipose tissue regeneration, hydrogel stiffness, and viscoelasticity should closely match native adipose tissue to enhance adipogenesis.^{112,340}

5.5. Bone Regeneration

Critical size bone defects that cannot heal autonomously and require clinical intervention can occur due to traumatic injury, tumor removal, degenerative diseases, or congenital defects. Bone regeneration using bioceramics, allografts, or autografts remains the common strategy for *in vivo* bone regeneration in the clinic. However, these treatment options are invasive and associated with the risk of infection and morbidity at the donor site.^{556,557} These drawbacks stress the need for novel bone graft materials such as osteocompatible self-healing injectable hydrogels that (i) can be administered in a minimally invasive manner to fill patient-specific defects, (ii) promote bone healing also for larger defects, and (iii) do not need to be surgically removed.⁵⁵⁸ Several reports have been published on self-healing injectable hydrogels to fill bone defects and support healing,^{559–561} often in combination with incorporated drugs, ions, growth factors, stem cells, or microRNA to further stimulate bone regeneration.^{212,218,561–568} A significant chal-

lenge of hydrogels for bone regeneration relates to their limited mineralization ability, i.e., the precipitation of calcium and phosphate ions as hydroxyapatite crystals. The most common strategy to promote bone mineralization is the incorporation of calcium phosphate or hydroxyapatite particles.^{562,569–571} Another common approach entails the incorporation of bioactive glasses in hydrogels due their bone regenerative capacity through apatite formation and ion release, as well as their pro-angiogenic activity.^{109,572–574} Other strategies comprise soaking of hydrogels in saturated calcium phosphate solutions, incorporation of enzymes that catalyze bone mineral deposition, or incorporation of matrix vesicles.⁵⁷⁵ The recently recognized effect of hydrogel viscoelasticity on cell activity and differentiation shows particular promise for bone regeneration. Fast relaxing hydrogels were shown to promote osteogenic differentiation of human mesenchymal stem cells^{112,576} and enhance bone regeneration *in vivo*,³⁸² as visualized in Figure 8G.

5.6. Vitreous Substitute and Ocular Delivery

Vitrectomy, i.e., the removal of parts or the entire vitreous humor, is a common ophthalmological procedure for the removal of vitreous hemorrhages and floaters or the treatment of retinal detachment, macula, or diabetic retinopathy. There has been a trend to perform vitrectomies in a less-invasive manner using syringes (small gauge vitrectomy).⁵⁷⁷ The removed vitreous humor is traditionally replaced by a gas or saline to maintain intraocular pressure.³⁰² More recently, self-healing injectable hydrogels have emerged as long-term vitreous substitutes which more closely resemble the mechanical and diffusive properties of vitreous humor (see Figure 8H).^{278,383,578–582} Injectable hydrogels for vitreous substitution should not only exhibit suitable mechanical properties but also long-term transparency and similar refractive index values as vitreous humor. Vitrectomy of large parts of the vitreous humor can impede ocular oxygen homeostasis, which causes oxidative stress and cataract formation. Antioxidant-loaded hydrogels can prevent such postvitrectomy cataract formation.⁵⁸³

Eye drops are facile topical ocular delivery systems, but they often fail to convey effective doses to the interior eye due to rapid dissolution and physiological barriers.⁵⁸⁴ Self-healing injectable hydrogels have been employed for the intraocular administration of CAR T-cells to treat retinoblastoma⁵⁸⁵ or prevent neovascularization by delivery of antivascular endothelial growth factors.^{586–592} Ocular neovascularization can occur following infection or trauma and is a major cause of macular degeneration.⁵⁹³ Self-healing injectable hydrogels are able to provide a long-term continuous effective drug dose required to halt degenerative eye diseases.⁵⁹⁴ To prolong drug delivery periods, drugs are occasionally encapsulated in biodegradable microspheres dispersed in the hydrogel matrix, thereby pushing drug release periods to up to 6 months.^{595–598} Other strategies to prevent macular degeneration entail the injection of antioxidative hydrogels^{360,599} or delivery of stem or progenitor cells.^{600–603} Promising results were also obtained by cell encapsulation therapy, i.e., the administration of hydrogels containing genetically engineered cells which continuously secrete antivascular endothelial growth factors to provide long-term effects against ocular neovascularization.^{338,339}

6. SELF-HEALING INJECTABLE HYDROGELS FOR 3D (BIO)PRINTING

3D (bio)printing is one of the fastest evolving fields in biomedical engineering. 3D printing refers to the use of additive

manufacturing, in context of hydrogels mostly extrusion printing, for the automated and computer assisted biofabrication of complex structures. Hydrogels or hydrogel precursors are commonly used inks, also called bioinks when loaded with cells⁶⁰⁴ or living inks when containing bacteria.⁶⁰⁵ In addition, self-healing hydrogels are also frequently used as support baths in freeform 3D printing. Therein, an ink is printed into a support matrix that temporarily fluidizes followed by self-healing and spatial confinement of the printed structure, allowing for almost unlimited structural freedom (see Figure 9).^{49,606} There have

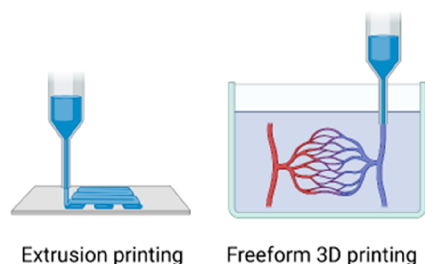


Figure 9. Schematic overview of applications of self-healing injectable hydrogels as 3D extrusion printing inks and/or support matrices in freeform 3D printing.

been several recent reviews focusing on 3D (bio)printing and its promises in biomedical engineering.^{46–48,258,259,607–610} Hence, we will herein focus on the printability of self-healing injectable hydrogels and their use as 3D extrusion printing inks or as support matrix in freeform 3D printing to obtain complex tissue and organ-like structures.

6.1. Hydrogel Printability

The ability of self-healing injectable hydrogels to fluidize under shear stress followed by rapid self-healing renders them versatile platforms for 3D printing inks. However, the formulation of self-healing printable hydrogels is far from trivial. Rheological tests used to assess hydrogels as 3D printing inks generally aim to determine hydrogel apparent yield stress or viscoelasticity at rest, their shear-thinning flow, and their fast self-healing, i.e., recovery of apparent yield stress or viscoelasticity after flow.^{260,267} The suitable rheological tests were discussed in detail in section 4. However, there is currently a lack of clear rheological benchmarks that a hydrogel should possess in order to qualify as 3D printing ink, strongly impeding the translation of hydrogels from the rheometer to the printer. Hereafter, we will discuss the current characterization parameters of hydrogels as 3D printing inks, followed by an outlook of how it can potentially be improved.

The suitability of hydrogels for printing is often summarized by the general term “printability”, which remains a loosely defined term that has been associated with a plethora of rheological tests and qualitative visual assessments.^{258,259} Printability is usually divided into the subcategories “extrudability”, “filament classification”, and “shape fidelity”. Extrudability refers to the ability to extrude the ink through a small needle or nozzle at reasonable pressure and is associated with a sufficiently low viscosity or shear-thinning behavior. Filament classification assesses the quality of the printed filament visually, which is ideally continuous and uniform. Filament quality is mostly an ink formulation challenge, with under-gelled inks leading to drop formation due to surface tension and overgelled inks leading to nonuniform bumpy filaments.^{611–613} Shape fidelity characterizes the ability of the printed filaments to retain

their structure after printing and avoid filament fusion due to surface tension or collapse due to gravity, particularly upon printing of multiple layers. Fast self-healing kinetics (i.e., recovery of viscosity, elasticity, or yield stress) is crucial for the shape fidelity of inks.^{267,614} Ouyang et al.⁶¹² introduced the widely applied printability factor Pr , which characterizes the shape of squares in a printed grid according to $Pr = L^2/16A$, where L is the perimeter and A the area of the squares in the grid. An ink that is printed as smooth filament and fully retains its structure after printing would result in near-perfect squares ($Pr = 1$), while under-gelled inks lead to filament fusion and round shapes due to surface tension ($Pr < 1$) and overgelled inks lead to irregular shapes ($Pr > 1$). Although Pr provides a certain mean of quantification for hydrogel printability and allows comparison of different inks, it is not fully clear which rheological ink parameters favor a $Pr \approx 1$. Furthermore, the used printers, nozzles, and print settings largely vary among laboratories, impairing a universal comparability of Pr .

Hence, a major bottleneck in the development of hydrogels as 3D printing inks is the lack of clear rheological benchmarks. As most hydrogels are shear-thinning power-law fluids, a straightforward approach to define a “printability window” is to find the range of the consistency index k and flow behavior index n that facilitate printing. For instance, Liu et al.²⁸⁴ found an improved printability for $k \approx 1000–1800 \text{ Pa}\cdot\text{s}^n$ and $n \approx 0.15–0.3$. While this approach facilitates to predict printability based on simple rheological experiments, it remains unclear how the data obtained by shear rheology translates to the hydrogel flow in printing nozzles. As discussed in detail in Section 4, the capillary plug flow of hydrogels cannot be adequately reproduced by shear rheology and can yield misleading flow curves.²²⁷ Furthermore, the actual shear stress and therefore the viscosity in the printing nozzle are often unknown. A potential solution for this problem is based on the use of nozzles with an incorporated pressure sensor that act as in-line capillary rheometers.²⁸² X-ray or neutron scattering techniques can be applied to capture the structure of hydrogels during flow or their self-healing kinetics after printing.^{261,276,615} Alternatively, numerical simulations can help to understand the shear stress and viscosity of hydrogels during 3D printing.^{220,284,616}

Overall, the field of 3D printing has emerged very rapidly in the past decade, and the technological advance has partially outpaced the fundamental understanding of many involved physical processes. As a consequence, the design of self-healing hydrogels for 3D printing is currently hampered by a lack of objective quantitative parameters associated with printability and often relies on a time-consuming trial-and-error approach. As specific measures to improve development, translation, and universal comparability of hydrogels designed for 3D printing, we recommend (i) the use of more suitable rheological tests (capillary or in-line rheology), (ii) establishing specific rheological benchmarks that determine printability, and (iii) increased efforts to understand the structuring of hydrogels in printing nozzles and recovery thereafter.

6.2. Self-Healing Hydrogels for 3D (Bio)printing of Complex Tissue Constructs

3D (bio)printing of self-healing hydrogels allows the fabrication of tissue mimetics or organoids as implantable biomaterials, tissue engineering scaffolds, or in vitro models to test novel drugs or therapies in a physiologically relevant environment without the need for animal experimentation.^{46,47,617} Compared to other manufacturing techniques, 3D bioprinting offers a more

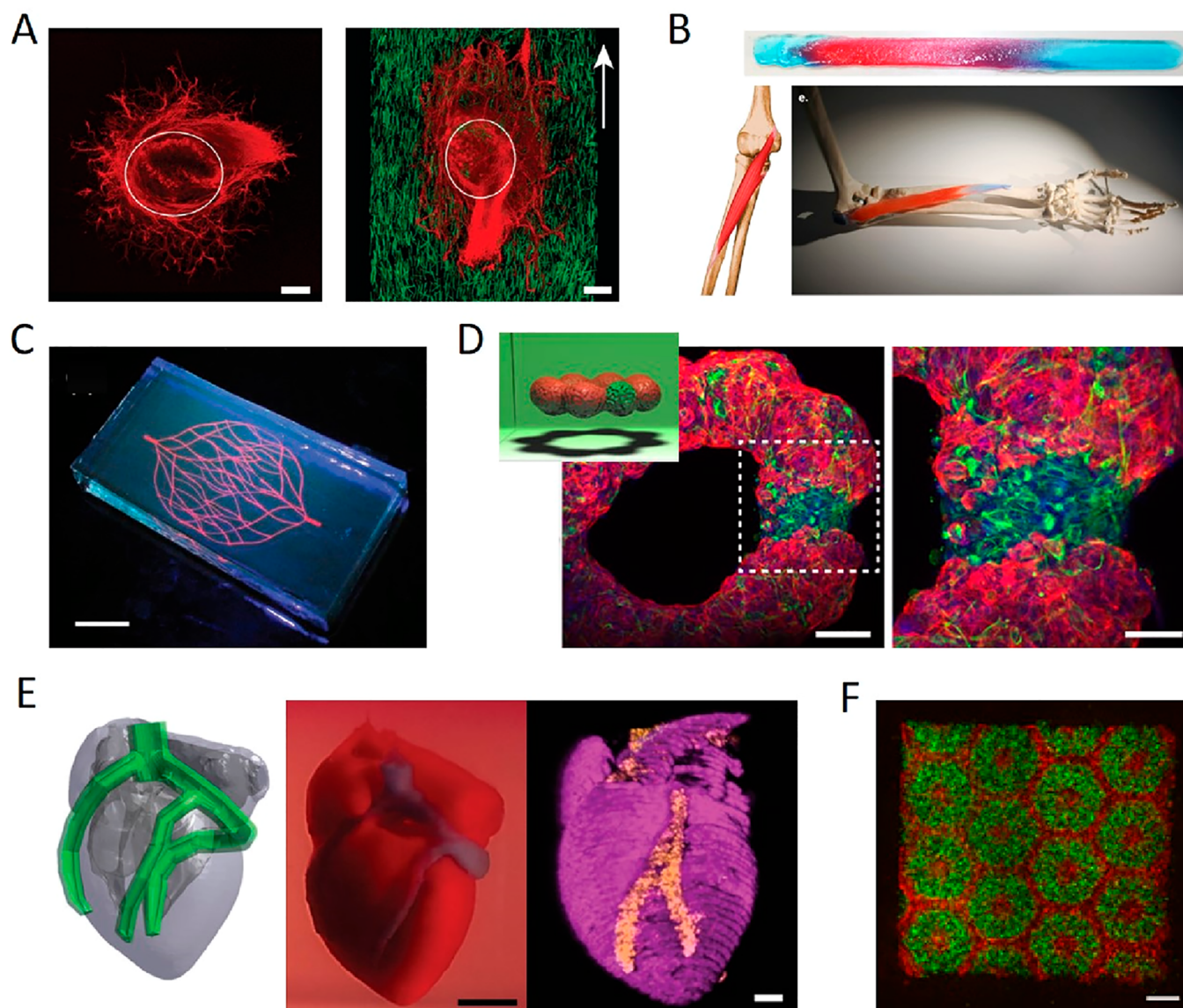


Figure 10. Overview of self-healing injectable hydrogels to obtain complex tissue constructs and organ-like structures. (A) Dorsal root ganglions (red) in isotropic fibrin hydrogels (left) and with anisotropic magnetically aligned microgels (right, green) promoting directed neurite growth. Reproduced with permission from ref 402. Copyright 2017 American Chemical Society. (B) Multimaterial printing of a human tendon muscle replacement with gradient mechanical properties and rigid UV-curable contact points (E-MAX 904, blue) and elastic alginate/polyacrylamide composite (red). Reproduced with permission from ref 629. Copyright 2017 Elsevier. (C) Freeform 3D printing of a sacrificial ink in a UV-curable hydrogel matrix allows omnidirectional printing of complex hollow vasculature structures (scale bar = 10 mm). Reproduced with permission from ref 606. Copyright 2019 Wiley. (D) Deposition of cell spheroids rich in cardiomyocytes (red, “healthy”) or rich in fibroblasts (green, “scarred”) in a hydrogel matrix to obtain complex microtissues for the study of tissue defects and drug screening (scale bar = 100 μm , zoom in = 50 μm). Reproduced with permission from ref 654. Copyright 2021 Springer Nature. (E) Personalized multicellular 3D printed heart with hollow structures and vasculature. From left: The CAD model, the printed heart in the support hydrogel (scale bar = 5 mm), and 3D confocal image showing cardiomyocytes (pink) and endothelial cells (orange, scale bar = 1 mm). Reproduced with permission from ref 639. Copyright 2019 Wiley. (F) 3D printed triculture liver model with physiologically relevant hexagonal architecture enhances morphological organization, liver-specific gene expression, and metabolic activity of hepatic progenitor cells (green, red = supporting endodermal and mesodermal cells, scale bar = 500 μm). Reproduced with permission from ref 655. Copyright 2016 National Academy of Sciences.

precise control over 3D structure and spatiotemporal distribution of materials, cells, and/or bioactive molecules. As discussed above in section 4, hydrogels are generally conveyed in a plug flow in 3D printing nozzles (Figure 6E), and regions of high shear forces and structural alignment are therefore often limited to the outer boundary layer.^{44,227,234,261,275} The wide plug flow with limited shear rate in the center facilitates cell survival in bioinks compared to suspensions.^{43,44,326–328} In fact, most detrimental to cell survival is the extensional flow at the entrance

of the syringe rather than wall shear stresses.⁴³ Nevertheless, highly concentrated inks can impede cell survival due to an increase in shear stresses.^{43,612,618} To further preserve cell viability, other parameters like printing temperature and time have to be considered. A detailed overview how to optimize bioinks for cell survival is provided by Rutz et al.⁶¹⁹

Despite plug flow and limited alignment, several studies have reported strategies to print biomaterials with high degree of alignment and anisotropy to direct cell growth, as shown in

Figure 10A. Material anisotropy may be achieved by exploiting shear and extensional flow during printing^{234,405} or by incorporating magnetic particles that enable alignment triggered by the application of a magnetic field.^{228,402–404} Multimaterial 3D printing allows printing of spatially controlled heterogeneous structures that reflect the mechanical and structural complexity of native tissue more closely,^{620–629} as shown exemplarily for a biofabricated human tendon muscle with rigid contact points and stretchable centerpiece in Figure 10B. 3D hydrogel printing further facilitates the design of biomaterials with spatiotemporally defined patterns of cells or bioactive molecules.^{628,630–633} Material constructs with locally concentrated growth factors were shown to be more effective at promoting angiogenesis compared to materials with homogeneously distributed growth factors.^{634,635}

The structural freedom of 3D bioprinting is limited by the self-support capacity of the used hydrogel as well as its self-healing kinetics. Layer-by-layer printing is thus often not suitable for printing of branched, hollow or overhanging structures as encountered for many complex tissues or organs. These structural limitations may be circumvented by printing the ink into a support matrix, which is often also a self-healing hydrogel or a suspension bath.^{49,56,606} The printing nozzle is dragged through the support matrix which temporarily fluidizes followed by rapid self-healing to confine and support the printed structure. Using this freeform 3D printing, also termed as freeform reversible embedding or fluid bath-assisted 3D printing, complex branched structures can be printed at full structural freedom beyond the technological limitations of traditional layer-by-layer deposition.^{49,606,636–640} This highly attractive feature is exploited in particular to print vascularized structures that facilitate nutrient and waste transport as shown in Figure 10C, which has been a notorious bottleneck for the design of tissue constructs.^{633,641–647} Furthermore, more liquid low-viscosity inks that are not stable during extrusion 3D printing can be employed in freeform 3D printing due to the structural support of the matrix, thereby increasing the palette of potential ink formulations.^{56,648} The printed ink can be cured followed by removal of the support matrix (support bath-enabled 3D printing). Alternatively, the support matrix may be cured (embedded 3D printing) and the printed ink may be removed (sacrificial ink) or left in place (functional ink).⁶⁴⁹ Despite the vast potential of freeform 3D printing, the harmonization of ink and bath rheology as well as print settings are challenging, as they all affect the yielded region of the support matrix and resulting filament deposition.^{650–652} Instead of printing an ink, cell spheroids may be deposited into the support hydrogel which then fuse into high-cell density microtissues and can be used as complex tissue models.⁶⁵³ Daly et al.⁶⁵⁴ have exploited this approach to create heterogeneous tissue constructs, as shown in Figure 10D. One spheroid rich in fibroblasts was incorporated in a ring of “healthy” spheres rich in cardiomyocytes to study the contractile output and electrical synchronization of scarred cardiac tissue and efficacy of miRNA treatments.

Ultimately, combining these tools of printing anisotropic or gradient structures, multimaterial constructs, vascularized networks, and multicellular microtissues allows the printing of complex tissue and organ-like structures that facilitate personal medicine and provide better cell culture models to mimic disease or drug screening. For instance, Noor et al.⁶³⁹ have demonstrated the printing of personalized cardiac patches and hearts based on ECM hydrogels, cardiomyocytes, and

endothelial cells previously obtained from a patient biopsy, as shown in Figure 10E. Ma et al.⁶⁵⁵ have shown that hepatic progenitor cells show enhanced morphological organization, liver-specific gene expression, and metabolic activity in a 3D printed triculture model with physiologically relevant hexagonal structure with supporting endodermal and mesodermal cells (Figure 10). For a more extensive overview of the current status of tissue and organ bioprinting, the interested reader is referred to the recent overviews provided by Mota et al.⁴⁶ and Fonseca et al.⁴⁷ An exciting new application area, which however remains in its infancy for the time being, is intravital 3D printing. Here, biomaterials are printed in situ, either in open surgery or by hydrogel injection followed by noninvasive patterning using a near-infrared laser.^{656–658}

7. CONCLUSIONS

7.1. Design Strategies

Self-healing injectable hydrogels for biomedical applications need to fulfill a wide range of design criteria. Most importantly, hydrogels that can fluidize during injection followed by self-healing require the use of reversible (i.e., noncovalent and/or dynamic covalent) chemistry. At the same time, these hydrogels should be physically stable in situ to avoid premature disintegration and allow for spatiotemporal control over hydrogel integrity and release of encapsulated therapeutics. This trade-off between injectability and self-healing capacity vs physical stability and integrity needs to be carefully balanced in the design of self-healing injectable hydrogels. Furthermore, tailoring the self-healing kinetics to the specific time scales of injection/printing applications can be challenging. The equilibrium binding constant K_{eq} and the bond lifetime τ_B provide useful chemical modulators for self-healing kinetics, while rheology provides a suitable measure for the mechanical recovery of hydrogels (see below). In the past decade, an extensive library of suitable materials and reversible chemistries for self-healing injectable hydrogels has been established. A recent trend involves the formulation of hydrogels beyond monolithic polymer-based hydrogels that provide even more degrees of freedom, most prominently owing to the use of multiple chemistries (dual cross-linked) or multiple polymers (double network). Furthermore, the urge for more realistic ECM models has pushed several new physical design strategies such as fibrous hydrogels, colloidal/granular hydrogels, and particularly combinations thereof. These mixed systems can circumvent drawbacks of monolithic hydrogels by combining “weaker” with “stronger” bonds or large polymers with small particles, thereby optimizing the balance between reversibility and physical stability required for self-healing injectable hydrogels.

7.2. Rheological Characterization

Rheology is the established method to characterize self-healing hydrogels for injection or 3D printing applications. It is well accepted that a self-healing injectable hydrogel should possess an apparent yield stress, be extrudable, and at least partially recover its mechanical properties after capillary flow. However, it is not yet clear which set of rheological protocols or parameters unambiguously qualify a hydrogel as self-healing and injectable. In the case of apparent yield stresses, this ambiguity is a direct consequence of the plethora of rheological techniques reported to determine “The” yield stress. We have outlined three possible experiments which produce similar stress values. Moreover, the plug flow of hydrogels in capillaries cannot be adequately

reproduced by oscillatory or steady shear rheology, and respective flow curves over- or underestimate hydrogel viscosity. This methodological shortcoming impedes translation particularly of 3D printing inks from the rheometer to the printer due to a diverging flow profile in the printer nozzle. The increased usage of capillary rheology poses a straightforward solution to avoid such discrepancies. On the other hand, assessment of self-healing kinetics by oscillatory time sweeps following destructive shear is uncontested, although it is also impeded by the inability of rotational rheology to mimic the destructive shear experienced by hydrogels during capillary flow. Above all, the establishment of quantitative rheological benchmarks, which render a hydrogel suitable for specific applications, are an important step to facilitate the translation of self-healing hydrogels for injection or 3D printing.

7.3. Applications in Tissue Regeneration

The main advantage of self-healing injectable hydrogels for tissue regeneration is that these biomaterials can be administered in a minimally invasive manner through a narrow needle, while the subsequent self-healing allows for spatial confinement of hydrogels and incorporated therapeutics. The past decade has therefore witnessed the emergence of self-healing injectable hydrogels as a third generation of self-healing biomaterials designed for regeneration of a wide variety of tissues. The regenerative capabilities of these hydrogels range from simple mechanical support, encapsulation, and spatiotemporally controlled release of therapeutics or cells, to multifunctional and responsive materials that fulfill a cascade of functions over the various stages of regeneration. Self-healing injectable hydrogels are particularly advantageous for administration to sites that are otherwise difficult or dangerous to access, such as the central nervous system, where injectable hydrogels can be used to bridge spinal cord lesions. Clinical indications which require a fast intervention can greatly benefit from self-healing injectable hydrogels, e.g., to prevent pathological remodeling after myocardial infarction or secondary injury after ischemic stroke. Great potential lies in the use of noninvasive imaging techniques, which can be exploited to tailor the volume, location, and even stiffness of the administered hydrogel to the patient-specific injury, allowing for personalized interventions. Self-healing injectable hydrogels can act as long-term depots for local delivery of drugs or bioactive molecules in a sustained manner. Promising results have already been achieved in cancer therapy by intra- or peritumoral injection of hydrogels for local delivery of chemotherapeutics or radio- or photothermal therapy. Hydrogels with particularly long drug release profiles could facilitate the treatment of degenerative diseases like Parkinson's, Huntington's, or macular degeneration. There is a clear tendency to design self-healing injectable hydrogels with increasingly complex functionalities. For instance, multifunctional or stimuli-responsive hydrogels are developed which can aid healing over multiple stages of tissue regeneration or be reloaded with systemically administered drugs that are modified to be actively captured by the hydrogel from the bloodstream. Self-healing injectable hydrogels have also been recognized as promising candidates for immunotherapy. To this end, they can promote survival of engineered CAR T-cells or locally recruit dendritic cells, present tumor antigens, and trigger dendritic cell migration to lymph nodes and T-cell priming to induce specific and protective antitumor immunity. In conclusion, self-healing injectable hydrogels show great promise for various tissue regeneration strategies. The main challenge for the near future

will be to confirm these results in preclinical and clinical studies and ultimately translate them toward safe and effective treatment options that meet regulatory standards and can be marketed at large scale.

7.4. Applications as 3D (Bio)printing Inks and Support Baths

3D printing for biomedical engineering has evolved rapidly in the past decade, and self-healing injectable hydrogels are expected to be crucial enabling tools to foster further progress in this area. While increasingly complex tissue constructs are already being developed, fundamental physical aspects of the 3D (bio)printing process are still poorly understood. Most pressing, understanding of ink flow in 3D printing nozzles and its assessment using rheology, imaging, or simulations is still limited. As a consequence, the complex interplay of ink formulation and print settings often relies on qualitative visual assessment and a time-consuming trial-and-error approach. To overcome these bottlenecks, we proposed (i) the use of more suitable rheological tests (capillary or in-line rheology), (ii) establishment of specific rheological benchmarks that determine printability, and (iii) increased efforts to understand the structuring of hydrogels in printing nozzles. At the same, rapid advances in printing increasingly complex multimaterial constructs, anisotropic or gradient structures, vascularized networks, and multicellular microtissues have paved the way to print more realistic tissue and organ models that facilitate the study of disease, drug screening, or organ development. Eventually, this will allow printing of personalized tissue or organ implants and reduce the need for animal experiments.

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Notes

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Biographies

Pascal Bertsch received his Ph.D. from ETH Zurich, where he investigated the assembly of biopolymer building blocks into functional 3D soft materials as well as their adsorption behavior at fluid interfaces. His research yielded several promising biomaterial systems, including self-healing injectable hydrogels for drug delivery and emulsions with tailored digestibility for oral delivery and appetite control. He is currently a postdoc in the Regenerative Biomaterials Group at Radboud University Medical Center, developing novel biomaterials that stimulate cell activity and promote tissue regeneration.

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David Mooney is the Pinkas Family Professor of Bioengineering in the Harvard School of Engineering and Applied Sciences, and a Core Faculty Member of the Wyss Institute. His laboratory designs biomaterials to promote regeneration and immunotherapy. He is a member of the National Academy of Engineering, the National Academy of Medicine, and the National Academy of Inventors. His inventions have been licensed by over 15 companies, leading to commercialized products. He has founded companies and is active on industrial scientific advisory boards.

Sander C. G. Leeuwenburgh is Professor of Regenerative Biomaterials at Radboud University Medical Center in Nijmegen, The Netherlands. His research group aims to unravel how biomaterials are able to trigger the natural self-healing capacity of hard tissues. He pioneered the design and preclinical evaluation of a wide range of nano- and microstructured biomaterials, including self-healing colloidal composite biomaterials, tissue-adhesive barrier membranes, tissue-regenerative implant surface modifications, and organic or inorganic nanoparticles for drug delivery applications in regenerative medicine. His research led to several patents, licenses with industry, and the creation of spinoff companies. He is active on various grant review panels and industrial scientific advisory boards.

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REFERENCES

- (1) Ratner, B. D.; Bryant, S. J. Biomaterials: Where We Have Been and Where We Are Going. *Annu. Rev. Biomed. Eng.* **2004**, *6*, 41–75.
- (2) Ratner, B. D.; Zhang, G. A History of Biomaterials. In *Biomaterials Science*; Elsevier, 2020; pp 21–34.
- (3) Brochu, A. B. W.; Craig, S. L.; Reichert, W. M. Self-Healing Biomaterials. *J. Biomed. Mater. Res.: Part A* **2011**, *96A*, 492–506.
- (4) Diba, M.; Spaans, S.; Ning, K.; Ippel, B. D.; Yang, F.; Loomans, B.; Dankers, P. Y. W.; Leeuwenburgh, S. C. G. Self-Healing Biomaterials: From Molecular Concepts to Clinical Applications. *Adv. Mater. Interfaces* **2018**, *5*, 1800118.
- (5) Menikheim, S. D.; Lavik, E. B. Self-healing Biomaterials: The next Generation Is Nano. *WIREs Nanomed. Nanobiotechnol.* **2020**, *12*, e1641.

- (6) Cremaldi, J. C.; Bhushan, B. Bioinspired Self-Healing Materials: Lessons from Nature. *Beilstein J. Nanotechnol.* **2018**, *9*, 907–935.
- (7) Harrington, M. J.; Speck, O.; Speck, T.; Wagner, S.; Weinkamer, R. Biological Archetypes for Self-Healing Materials. In *Advances in Polymer Science*; Hager, M. D., van der Zwaag, S.; Schubert, U. S., Eds.; Springer International Publishing: Cham, 2016; Vol. 273, pp 307–344.
- (8) Ashammakhi, N.; Hoque Apu, E.; Catersen, E. J. Self-Healing Biomaterials to Heal Tissues. *J. Craniofac. Surg.* **2021**, *32*, 819–820.
- (9) Yang, Y.; Urban, M. W. Self-Healing Polymeric Materials. *Chem. Soc. Rev.* **2013**, *42*, 7446–7467.
- (10) Taylor, D. L.; in het Panhuis, M. Self-Healing Hydrogels. *Adv. Mater.* **2016**, *28*, 9060–9093.
- (11) Tu, Y.; Chen, N.; Li, C.; Liu, H.; Zhu, R.; Chen, S.; Xiao, Q.; Liu, J.; Ramakrishna, S.; He, L. Advances in Injectable Self-Healing Biomedical Hydrogels. *Acta Biomater.* **2019**, *90*, 1–20.
- (12) Uman, S.; Dhand, A.; Burdick, J. A. Recent Advances in Shear-thinning and Self-healing Hydrogels for Biomedical Applications. *J. Appl. Polym. Sci.* **2020**, *137*, 48668.
- (13) Talebian, S.; Mehrali, M.; Taebnia, N.; Pennisi, C. P.; Kadumudi, F. B.; Foroughi, J.; Hasany, M.; Nikkhah, M.; Akbari, M.; Orive, G.; Dolatshahi-Pirouz, A. Self-Healing Hydrogels: The Next Paradigm Shift in Tissue Engineering? *Adv. Sci.* **2019**, *6*, 1801664.
- (14) Hoffman, A. S. Hydrogels for Biomedical Applications. *Adv. Drug Delivery Rev.* **2012**, *64*, 18–23.
- (15) Hunt, J. A.; Chen, R.; Van Veen, T.; Bryan, N. Hydrogels for Tissue Engineering and Regenerative Medicine. *J. Mater. Chem. B* **2014**, *2*, 5319–5338.
- (16) Correa, S.; Grosskopf, A. K.; Lopez Hernandez, H.; Chan, D.; Yu, A. C.; Stapleton, L. M.; Appel, E. A. Translational Applications of Hydrogels. *Chem. Rev.* **2021**, *121*, 11385–11457.
- (17) Lutolf, M. P.; Hubbell, J. A. Synthetic Biomaterials as Instructive Extracellular Microenvironments for Morphogenesis in Tissue Engineering. *Nat. Biotechnol.* **2005**, *23*, 47–55.
- (18) Chaudhuri, O.; Cooper-White, J.; Janmey, P. A.; Mooney, D. J.; Shenoy, V. B. Effects of Extracellular Matrix Viscoelasticity on Cellular Behaviour. *Nature* **2020**, *584*, 535–546.
- (19) Jose, G.; Shalumon, K. T.; Chen, J.-P. Natural Polymers Based Hydrogels for Cell Culture Applications. *Curr. Med. Chem.* **2020**, *27*, 2734–2776.
- (20) Langer, R.; Vacanti, J. P. Tissue Engineering. *Science (80-)* **1993**, *260*, 920–926.
- (21) Lee, K. Y.; Mooney, D. J. Hydrogels for Tissue Engineering. *Chem. Rev.* **2001**, *101*, 1869–1879.
- (22) Drury, J. L.; Mooney, D. J. Hydrogels for Tissue Engineering: Scaffold Design Variables and Applications. *Biomaterials* **2003**, *24*, 4337–4351.
- (23) Petersen, O. W.; Ronnov-Jessen, L.; Howlett, A. R.; Bissell, M. J. Interaction with Basement Membrane Serves to Rapidly Distinguish Growth and Differentiation Pattern of Normal and Malignant Human Breast Epithelial Cells. *Proc. Natl. Acad. Sci. U. S. A.* **1992**, *89*, 9064–9068.
- (24) Tanaka, H.; Murphy, C. L.; Murphy, C.; Kimura, M.; Kawai, S.; Polak, J. M. Chondrogenic Differentiation of Murine Embryonic Stem Cells: Effects of Culture Conditions and Dexamethasone. *J. Cell. Biochem.* **2004**, *93*, 454–462.
- (25) Tibbitt, M. W.; Anseth, K. S. Hydrogels as Extracellular Matrix Mimics for 3D Cell Culture. *Biotechnol. Bioeng.* **2009**, *103*, 655–663.
- (26) Caliri, S. R.; Burdick, J. A. A Practical Guide to Hydrogels for Cell Culture. *Nat. Methods* **2016**, *13*, 405–414.
- (27) Ruedinger, F.; Lavrentieva, A.; Blume, C.; Pepelanova, I.; Scheper, T. Hydrogels for 3D Mammalian Cell Culture: A Starting Guide for Laboratory Practice. *Appl. Microbiol. Biotechnol.* **2015**, *99*, 623–636.
- (28) Ravi, M.; Paramesh, V.; Kaviya, S. R.; Anuradha, E.; Solomon, F. D. P. 3D Cell Culture Systems: Advantages and Applications. *J. Cell. Physiol.* **2015**, *230*, 16–26.
- (29) Charbonier, F.; Indana, D.; Chaudhuri, O. Tuning Viscoelasticity in Alginate Hydrogels for 3D Cell Culture Studies. *Curr. Protoc.* **2021**, *1*, e124.

- (30) Guvendiren, M.; Lu, H. D.; Burdick, J. A. Shear-Thinning Hydrogels for Biomedical Applications. *Soft Matter* **2012**, *8*, 260–272.
- (31) Chen, M. H.; Wang, L. L.; Chung, J. J.; Kim, Y.-H.; Atluri, P.; Burdick, J. A. Methods to Assess Shear-Thinning Hydrogels for Application as Injectable Biomaterials. *ACS Biomater. Sci. Eng.* **2017**, *3*, 3146–3160.
- (32) Loebel, C.; Rodell, C. B.; Chen, M. H.; Burdick, J. A. Shear-Thinning and Self-Healing Hydrogels as Injectable Therapeutics and for 3D-Printing. *Nat. Protoc.* **2017**, *12*, 1521–1541.
- (33) Tous, E.; Purcell, B.; Ifkovits, J. L.; Burdick, J. A. Injectable Acellular Hydrogels for Cardiac Repair. *J. Cardiovasc. Transl. Res.* **2011**, *4*, 528–542.
- (34) Nih, L. R.; Carmichael, S. T.; Segura, T. Hydrogels for Brain Repair after Stroke: An Emerging Treatment Option. *Curr. Opin. Biotechnol.* **2016**, *40*, 155–163.
- (35) Dorsey, S. M.; McGarvey, J. R.; Wang, H.; Nikou, A.; Arama, L.; Koomalsingh, K. J.; Kondo, N.; Gorman, J. H.; Pilla, J. J.; Gorman, R. C.; Wenk, J. F.; Burdick, J. A. MRI Evaluation of Injectable Hyaluronic Acid-Based Hydrogel Therapy to Limit Ventricular Remodeling after Myocardial Infarction. *Biomaterials* **2015**, *69*, 65–75.
- (36) Massensini, A. R.; Ghuman, H.; Saldin, L. T.; Medberry, C. J.; Keane, T. J.; Nicholls, F. J.; Velankar, S. S.; Badylak, S. F.; Modo, M. Concentration-Dependent Rheological Properties of ECM Hydrogel for Intracerebral Delivery to a Stroke Cavity. *Acta Biomater.* **2015**, *27*, 116–130.
- (37) Wang, H.; Rodell, C. B.; Zhang, X.; Dusaj, N. N.; Gorman, J. H.; Pilla, J. J.; Jackson, B. M.; Burdick, J. A.; Gorman, R. C.; Wenk, J. F. Effects of Hydrogel Injection on Borderzone Contractility Post-Myocardial Infarction. *Biomech. Model. Mechanobiol.* **2018**, *17*, 1533–1542.
- (38) Schotman, M. J. G.; Dankers, P. Y. W. Factors Influencing Retention of Injected Biomaterials to Treat Myocardial Infarction. *Adv. Mater. Interfaces* **2022**, *9*, 2100942.
- (39) Brandl, F.; Kastner, F.; Gschwind, R. M.; Blunk, T.; Teßmar, J.; Göpferich, A. Hydrogel-Based Drug Delivery Systems: Comparison of Drug Diffusivity and Release Kinetics. *J. Controlled Release* **2010**, *142*, 221–228.
- (40) Vermonden, T.; Censi, R.; Hennink, W. E. Hydrogels for Protein Delivery. *Chem. Rev.* **2012**, *112*, 2853–2888.
- (41) Buwalda, S. J.; Vermonden, T.; Hennink, W. E. Hydrogels for Therapeutic Delivery: Current Developments and Future Directions. *Biomacromolecules* **2017**, *18*, 316–330.
- (42) Li, J.; Mooney, D. J. Designing Hydrogels for Controlled Drug Delivery. *Nat. Rev. Mater.* **2016**, *1*, 16071.
- (43) Aguado, B. A.; Mulyasmita, W.; Su, J.; Lampe, K. J.; Heilshorn, S. C. Improving Viability of Stem Cells during Syringe Needle Flow through the Design of Hydrogel Cell Carriers. *Tissue Eng. Part A* **2012**, *18*, 806–815.
- (44) Yan, C.; Mackay, M. E.; Czymmek, K.; Nagarkar, R. P.; Schneider, J. P.; Pochan, D. J. Injectable Solid Peptide Hydrogel as a Cell Carrier: Effects of Shear Flow on Hydrogels and Cell Payload. *Langmuir* **2012**, *28*, 6076–6087.
- (45) Gaffey, A. C.; Chen, M. H.; Venkataraman, C. M.; Trubelja, A.; Rodell, C. B.; Dinh, P. V.; Hung, G.; Macarthur, J. W.; Soopan, R. V.; Burdick, J. A.; Atluri, P. Injectable Shear-Thinning Hydrogels Used to Deliver Endothelial Progenitor Cells, Enhance Cell Engraftment, and Improve Ischemic Myocardium. *J. Thorac. Cardiovasc. Surg.* **2015**, *150*, 1268–1276.
- (46) Mota, C.; Camarero-Espinosa, S.; Baker, M. B.; Wieringa, P.; Moroni, L. Bioprinting: From Tissue and Organ Development to in Vitro Models. *Chem. Rev.* **2020**, *120*, 10547–10607.
- (47) Fonseca, A. C.; Melchels, F. P. W.; Ferreira, M. J. S.; Moxon, S. R.; Potjewyd, G.; Dargaville, T. R.; Kimber, S. J.; Domingos, M. Emulating Human Tissues and Organs: A Bioprinting Perspective Toward Personalized Medicine. *Chem. Rev.* **2020**, *120*, 11093–11139.
- (48) Ramiah, P.; du Toit, L. C.; Choonara, Y. E.; Kondiah, P. P. D.; Pillay, V. Hydrogel-Based Bioinks for 3D Bioprinting in Tissue Regeneration. *Front. Mater.* **2020**, *7*, 76.
- (49) Highley, C. B.; Rodell, C. B.; Burdick, J. A. Direct 3D Printing of Shear-Thinning Hydrogels into Self-Healing Hydrogels. *Adv. Mater.* **2015**, *27*, 5075–5079.
- (50) Zhou, B. L. Improvement of Mechanical Properties of Materials by Biomimetic Treatment. *Key Eng. Mater.* **1997**, *145–149*, 765–774.
- (51) Koole, L. H.; Kruft, M. A. B.; Aldenhoff, Y. B. J.; Van 't Oost, N. E.; Van Kroonenburgh, M. J. P. G.; Van Der Veen, F. H. Sustained Local Drug Delivery from a Radiopaque Implanted Reservoir. *Nat. Biotechnol.* **1998**, *16*, 172–176.
- (52) Ramakrishna, S.; Mayer, J.; Wintermantel, E.; Leong, K. W. Biomedical Applications of Polymer-Composite Materials: A Review. *Compos. Sci. Technol.* **2001**, *61*, 1189–1224.
- (53) White, S. R.; Sottos, N. R.; Geubelle, P. H.; Moore, J. S.; Kessler, M. R.; Sriram, S. R.; Brown, E. N.; Viswanathan, S. Autonomic Healing of Polymer Composites. *Nature* **2001**, *409*, 794–797.
- (54) Blaiszik, B. J.; Kramer, S. L. B.; Olugebefola, S. C.; Moore, J. S.; Sottos, N. R.; White, S. R. Self-Healing Polymers and Composites. *Annu. Rev. Mater. Res.* **2010**, *40*, 179–211.
- (55) Del Prado-Audelo, M. L.; Caballero-Florán, I. H.; Mendoza-Muñoz, N.; Giraldo-Gomez, D.; Sharifi-Rad, J.; Patra, J. K.; González-Torres, M.; Florán, B.; Cortes, H.; Leyva-Gómez, G. Current Progress of Self-Healing Polymers for Medical Applications in Tissue Engineering. *Iran. Polym. J.* **2022**, *31*, 7–29.
- (56) McCormack, A.; Highley, C. B.; Leslie, N. R.; Melchels, F. P. W. 3D Printing in Suspension Baths: Keeping the Promises of Bioprinting Afloat. *Trends Biotechnol.* **2020**, *38*, 584–593.
- (57) Bertsch, P.; Sánchez-Ferrer, A.; Bagnani, M.; Isabetini, S.; Kohlbrecher, J.; Mezzenga, R.; Fischer, P. Ion-Induced Formation of Nanocrystalline Cellulose Colloidal Glasses Containing Nematic Domains. *Langmuir* **2019**, *35*, 4117–4124.
- (58) Sommer, M. R.; Alison, L.; Minas, C.; Tervoort, E.; Rühls, P. A.; Studart, A. R. 3D Printing of Concentrated Emulsions into Multiphase Biocompatible Soft Materials. *Soft Matter* **2017**, *13*, 1794–1803.
- (59) Huan, S.; Mattos, B. D.; Ajdary, R.; Xiang, W.; Bai, L.; Rojas, O. J. Two-phase Emulgels for Direct Ink Writing of Skin-bearing Architectures. *Adv. Funct. Mater.* **2019**, *29*, 1902990.
- (60) Calabrese, V.; Varchanis, S.; Haward, S. J.; Tsamopoulos, J.; Shen, A. Q. Structure-Property Relationship of a Soft Colloidal Glass in Simple and Mixed Flows. *J. Colloid Interface Sci.* **2021**, *601*, 454–466.
- (61) Diba, M.; Wang, H.; Kodger, T. E.; Parsa, S.; Leeuwenburgh, S. C. G. Highly Elastic and Self-Healing Composite Colloidal Gels. *Adv. Mater.* **2017**, *29*, 1604672.
- (62) Wang, H.; Hansen, M. B.; Löwik, D. W. P. M.; Van Hest, J. C. M.; Li, Y.; Jansen, J. A.; Leeuwenburgh, S. C. G. Oppositely Charged Gelatin Nanospheres as Building Blocks for Injectable and Biodegradable Gels. *Adv. Mater.* **2011**, *23*, H119–H124.
- (63) Vert, M.; Doi, Y.; Hellwich, K.-H.; Hess, M.; Hodge, P.; Kubisa, P.; Rinaudo, M.; Schué, F. Terminology for Biorelated Polymers and Applications (IUPAC Recommendations 2012). *Pure Appl. Chem.* **2012**, *84*, 377–410.
- (64) Deuel, H.; Neukom, H.; Weber, F. Reaction of Boric Acid with Polysaccharides. *Nature* **1948**, *161*, 96–97.
- (65) Deuel, V. H.; Neukom, H. Über Die Reaktion von Borsäure Und Borax Mit Polysacchariden Und Anderen Hochmolekularen Polyoxy-Verbindungen. *Makromol. Chemie* **1949**, *3*, 13–30.
- (66) Pezron, E.; Ricard, A.; Lafuma, F.; Audebert, R. Reversible Gel Formation Induced by Ion Complexation. 1. Borax-Galactomannan Interactions. *Macromolecules* **1988**, *21*, 1121–1125.
- (67) Pezron, E.; Leibler, L.; Ricard, A.; Audebert, R. Reversible Gel Formation Induced by Ion Complexation. 2. Phase Diagrams. *Macromolecules* **1988**, *21*, 1126–1131.
- (68) Kamata, H.; Akagi, Y.; Kayasuga-Kariya, Y.; Chung, U.; Sakai, T. Nonswellable Hydrogel Without Mechanical Hysteresis. *Science (80-)* **2014**, *343*, 873–875.
- (69) Chai, Q.; Jiao, Y.; Yu, X. Hydrogels for Biomedical Applications: Their Characteristics and the Mechanisms behind Them. *Gels* **2017**, *3*, 6.
- (70) Hutchinson, J. M. Physical Aging of Polymers. *Prog. Polym. Sci.* **1995**, *20*, 703–760.

- (71) Webber, M. J.; Tibbitt, M. W. Dynamic and Reconfigurable Materials from Reversible Network Interactions. *Nat. Rev. Mater.* **2022**, *7*, 541–556.
- (72) Shi, L.; Ding, P.; Wang, Y.; Zhang, Y.; Ossipov, D.; Hilborn, J. Self-Healing Polymeric Hydrogel Formed by Metal-Ligand Coordination Assembly: Design, Fabrication, and Biomedical Applications. *Macromol. Rapid Commun.* **2019**, *40*, 1800837.
- (73) Wang, H.; Heilshorn, S. C. Adaptable Hydrogel Networks with Reversible Linkages for Tissue Engineering. *Adv. Mater.* **2015**, *27*, 3717–3736.
- (74) Yu, A. C.; Lian, H.; Kong, X.; Lopez Hernandez, H.; Qin, J.; Appel, E. A. Physical Networks from Entropy-Driven Non-Covalent Interactions. *Nat. Commun.* **2021**, *12*, 746.
- (75) Stukalin, E. B.; Cai, L. H.; Kumar, N. A.; Leibler, L.; Rubinstein, M. Self-Healing of Unentangled Polymer Networks with Reversible Bonds. *Macromolecules* **2013**, *46*, 7525–7541.
- (76) Xu, D.; Liu, C.-Y.; Craig, S. L. Divergent Shear Thinning and Shear Thickening Behavior of Supramolecular Polymer Networks in Semidilute Entangled Polymer Solutions. *Macromolecules* **2011**, *44*, 2343–2353.
- (77) Aida, T.; Meijer, E. W.; Stupp, S. I. Functional Supramolecular Polymers. *Science (80-)* **2012**, *335*, 813–817.
- (78) Bose, R. K.; Hohlbein, N.; Garcia, S. J.; Schmidt, A. M.; van der Zwaag, S. Connecting Supramolecular Bond Lifetime and Network Mobility for Scratch Healing in Poly(Butyl Acrylate) Ionomers Containing Sodium, Zinc and Cobalt. *Phys. Chem. Chem. Phys.* **2015**, *17*, 1697–1704.
- (79) Avdeef, A.; Sofen, S. R.; Bregante, T. L.; Raymond, K. N. Coordination Chemistry of Microbial Iron Transport Compounds. 9.1 Stability Constants for Catechol Models of Enterobactin. *J. Am. Chem. Soc.* **1978**, *100*, 5362–5370.
- (80) Kubiček, V.; Kotek, J.; Hermann, P.; Lukeš, I. Aminoalkylbis-(Phosphonates): Their Complexation Properties in Solution and in the Solid State. *Eur. J. Inorg. Chem.* **2007**, *2007*, 333–344.
- (81) Sundberg, R. J.; Martin, R. B. Interactions of Histidine and Other Imidazole Derivatives with Transition Metal Ions in Chemical and Biological Systems. *Chem. Rev.* **1974**, *74*, 471–517.
- (82) Chen, G.; Jiang, M. Cyclodextrin-Based Inclusion Complexation Bridging Supramolecular Chemistry and Macromolecular Self-Assembly. *Chem. Soc. Rev.* **2011**, *40*, 2254–2266.
- (83) Rodell, C. B.; Kaminski, A. L.; Burdick, J. A. Rational Design of Network Properties in Guest-Host Assembled and Shear-Thinning Hyaluronic Acid Hydrogels. *Biomacromolecules* **2013**, *14*, 4125–4134.
- (84) Söntjens, S. H. M.; Sijbesma, R. P.; Van Genderen, M. H. P.; Meijer, E. W. Stability and Lifetime of Quadruply Hydrogen Bonded 2-Ureido-4[1H]-Pyrimidinone Dimers. *J. Am. Chem. Soc.* **2000**, *122*, 7487–7493.
- (85) Adzima, B. J.; Aguirre, H. A.; Kloxin, C. J.; Scott, T. F.; Bowman, C. N. Rheological and Chemical Analysis of Reverse Gelation in a Covalently Cross-Linked Diels-Alder Polymer Network. *Macromolecules* **2008**, *41*, 9112–9117.
- (86) Dirksen, A.; Dawson, P. E. Rapid Oxime and Hydrazone Ligations with Aromatic Aldehydes for Biomolecular Labeling. *Bioconjugate Chem.* **2008**, *19*, 2543–2548.
- (87) Kölmel, D. K.; Kool, E. T. Oximes and Hydrazones in Bioconjugation: Mechanism and Catalysis. *Chem. Rev.* **2017**, *117*, 10358–10376.
- (88) Lee, H.; Scherer, N. F.; Messersmith, P. B. Single-Molecule Mechanics of Mussel Adhesion. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 12999–13003.
- (89) Rühs, P. A.; Bergfreund, J.; Bertsch, P.; Gstöhl, S. J.; Fischer, P. Complex Fluids in Animal Survival Strategies. *Soft Matter* **2021**, *17*, 3022–3036.
- (90) Böni, L. J.; Zurflüh, R.; Baumgartner, M. E.; Windhab, E. J.; Fischer, P.; Kuster, S.; Rühs, P. A. Effect of Ionic Strength and Seawater Cations on Hagfish Slime Formation. *Sci. Rep.* **2018**, *8*, 9867.
- (91) Zhang, J.; Chen, L.; Shen, B.; Wang, Y.; Peng, P.; Tang, F.; Feng, J. Highly Transparent, Self-Healing, Injectable and Self-Adhesive Chitosan/Polyzwitterion-Based Double Network Hydrogel for Potential 3D Printing Wearable Strain Sensor. *Mater. Sci. Eng., C* **2020**, *117*, 111298.
- (92) Holten-Andersen, N.; Harrington, M. J.; Birkedal, H.; Lee, B. P.; Messersmith, P. B.; Lee, K. Y. C.; Waite, J. H. pH-Induced Metal-Ligand Cross-Links Inspired by Mussel Yield Self-Healing Polymer Networks with near-Covalent Elastic Moduli. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 2651–2655.
- (93) Zhao, D.; Tang, Q.; Zhou, Q.; Peng, K.; Yang, H.; Zhang, X. A Photo-Degradable Injectable Self-Healing Hydrogel Based on Star Poly(Ethylene Glycol)-B-Polypeptide as a Potential Pharmaceuticals Delivery Carrier. *Soft Matter* **2018**, *14*, 7420–7428.
- (94) Sun, T. L.; Kurokawa, T.; Kuroda, S.; Bin Ihsan, A.; Akasaki, T.; Sato, K.; Haque, M. A.; Nakajima, T.; Gong, J. P. Physical Hydrogels Composed of Polyampholytes Demonstrate High Toughness and Viscoelasticity. *Nat. Mater.* **2013**, *12*, 932–937.
- (95) Luo, F.; Sun, T. L.; Nakajima, T.; Kurokawa, T.; Li, X.; Guo, H.; Huang, Y.; Zhang, H.; Gong, J. P. Tough Polyion-Complex Hydrogels from Soft to Stiff Controlled by Monomer Structure. *Polymer (Guildf)* **2017**, *116*, 487–497.
- (96) Sharp, K. A.; Honig, B. Electrostatic Interactions in Macromolecules: Theory and Applications. *Annu. Rev. Biophys. Biophys. Chem.* **1990**, *19*, 301–332.
- (97) Jaspers, M.; Rowan, A. E.; Kouwer, P. H. J. Tuning Hydrogel Mechanics Using the Hofmeister Effect. *Adv. Funct. Mater.* **2015**, *25*, 6503–6510.
- (98) Yesilyurt, V.; Webber, M. J.; Appel, E. A.; Godwin, C.; Langer, R.; Anderson, D. G. Injectable Self-Healing Glucose-Responsive Hydrogels with pH-Regulated Mechanical Properties. *Adv. Mater.* **2016**, *28*, 86–91.
- (99) Vatankhah-Varnoosfaderani, M.; Hashmi, S.; Ghavaminejad, A.; Stadler, F. J. Rapid Self-Healing and Triple Stimuli Responsiveness of a Supramolecular Polymer Gel Based on Boron-Catechol Interactions in a Novel Water-Soluble Mussel-Inspired Copolymer. *Polym. Chem.* **2014**, *5*, 512–523.
- (100) Khare, E.; Holten-Andersen, N.; Buehler, M. J. Transition-Metal Coordinate Bonds for Bioinspired Macromolecules with Tunable Mechanical Properties. *Nat. Rev. Mater.* **2021**, *6*, 421–436.
- (101) Harrington, M. J.; Masic, A.; Holten-Andersen, N.; Waite, J. H.; Fratzl, P. Iron-Clad Fibers: A Metal-Based Biological Strategy for Hard Flexible Coatings. *Science (80-)* **2010**, *328*, 216–220.
- (102) Yavvari, P. S.; Pal, S.; Kumar, S.; Kar, A.; Awasthi, A. K.; Naaz, A.; Srivastava, A.; Bajaj, A. Injectable, Self-Healing Chimeric Catechol-Fe(III) Hydrogel for Localized Combination Cancer Therapy. *ACS Biomater. Sci. Eng.* **2017**, *3*, 3404–3413.
- (103) Li, L.; Smitthipong, W.; Zeng, H. Mussel-Inspired Hydrogels for Biomedical and Environmental Applications. *Polym. Chem.* **2015**, *6*, 353–358.
- (104) Tang, Q.; Zhao, D.; Zhou, Q.; Yang, H.; Peng, K.; Zhang, X. Polyhistidine-Based Metal Coordination Hydrogels with Physiologically Relevant pH Responsiveness and Enhanced Stability through a Novel Synthesis. *Macromol. Rapid Commun.* **2018**, *39*, 1800109.
- (105) Tang, Q.; Zhao, D.; Yang, H.; Wang, L.; Zhang, X. A pH-Responsive Self-Healing Hydrogel Based on Multivalent Coordination of Ni²⁺ with Polyhistidine-Terminated PEG and IDA-Modified Oligochitosan. *J. Mater. Chem. B* **2019**, *7*, 30–42.
- (106) Shi, L.; Wang, F.; Zhu, W.; Xu, Z.; Fuchs, S.; Hilborn, J.; Zhu, L.; Ma, Q.; Wang, Y.; Weng, X.; Ossipov, D. A. Self-Healing Silk Fibroin-Based Hydrogel for Bone Regeneration: Dynamic Metal-Ligand Self-Assembly Approach. *Adv. Funct. Mater.* **2017**, *27*, 1700591.
- (107) Wang, B.; Liu, J.; Niu, D.; Wu, N.; Yun, W.; Wang, W.; Zhang, K.; Li, G.; Yan, S.; Xu, G.; Yin, J. Mussel-Inspired Bisphosphonated Injectable Nanocomposite Hydrogels with Adhesive, Self-Healing, and Osteogenic Properties for Bone Regeneration. *ACS Appl. Mater. Interfaces* **2021**, *13*, 32673–32689.
- (108) Diba, M.; An, J.; Schmidt, S.; Hembury, M.; Ossipov, D.; Boccaccini, A. R.; Leeuwenburgh, S. C. G. Exploiting Bisphosphonate-Bioactive-Glass Interactions for the Development of Self-Healing and Bioactive Composite Hydrogels. *Macromol. Rapid Commun.* **2016**, *37*, 1952–1959.

- (109) Diba, M.; Camargo, W. A.; Brindisi, M.; Farbod, K.; Klymov, A.; Schmidt, S.; Harrington, M. J.; Draghi, L.; Boccaccini, A. R.; Jansen, J. A.; van den Beucken, J. J. P.; Leeuwenburgh, S. C. G. Composite Colloidal Gels Made of Bisphosphonate-Functionalized Gelatin and Bioactive Glass Particles for Regeneration of Osteoporotic Bone Defects. *Adv. Funct. Mater.* **2017**, *27*, 1703438.
- (110) Nejadnik, M. R.; Yang, X.; Bongio, M.; Alghamdi, H. S.; Van den Beucken, J. J. P.; Huysmans, M. C.; Jansen, J. A.; Hilborn, J.; Ossipov, D.; Leeuwenburgh, S. C. G. Self-Healing Hybrid Nanocomposites Consisting of Bisphosphonated Hyaluronan and Calcium Phosphate Nanoparticles. *Biomaterials* **2014**, *35*, 6918–6929.
- (111) Zhang, K.; Feng, Q.; Xu, J.; Xu, X.; Tian, F.; Yeung, K. W. K.; Bian, L. Self-Assembled Injectable Nanocomposite Hydrogels Stabilized by Bisphosphonate-Magnesium (Mg^{2+}) Coordination Regulates the Differentiation of Encapsulated Stem Cells via Dual Crosslinking. *Adv. Funct. Mater.* **2017**, *27*, 1701642.
- (112) Chaudhuri, O.; Gu, L.; Klumpers, D.; Darnell, M.; Bencherif, S. A.; Weaver, J. C.; Huebsch, N.; Lee, H. P.; Lippens, E.; Duda, G. N.; Mooney, D. J. Hydrogels with Tunable Stress Relaxation Regulate Stem Cell Fate and Activity. *Nat. Mater.* **2016**, *15*, 326–334.
- (113) Nam, S.; Stowers, R.; Lou, J.; Xia, Y.; Chaudhuri, O. Varying PEG Density to Control Stress Relaxation in Alginate-PEG Hydrogels for 3D Cell Culture Studies. *Biomaterials* **2019**, *200*, 15–24.
- (114) Wisdom, K. M.; Adebawale, K.; Chang, J.; Lee, J. Y.; Nam, S.; Desai, R.; Rossen, N. S.; Rafat, M.; West, R. B.; Hodgson, L.; Chaudhuri, O. Matrix Mechanical Plasticity Regulates Cancer Cell Migration through Confining Microenvironments. *Nat. Commun.* **2018**, *9*, 4144.
- (115) Alsberg, E.; Anderson, K. W.; Albeiruti, A.; Franceschi, R. T.; Mooney, D. J. Cell-Interactive Alginate Hydrogels for Bone Tissue Engineering. *J. Dent. Res.* **2001**, *80*, 2025–2029.
- (116) Stilhano, R. S.; Madrigal, J. L.; Wong, K.; Williams, P. A.; Martin, P. K. M.; Yamaguchi, F. S. M.; Samoto, V. Y.; Han, S. W.; Silva, E. A. Injectable Alginate Hydrogel for Enhanced Spatiotemporal Control of Lentivector Delivery in Murine Skeletal Muscle. *J. Controlled Release* **2016**, *237*, 42–49.
- (117) Bidarra, S. J.; Barrias, C. C.; Granja, P. L. Injectable Alginate Hydrogels for Cell Delivery in Tissue Engineering. *Acta Biomater.* **2014**, *10*, 1646–1662.
- (118) Kim, W. S.; Mooney, D. J.; Arany, P. R.; Lee, K.; Huebsch, N.; Kim, J. Adipose Tissue Engineering Using Injectable, Oxidized Alginate Hydrogels. *Tissue Eng. - Part A* **2012**, *18*, 737–743.
- (119) Huebsch, N.; Kearney, C. J.; Zhao, X.; Kim, J.; Cezar, C. A.; Suo, Z.; Mooney, D. J. Ultrasound-Triggered Disruption and Self-Healing of Reversibly Cross-Linked Hydrogels for Drug Delivery and Enhanced Chemotherapy. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, 9762–9767.
- (120) Liu, S.; Li, L. Recoverable and Self-Healing Double Network Hydrogel Based on κ -Carrageenan. *ACS Appl. Mater. Interfaces* **2016**, *8*, 29749–29758.
- (121) Deng, Y.; Huang, M.; Sun, D.; Hou, Y.; Li, Y.; Dong, T.; Wang, X.; Zhang, L.; Yang, W. Dual Physically Cross-Linked κ -Carrageenan-Based Double Network Hydrogels with Superior Self-Healing Performance for Biomedical Application. *ACS Appl. Mater. Interfaces* **2018**, *10*, 37544–37554.
- (122) Diener, M.; Adamcik, J.; Sánchez-Ferrer, A.; Jaedig, F.; Schefer, L.; Mezzenga, R. Primary, Secondary, Tertiary and Quaternary Structure Levels in Linear Polysaccharides: From Random Coil, to Single Helix to Supramolecular Assembly. *Biomacromolecules* **2019**, *20*, 1731–1739.
- (123) Meyer, E. E.; Rosenberg, K. J.; Israelachvili, J. Recent Progress in Understanding Hydrophobic Interactions. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 15739–15746.
- (124) Tuncaboylu, D. C.; Argun, A.; Sahin, M.; Sari, M.; Okay, O. Structure Optimization of Self-Healing Hydrogels Formed via Hydrophobic Interactions. *Polymer (Guildf)* **2012**, *53*, 5513–5522.
- (125) Sugioka, Y.; Nakamura, J.; Ohtsuki, C.; Sugawara-narutaki, A. Thixotropic Hydrogels Composed of Self-assembled Nanofibers of Double-hydrophobic Elastin-like Block Polypeptides. *Int. J. Mol. Sci.* **2021**, *22*, 4104.
- (126) Foster, A. A.; Dewi, R. E.; Cai, L.; Hou, L.; Strassberg, Z.; Alcazar, C. A.; Heilshorn, S. C.; Huang, N. F. Protein-Engineered Hydrogels Enhance the Survival of Induced Pluripotent Stem Cell-Derived Endothelial Cells for Treatment of Peripheral Arterial Disease. *Biomater. Sci.* **2018**, *6*, 614–622.
- (127) Feng, Q.; Wei, K.; Lin, S.; Xu, Z.; Sun, Y.; Shi, P.; Li, G.; Bian, L. Mechanically Resilient, Injectable, and Bioadhesive Supramolecular Gelatin Hydrogels Crosslinked by Weak Host-Guest Interactions Assist Cell Infiltration and in Situ Tissue Regeneration. *Biomaterials* **2016**, *101*, 217–228.
- (128) Peng, L.; Zhang, H.; Feng, A.; Huo, M.; Wang, Z.; Hu, J.; Gao, W.; Yuan, J. Electrochemical Redox Responsive Supramolecular Self-Healing Hydrogels Based on Host-Guest Interaction. *Polym. Chem.* **2015**, *6*, 3652–3659.
- (129) Zhou, Y.; Zhang, Y.; Dai, Z.; Jiang, F.; Tian, J.; Zhang, W. A Super-Stretchable, Self-Healing and Injectable Supramolecular Hydrogel Constructed by a Host-Guest Crosslinker. *Biomater. Sci.* **2020**, *8*, 3359–3369.
- (130) Loh, X. J. Supramolecular Host-Guest Polymeric Materials for Biomedical Applications. *Mater. Horizons* **2014**, *1*, 185–195.
- (131) Appel, E. A.; Biedermann, F.; Rauwald, U.; Jones, S. T.; Zayed, J. M.; Scherpan, O. A. Supramolecular Cross-Linked Networks via Host-Guest Complexation with Cucurbit[8]Uril. *J. Am. Chem. Soc.* **2010**, *132*, 14251–14260.
- (132) Feng, Q.; Xu, J.; Zhang, K.; Yao, H.; Zheng, N.; Zheng, L.; Wang, J.; Wei, K.; Xiao, X.; Qin, L.; Bian, L. Dynamic and Cell-Infiltrable Hydrogels as Injectable Carrier of Therapeutic Cells and Drugs for Treating Challenging Bone Defects. *ACS Cent. Sci.* **2019**, *5*, 440–450.
- (133) Xu, J.; Feng, Q.; Lin, S.; Yuan, W.; Li, R.; Li, J.; Wei, K.; Chen, X.; Zhang, K.; Yang, Y.; Wu, T.; Wang, B.; Zhu, M.; Guo, R.; Li, G.; Bian, L. Injectable Stem Cell-Laden Supramolecular Hydrogels Enhance in Situ Osteochondral Regeneration via the Sustained Co-Delivery of Hydrophilic and Hydrophobic Chondrogenic Molecules. *Biomaterials* **2019**, *210*, 51–61.
- (134) Li, S.; Yu, J.; Zhang, M.; Ma, Z.; Chen, N.; Li, X.; Ban, J.; Xie, J.; Chen, Z.; Ma, J.; Tian, C.; Qin, Y.; Wang, J.; Gao, W.; Long, L.; Zhao, J.; Hou, X.; Yuan, X. An Intermediate Unit-Mediated, Continuous Structural Inheritance Strategy for the Dilemma between Injectability and Robustness of Hydrogels. *Adv. Funct. Mater.* **2022**, *32*, 2110617.
- (135) Diba, M.; Spaans, S.; Hendrikse, S. I. S.; Bastings, M. M. C.; Schotman, M. J. G.; van Sprang, J. F.; Wu, D. J.; Hoeben, F. J. M.; Janssen, H. M.; Dankers, P. Y. W. Engineering the Dynamics of Cell Adhesion Cues in Supramolecular Hydrogels for Facile Control over Cell Encapsulation and Behavior. *Adv. Mater.* **2021**, *33*, 2008111.
- (136) Bastings, M. M. C.; Koudstaal, S.; Kieleyka, R. E.; Nakano, Y.; Pape, A. C. H.; Feyen, D. A. M.; van Slochteren, F. J.; Doevendans, P. A.; Sluijter, J. P. G.; Meijer, E. W.; Chamuleau, S. A. J.; Dankers, P. Y. W. A Fast PH-Switchable and Self-Healing Supramolecular Hydrogel Carrier for Guided, Local Catheter Injection in the Infarcted Myocardium. *Adv. Healthc. Mater.* **2014**, *3*, 70–78.
- (137) Kieleyka, R. E.; Pape, A. C. H.; Albertazzi, L.; Nakano, Y.; Bastings, M. M. C.; Voets, I. K.; Dankers, P. Y. W.; Meijer, E. W. Mesoscale Modulation of Supramolecular Ureidopyrimidinone-Based Poly(Ethylene Glycol) Transient Networks in Water. *J. Am. Chem. Soc.* **2013**, *135*, 11159–11164.
- (138) Pape, A.; Bastings, M.; Kieleyka, R.; Wyss, H.; Voets, I.; Meijer, E.; Dankers, P. Mesoscale Characterization of Supramolecular Transient Networks Using SAXS and Rheology. *Int. J. Mol. Sci.* **2014**, *15*, 1096–1111.
- (139) Spaans, S.; Fransen, P. P. K. H.; Schotman, M. J. G.; Van Der Wulp, R.; Lafleur, R. P. M.; Kluijtmans, S. G. J. M.; Dankers, P. Y. W. Supramolecular Modification of a Sequence-Controlled Collagen-Mimicking Polymer. *Biomacromolecules* **2019**, *20*, 2360–2371.
- (140) Zhang, G.; Ngai, T.; Deng, Y.; Wang, C. An Injectable Hydrogel with Excellent Self-Healing Property Based on Quadruple Hydrogen Bonding. *Macromol. Chem. Phys.* **2016**, *217*, 2172–2181.
- (141) Chirila, T. V.; Lee, H. H.; Odon, M.; Nieuwenhuizen, M. M. L.; Blakey, I.; Nicholson, T. M. Hydrogen-Bonded Supramolecular

Polymers as Self-Healing Hydrogels: Effect of a Bulky Adamantyl Substituent in the Ureido-Pyrimidinone Monomer. *J. Appl. Polym. Sci.* **2014**, *131*, 4.

(142) Li, L.; Yan, B.; Yang, J.; Huang, W.; Chen, L.; Zeng, H. Injectable Self-Healing Hydrogel with Antimicrobial and Antifouling Properties. *ACS Appl. Mater. Interfaces* **2017**, *9*, 9221–9225.

(143) Li, L.; Yan, B.; Yang, J.; Chen, L.; Zeng, H. Novel Mussel-Inspired Injectable Self-Healing Hydrogel with Anti-Biofouling Property. *Adv. Mater.* **2015**, *27*, 1294–1299.

(144) Zhang, J.; Guo, Y.; Pan, G.; Wang, P.; Li, Y.; Zhu, X.; Zhang, C. Injectable Drug-Conjugated DNA Hydrogel for Local Chemotherapy to Prevent Tumor Recurrence. *ACS Appl. Mater. Interfaces* **2020**, *12*, 21441–21449.

(145) Ma, X.; Wang, C.; Yuan, W.; Xie, X.; Song, Y. Highly Adhesive, Conductive, and Self-Healing Hydrogel with Triple Cross-Linking Inspired by Mussel and DNA for Wound Adhesion and Human Motion Sensing. *ACS Appl. Polym. Mater.* **2021**, *3*, 6586–6597.

(146) Wei, Z.; Yang, J. H.; Du, X. J.; Xu, F.; Zrinyi, M.; Osada, Y.; Li, F.; Chen, Y. M. Dextran-Based Self-Healing Hydrogels Formed by Reversible Diels-Alder Reaction under Physiological Conditions. *Macromol. Rapid Commun.* **2013**, *34*, 1464–1470.

(147) Yang, B.; Zhang, Y.; Zhang, X.; Tao, L.; Li, S.; Wei, Y. Facilely Prepared Inexpensive and Biocompatible Self-Healing Hydrogel: A New Injectable Cell Therapy Carrier. *Polym. Chem.* **2012**, *3*, 3235–3238.

(148) Casuso, P.; Odriozola, I.; Pérez-San Vicente, A.; Loinaz, I.; Cabañero, G.; Grande, H. J.; Dupin, D. Injectable and Self-Healing Dynamic Hydrogels Based on Metal(I)-Thiolate/Disulfide Exchange as Biomaterials with Tunable Mechanical Properties. *Biomacromolecules* **2015**, *16*, 3552–3561.

(149) Tasdelen, M. A. Diels-Alder “Click” Reactions: Recent Applications in Polymer and Material Science. *Polym. Chem.* **2011**, *2*, 2133–2145.

(150) Madl, C. M.; Heilshorn, S. C. Bioorthogonal Strategies for Engineering Extracellular Matrices. *Adv. Funct. Mater.* **2018**, *28*, 1706046.

(151) Nimmo, C. M.; Owen, S. C.; Shoichet, M. S. Diels-Alder Click Cross-Linked Hyaluronic Acid Hydrogels for Tissue Engineering. *Biomacromolecules* **2011**, *12*, 824–830.

(152) Shao, C.; Wang, M.; Chang, H.; Xu, F.; Yang, J. A Self-Healing Cellulose Nanocrystal-Poly(Ethylene Glycol) Nanocomposite Hydrogel via Diels-Alder Click Reaction. *ACS Sustain. Chem. Eng.* **2017**, *5*, 6167–6174.

(153) Mo, C.; Xiang, L.; Chen, Y. Advances in Injectable and Self-Healing Polysaccharide Hydrogel Based on the Schiff Base Reaction. *Macromol. Rapid Commun.* **2021**, *42*, 2100025.

(154) Hafeez, S.; Ooi, H.; Morgan, F.; Mota, C.; Dettin, M.; van Blitterswijk, C.; Moroni, L.; Baker, M. Viscoelastic Oxidized Alginates with Reversible Imine Type Crosslinks: Self-Healing, Injectable, and Bioprintable Hydrogels. *Gels* **2018**, *4*, 85.

(155) Li, S.; Pei, M.; Wan, T.; Yang, H.; Gu, S.; Tao, Y.; Liu, X.; Zhou, Y.; Xu, W.; Xiao, P. Self-Healing Hyaluronic Acid Hydrogels Based on Dynamic Schiff Base Linkages as Biomaterials. *Carbohydr. Polym.* **2020**, *250*, 116922.

(156) Guo, B.; Qu, J.; Zhao, X.; Zhang, M. Degradable Conductive Self-Healing Hydrogels Based on Dextran-Graft-Tetraaniline and N-Carboxyethyl Chitosan as Injectable Carriers for Myoblast Cell Therapy and Muscle Regeneration. *Acta Biomater.* **2019**, *84*, 180–193.

(157) Wang, Y.; Xie, R.; Li, Q.; Dai, F.; Lan, G.; Shang, S.; Lu, F. A Self-Adapting Hydrogel Based on Chitosan/Oxidized Konjac Glucomannan/AgNPs for Repairing Irregular Wounds. *Biomater. Sci.* **2020**, *8*, 1910–1922.

(158) Panwar, V.; Babu, A.; Sharma, A.; Thomas, J.; Chopra, V.; Malik, P.; Rajput, S.; Mittal, M.; Guha, R.; Chattopadhyay, N.; Mandal, D.; Ghosh, D. Tunable, Conductive, Self-Healing, Adhesive and Injectable Hydrogels for Bioelectronics and Tissue Regeneration Applications. *J. Mater. Chem. B* **2021**, *9*, 6260–6270.

(159) Nagy, P. Kinetics and Mechanisms of Thiol-Disulfide Exchange Covering Direct Substitution and Thiol Oxidation-Mediated Pathways. *Antioxidants Redox Signal.* **2013**, *18*, 1623–1641.

(160) Yu, H.; Wang, Y.; Yang, H.; Peng, K.; Zhang, X. Injectable Self-Healing Hydrogels Formed via Thiol/Disulfide Exchange of Thiol Functionalized F127 and Dithiolane Modified PEG. *J. Mater. Chem. B* **2017**, *5*, 4121–4127.

(161) Yang, R.; Liu, X.; Ren, Y.; Xue, W.; Liu, S.; Wang, P.; Zhao, M.; Xu, H.; Chi, B. Injectable Adaptive Self-Healing Hyaluronic Acid/Poly (γ -Glutamic Acid) Hydrogel for Cutaneous Wound Healing. *Acta Biomater.* **2021**, *127*, 102–115.

(162) Wang, Q.; Xu, W.; Koppolu, R.; van Bochove, B.; Seppälä, J.; Hupa, L.; Willför, S.; Xu, C.; Wang, X. Injectable Thiol-Ene Hydrogel of Galactoglucosaminan and Cellulose Nanocrystals in Delivery of Therapeutic Inorganic Ions with Embedded Bioactive Glass Nanoparticles. *Carbohydr. Polym.* **2022**, *276*, 118780.

(163) Zhang, X.; Jiang, S.; Yan, T.; Fan, X.; Li, F.; Yang, X.; Ren, B.; Xu, J.; Liu, J. Injectable and Fast Self-Healing Protein Hydrogels. *Soft Matter* **2019**, *15*, 7583–7589.

(164) Pérez-San Vicente, A.; Peroglio, M.; Ernst, M.; Casuso, P.; Loinaz, I.; Grande, H. J.; Alini, M.; Eglin, D.; Dupin, D. Self-Healing Dynamic Hydrogel as Injectable Shock-Absorbing Artificial Nucleus Pulposus. *Biomacromolecules* **2017**, *18*, 2360–2370.

(165) Zhu, S.; Wang, J.; Yan, H.; Wang, Y.; Zhao, Y.; Feng, B.; Duan, K.; Weng, J. An Injectable Supramolecular Self-Healing Bio-Hydrogel with High Stretchability, Extensibility and Ductility, and a High Swelling Ratio. *J. Mater. Chem. B* **2017**, *5*, 7021–7034.

(166) Rodell, C. B.; Dusaj, N. N.; Highley, C. B.; Burdick, J. A. Injectable and Cytocompatible Tough Double-Network Hydrogels through Tandem Supramolecular and Covalent Crosslinking. *Adv. Mater.* **2016**, *28*, 8419–8424.

(167) Liu, S.; Qi, D.; Chen, Y.; Teng, L.; Jia, Y.; Ren, L. Quadruple Hydrogen Bonds and Thermo-Triggered Hydrophobic Interactions Generate Dynamic Hydrogels to Modulate Transplanted Cell Retention. *Biomater. Sci.* **2019**, *7*, 1286–1298.

(168) Ren, P.; Li, J.; Zhao, L.; Wang, A.; Wang, M.; Li, J.; Jian, H.; Li, X.; Yan, X.; Bai, S. Dipeptide Self-Assembled Hydrogels with Shear-Thinning and Instantaneous Self-Healing Properties Determined by Peptide Sequences. *ACS Appl. Mater. Interfaces* **2020**, *12*, 21433–21440.

(169) Li, D.; Fei, X.; Wang, K.; Xu, L.; Wang, Y.; Tian, J.; Li, Y. A Novel Self-Healing Triple Physical Cross-Linked Hydrogel for Antibacterial Dressing. *J. Mater. Chem. B* **2021**, *9*, 6844–6855.

(170) Meng, L.; Shao, C.; Cui, C.; Xu, F.; Lei, J.; Yang, J. Autonomous Self-Healing Silk Fibroin Injectable Hydrogels Formed via Surfactant-Free Hydrophobic Association. *ACS Appl. Mater. Interfaces* **2020**, *12*, 1628–1639.

(171) Guo, H.; Huang, S.; Yang, X.; Wu, J.; Kirk, T. B.; Xu, J.; Xu, A.; Xue, W. Injectable and Self-Healing Hydrogels with Double-Dynamic Bond Tunable Mechanical, Gel-Sol Transition and Drug Delivery Properties for Promoting Periodontium Regeneration in Periodontitis. *ACS Appl. Mater. Interfaces* **2021**, *13*, 61638–61652.

(172) Liang, Y.; Li, Z.; Huang, Y.; Yu, R.; Guo, B. Dual-Dynamic-Bond Cross-Linked Antibacterial Adhesive Hydrogel Sealants with On-Demand Removability for Post-Wound-Closure and Infected Wound Healing. *ACS Nano* **2021**, *15*, 7078–7093.

(173) Bai, Q.; Teng, L.; Zhang, X.; Dong, C. Multifunctional Single-Component Polypeptide Hydrogels: The Gelation Mechanism, Superior Biocompatibility, High Performance Hemostasis, and Scarless Wound Healing. *Adv. Healthc. Mater.* **2022**, *11*, e2101809.

(174) Wang, Y.; Garcia, C. R.; Ding, Z.; Gabriliska, R.; Rumbaugh, K. P.; Wu, J.; Liu, Q.; Li, W. Adhesive, Self-Healing, and Antibacterial Chitosan Hydrogels with Tunable Two-Layer Structures. *ACS Sustain. Chem. Eng.* **2020**, *8*, 18006–18014.

(175) Wang, L.; Deng, F.; Wang, W.; Li, A.; Lu, C.; Chen, H.; Wu, G.; Nan, K.; Li, L. Construction of Injectable Self-Healing Macroporous Hydrogels via a Template-Free Method for Tissue Engineering and Drug Delivery. *ACS Appl. Mater. Interfaces* **2018**, *10*, 36721–36732.

- (176) Fan, L.; He, Z.; Peng, X.; Xie, J.; Su, F.; Wei, D. X.; Zheng, Y.; Yao, D. Injectable, Intrinsically Antibacterial Conductive Hydrogels with Self-Healing and pH Stimulus Responsiveness for Epidermal Sensors and Wound Healing. *ACS Appl. Mater. Interfaces* **2021**, *13*, 53541–53552.
- (177) Wang, H.; Zhu, D.; Paul, A.; Cai, L.; Enejder, A.; Yang, F.; Heilshorn, S. C. Covalently Adaptable Elastin-Like Protein-Hyaluronic Acid (ELP-HA) Hybrid Hydrogels with Secondary Thermoresponsive Crosslinking for Injectable Stem Cell Delivery. *Adv. Funct. Mater.* **2017**, *27*, 1605609.
- (178) Yang, B.; Song, J.; Jiang, Y.; Li, M.; Wei, J.; Qin, J.; Peng, W.; Lasaosa, F. L.; He, Y.; Mao, H.; Yang, J.; Gu, Z. Injectable Adhesive Self-Healing Multicross-Linked Double-Network Hydrogel Facilitates Full-Thickness Skin Wound Healing. *ACS Appl. Mater. Interfaces* **2020**, *12*, 57782–57797.
- (179) Ding, X.; Wang, Y.; Liu, J.; Zhang, P.; Li, G.; Sun, T.; Xiao, C. Injectable in Situ Forming Double-Network Hydrogel to Enhance Transplanted Cell Viability and Retention. *Chem. Mater.* **2021**, *33*, 5885–5895.
- (180) Zhao, X.; Liang, Y.; Huang, Y.; He, J.; Han, Y.; Guo, B. Physical Double-Network Hydrogel Adhesives with Rapid Shape Adaptability, Fast Self-Healing, Antioxidant and NIR/pH Stimulus-Responsiveness for Multidrug-Resistant Bacterial Infection and Removable Wound Dressing. *Adv. Funct. Mater.* **2020**, *30*, 1910748.
- (181) Shi, L.; Carstensen, H.; Hözl, K.; Lunzer, M.; Li, H.; Hilborn, J.; Ovsianikov, A.; Ossipov, D. A. Dynamic Coordination Chemistry Enables Free Directional Printing of Biopolymer Hydrogel. *Chem. Mater.* **2017**, *29*, 5816–5823.
- (182) Ouyang, L.; Highley, C. B.; Rodell, C. B.; Sun, W.; Burdick, J. A. 3D Printing of Shear-Thinning Hyaluronic Acid Hydrogels with Secondary Cross-Linking. *ACS Biomater. Sci. Eng.* **2016**, *2*, 1743–1751.
- (183) Qiao, Y.; Xu, S.; Zhu, T.; Tang, N.; Bai, X.; Zheng, C. Preparation of Printable Double-Network Hydrogels with Rapid Self-Healing and High Elasticity Based on Hyaluronic Acid for Controlled Drug Release. *Polymer (Guildf)*. **2020**, *186*, 121994.
- (184) Diba, M.; Koons, G. L.; Bedell, M. L.; Mikos, A. G. 3D Printed Colloidal Biomaterials Based on Photo-Reactive Gelatin Nanoparticles. *Biomaterials* **2021**, *274*, 120871.
- (185) Rodell, C. B.; MacArthur, J. W.; Dorsey, S. M.; Wade, R. J.; Wang, L. L.; Woo, Y. J.; Burdick, J. A. Shear-Thinning Supramolecular Hydrogels with Secondary Autonomous Covalent Crosslinking to Modulate Viscoelastic Properties in Vivo. *Adv. Funct. Mater.* **2015**, *25*, 636–644.
- (186) Wang, L. L.; Highley, C. B.; Yeh, Y. C.; Galarraga, J. H.; Uman, S.; Burdick, J. A. Three-Dimensional Extrusion 3D Printing of Single- and Double-Network Hydrogels Containing Dynamic Covalent Crosslinks. *J. Biomed. Mater. Res. - Part A* **2018**, *106*, 865–875.
- (187) Ruan, L.; Zhang, H.; Luo, H.; Liu, J.; Tang, F.; Shi, Y. K.; Zhao, X. Designed Amphiphilic Peptide Forms Stable Nanoweb, Slowly Releases Encapsulated Hydrophobic Drug, and Accelerates Animal Hemostasis. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 5105–5110.
- (188) Jacob, R. S.; Ghosh, D.; Singh, P. K.; Basu, S. K.; Jha, N. N.; Das, S.; Sukul, P. K.; Patil, S.; Sathaye, S.; Kumar, A.; Chowdhury, A.; Malik, S.; Sen, S.; Maji, S. K. Self Healing Hydrogels Composed of Amyloid Nano Fibrils for Cell Culture and Stem Cell Differentiation. *Biomaterials* **2015**, *54*, 97–105.
- (189) Włodarczyk-Biegun, M. K.; Farbod, K.; Werten, M. W. T.; Slingerland, C. J.; De Wolf, F. A.; Van Den Beucken, J. J. P.; Leeuwenburgh, S. C. G.; Cohen Stuart, M. A.; Kamperman, M. Fibrous Hydrogels for Cell Encapsulation: A Modular and Supramolecular Approach. *PLoS One* **2016**, *11*, No. e0155625.
- (190) Xu, H.; Zhang, L.; Cai, J. Injectable, Self-Healing, β -Chitin-Based Hydrogels with Excellent Cytocompatibility, Antibacterial Activity, and Potential As Drug/Cell Carriers. *ACS Appl. Bio Mater.* **2019**, *2*, 196–204.
- (191) Diba, M.; Polini, A.; Petre, D. G.; Zhang, Y.; Leeuwenburgh, S. C. G. Fiber-Reinforced Colloidal Gels as Injectable and Moldable Biomaterials for Regenerative Medicine. *Mater. Sci. Eng., C* **2018**, *92*, 143–150.
- (192) Gantar, A.; Drnovšek, N.; Casuso, P.; Pérez-San Vicente, A.; Rodriguez, J.; Dupin, D.; Novak, S.; Loinaz, I. Injectable and Self-Healing Dynamic Hydrogel Containing Bioactive Glass Nanoparticles as a Potential Biomaterial for Bone Regeneration. *RSC Adv.* **2016**, *6*, 69156–69166.
- (193) Gu, Y.; Zhao, J.; Johnson, J. A. A (Macro)Molecular-Level Understanding of Polymer Network Topology. *Trends Chem.* **2019**, *1*, 318–334.
- (194) Orgel, J. P. R. O.; Irving, T. C.; Miller, A.; Wess, T. J. Microfibrillar Structure of Type I Collagen in Situ. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 9001–9005.
- (195) Licup, A. J.; Münster, S.; Sharma, A.; Sheinman, M.; Jawerth, L. M.; Fabry, B.; Weitz, D. A.; MacKintosh, F. C. Stress Controls the Mechanics of Collagen Networks. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 9573–9578.
- (196) Han, W.; Chen, S.; Yuan, W.; Fan, Q.; Tian, J.; Wang, X.; Chen, L.; Zhang, X.; Wei, W.; Liu, R.; Qu, J.; Jiao, Y.; Austin, R. H.; Liu, L. Oriented Collagen Fibers Direct Tumor Cell Intravasation. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, 11208–11213.
- (197) Bordbar, S.; Lotfi Bakhshaiesh, N.; Khanmohammadi, M.; Sayahpour, F. A.; Alini, M.; Baghaban Eslaminejad, M. Production and Evaluation of Decellularized Extracellular Matrix Hydrogel for Cartilage Regeneration Derived from Knee Cartilage. *J. Biomed. Mater. Res. - Part A* **2020**, *108*, 938–946.
- (198) Zhao, Y.; Fan, J.; Bai, S. Biocompatibility of Injectable Hydrogel from Decellularized Human Adipose Tissue in Vitro and in Vivo. *J. Biomed. Mater. Res. - Part B Appl. Biomater.* **2019**, *107*, 1684–1694.
- (199) Young, D. A.; Ibrahim, D. O.; Hu, D.; Christman, K. L. Injectable Hydrogel Scaffold from Decellularized Human Lipoaspirate. *Acta Biomater.* **2011**, *7*, 1040–1049.
- (200) Seif-Naraghi, S. B.; Singelyn, J. M.; Salvatore, M. A.; Osborn, K. G.; Wang, J. J.; Sampat, U.; Kwan, O. L.; Strachan, G. M.; Wong, J.; Schup-Magoffin, P. J.; Braden, R. L.; Bartels, K.; DeQuach, J. A.; Preul, M.; Kinsey, A. M.; DeMaria, A. N.; Dib, N.; Christman, K. L. Safety and Efficacy of an Injectable Extracellular Matrix Hydrogel for Treating Myocardial Infarction. *Sci. Transl. Med.* **2013**, *5*, 173ra25.
- (201) Borrelli, C.; Buckley, C. T. Injectable Disc-Derived ECM Hydrogel Functionalised with Chondroitin Sulfate for Intervertebral Disc Regeneration. *Acta Biomater.* **2020**, *117*, 142–155.
- (202) Zhang, L.; Zhou, Y.; Su, D.; Wu, S.; Zhou, J.; Chen, J. Injectable, Self-Healing and pH Responsive Stem Cell Factor Loaded Collagen Hydrogel as a Dynamic Bioadhesive Dressing for Diabetic Wound Repair. *J. Mater. Chem. B* **2021**, *9*, 5887–5897.
- (203) Ding, C.; Yang, Q.; Tian, M.; Guo, C.; Deng, F.; Dang, Y.; Zhang, M. Novel Collagen-Based Hydrogels with Injectable, Self-Healing, Wound-Healing Properties via a Dynamic Crosslinking Interaction. *Polym. Int.* **2020**, *69*, 858–866.
- (204) Yang, L.; Li, H.; Yao, L.; Yu, Y.; Ma, G. Amyloid-Based Injectable Hydrogel Derived from Hydrolyzed Hen Egg White Lysozyme. *ACS Omega* **2019**, *4*, 8071–8080.
- (205) Xing, R.; Li, S.; Zhang, N.; Shen, G.; Möhwalld, H.; Yan, X. Self-Assembled Injectable Peptide Hydrogels Capable of Triggering Antitumor Immune Response. *Biomacromolecules* **2017**, *18*, 3514–3523.
- (206) Abbas, M.; Xing, R.; Zhang, N.; Zou, Q.; Yan, X. Antitumor Photodynamic Therapy Based on Dipeptide Fibrous Hydrogels with Incorporation of Photosensitive Drugs. *ACS Biomater. Sci. Eng.* **2018**, *4*, 2046–2052.
- (207) Bertsch, P.; Andrée, L.; Besheli, N. H.; Leeuwenburgh, S. C. G. Colloidal Hydrogels Made of Gelatin Nanoparticles Exhibit Fast Stress Relaxation at Strains Relevant for Cell Activity. *Acta Biomater.* **2022**, *138*, 124–132.
- (208) Peak, C. W.; Stein, J.; Gold, K. A.; Gaharwar, A. K. Nanoengineered Colloidal Inks for 3D Bioprinting. *Langmuir* **2018**, *34*, 917–925.
- (209) Wang, Q.; Jamal, S.; Detamore, M. S.; Berkland, C. PLGA-Chitosan/PLGA-Alginate Nanoparticle Blends as Biodegradable Colloidal Gels for Seeding Human Umbilical Cord Mesenchymal Stem Cells. *J. Biomed. Mater. Res.: Part A* **2011**, *96A*, S20–S27.

- (210) Zhang, Y.; Gao, W.; Chen, Y.; Escajadillo, T.; Ungerleider, J.; Fang, R. H.; Christman, K.; Nizet, V.; Zhang, L. Self-Assembled Colloidal Gel Using Cell Membrane-Coated Nanosponges as Building Blocks. *ACS Nano* **2017**, *11*, 11923–11930.
- (211) Roux, R.; Ladavière, C.; Montembault, A.; David, L.; Delair, T. Shear Thinning Three-Dimensional Colloidal Assemblies of Chitosan and Poly(Lactic Acid) Nanoparticles. *J. Phys. Chem. B* **2013**, *117*, 7455–7464.
- (212) Wang, H.; Zou, Q.; Boerman, O. C.; Nijhuis, A. W. G.; Jansen, J. A.; Li, Y.; Leeuwenburgh, S. C. G. Combined Delivery of BMP-2 and BFGF from Nanostructured Colloidal Gelatin Gels and Its Effect on Bone Regeneration in Vivo. *J. Controlled Release* **2013**, *166*, 172–181.
- (213) Fakhari, A.; Phan, Q.; Berkland, C. Hyaluronic Acid Colloidal Gels as Self-Assembling Elastic Biomaterials. *J. Biomed. Mater. Res. - Part B Appl. Biomater.* **2014**, *102*, 612–618.
- (214) Dennis, S. C.; Detamore, M. S.; Kieweg, S. L.; Berkland, C. J. Mapping Glycosaminoglycan-Hydroxyapatite Colloidal Gels as Potential Tissue Defect Fillers. *Langmuir* **2014**, *30*, 3528–3537.
- (215) Muir, V. G.; Qazi, T. H.; Shan, J.; Groll, J.; Burdick, J. A. Influence of Microgel Fabrication Technique on Granular Hydrogel Properties. *ACS Biomater. Sci. Eng.* **2021**, *7*, 4269–4281.
- (216) Shin, M.; Song, K. H.; Burrell, J. C.; Cullen, D. K.; Burdick, J. A. Injectable and Conductive Granular Hydrogels for 3D Printing and Electroactive Tissue Support. *Adv. Sci.* **2019**, *6*, 1901229.
- (217) Mealy, J. E.; Chung, J. J.; Jeong, H. H.; Issadore, D.; Lee, D.; Atluri, P.; Burdick, J. A. Injectable Granular Hydrogels with Multifunctional Properties for Biomedical Applications. *Adv. Mater.* **2018**, *30*, 1705912.
- (218) Wang, H.; Boerman, O. C.; Sariibrahimoglu, K.; Li, Y.; Jansen, J. A.; Leeuwenburgh, S. C. G. Comparison of Micro- vs. Nanostructured Colloidal Gelatin Gels for Sustained Delivery of Osteogenic Proteins: Bone Morphogenetic Protein-2 and Alkaline Phosphatase. *Biomaterials* **2012**, *33*, 8695–8703.
- (219) Qazi, T. H.; Wu, J.; Muir, V. G.; Weintraub, S.; Gullbrand, S. E.; Lee, D.; Issadore, D.; Burdick, J. A. Anisotropic Rod-Shaped Particles Influence Injectable Granular Hydrogel Properties and Cell Invasion. *Adv. Mater.* **2022**, *34*, 2109194.
- (220) Xin, S.; Deo, K. A.; Dai, J.; Pandian, N. K. R.; Chimene, D.; Moebius, R. M.; Jain, A.; Han, A.; Gaharwar, A. K.; Alge, D. L. Generalizing Hydrogel Microparticles into a New Class of Bioinks for Extrusion Bioprinting. *Sci. Adv.* **2021**, *7*, No. eabk3087.
- (221) Douglas, A. M.; Fragkopoulos, A. A.; Gaines, M. K.; Lyon, L. A.; Fernandez-Nieves, A.; Barker, T. H. Dynamic Assembly of Ultrasoft Colloidal Networks Enables Cell Invasion within Restrictive Fibrillar Polymers. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 885–890.
- (222) Wang, Q.; Wang, L.; Detamore, M. S.; Berkland, C. Biodegradable Colloidal Gels as Moldable Tissue Engineering Scaffolds. *Adv. Mater.* **2008**, *20*, 236–239.
- (223) Wang, H.; Bongio, M.; Farbod, K.; Nijhuis, A. W. G.; Van Den Beucken, J.; Boerman, O. C.; Van Hest, J. C. M.; Li, Y.; Jansen, J. A.; Leeuwenburgh, S. C. G. Development of Injectable Organic/Inorganic Colloidal Composite Gels Made of Self-Assembling Gelatin Nanospheres and Calcium Phosphate Nanocrystals. *Acta Biomater.* **2014**, *10*, 508–519.
- (224) Wang, Q.; Gu, Z.; Jamal, S.; Detamore, M. S.; Berkland, C. Hybrid Hydroxyapatite Nanoparticle Colloidal Gels Are Injectable Fillers for Bone Tissue Engineering. *Tissue Eng. - Part A* **2013**, *19*, 2586–2593.
- (225) Wang, Q.; Wang, J.; Lu, Q.; Detamore, M. S.; Berkland, C. Injectable PLGA Based Colloidal Gels for Zero-Order Dexamethasone Release in Cranial Defects. *Biomaterials* **2010**, *31*, 4980–4986.
- (226) De France, K. J.; Badv, M.; Dorogin, J.; Siebers, E.; Panchal, V.; Babi, M.; Moran-Mirabal, J.; Lawlor, M.; Cranston, E. D.; Hoare, T. Tissue Response and Biodistribution of Injectable Cellulose Nanocrystal Composite Hydrogels. *ACS Biomater. Sci. Eng.* **2019**, *5*, 2235–2246.
- (227) Bertsch, P.; Schneider, L.; Bovone, G.; Tibbitt, M. W.; Fischer, P.; Gstöhl, S. Injectable Biocompatible Hydrogels from Cellulose Nanocrystals for Locally Targeted Sustained Drug Release. *ACS Appl. Mater. Interfaces* **2019**, *11*, 38578–38585.
- (228) De France, K. J.; Yager, K. G.; Chan, K. J. W.; Corbett, B.; Cranston, E. D.; Hoare, T. Injectable Anisotropic Nanocomposite Hydrogels Direct in Situ Growth and Alignment of Myotubes. *Nano Lett.* **2017**, *17*, 6487–6495.
- (229) Tang, J.; Javadi, M. U.; Pan, C.; Yu, G.; Berry, R. M.; Tam, K. C. Self-Healing Stimuli-Responsive Cellulose Nanocrystal Hydrogels. *Carbohydr. Polym.* **2020**, *229*, 115486.
- (230) Markstedt, K.; Mantas, A.; Tournier, I.; Martínez Ávila, H.; Hägg, D.; Gatenholm, P. 3D Bioprinting Human Chondrocytes with Nanocellulose-Alginate Bioink for Cartilage Tissue Engineering Applications. *Biomacromolecules* **2015**, *16*, 1489–1496.
- (231) Sultan, S.; Siqueira, G.; Zimmermann, T.; Mathew, A. P. 3D Printing of Nano-Cellulosic Biomaterials for Medical Applications. *Curr. Opin. Biomed. Eng.* **2017**, *2*, 29–34.
- (232) Ajdary, R.; Huan, S.; Zanjaniadeh Ezazi, N.; Xiang, W.; Grande, R.; Santos, H. A.; Rojas, O. J. Acetylated Nanocellulose for Single-Component Bioinks and Cell Proliferation on 3D-Printed Scaffolds. *Biomacromolecules* **2019**, *20*, 2770–2778.
- (233) Siqueira, G.; Kokkinis, D.; Libanori, R.; Hausmann, M. K.; Gladman, A. S.; Neels, A.; Tingaut, P.; Zimmermann, T.; Lewis, J. A.; Studart, A. R. Cellulose Nanocrystal Inks for 3D Printing of Textured Cellular Architectures. *Adv. Funct. Mater.* **2017**, *27*, 1604619.
- (234) Hausmann, M. K.; Rühls, P. A.; Siqueira, G.; Läger, J.; Libanori, R.; Zimmermann, T.; Studart, A. R. Dynamics of Cellulose Nanocrystal Alignment during 3D Printing. *ACS Nano* **2018**, *12*, 6926–6937.
- (235) Van Der Stok, J.; Wang, H.; Amin Yavari, S.; Siebelt, M.; Sandker, M.; Waarsing, J. H.; Verhaar, J. A. N.; Jahr, H.; Zadpoor, A. A.; Leeuwenburgh, S. C. G.; Weinans, H. Enhanced Bone Regeneration of Cortical Segmental Bone Defects Using Porous Titanium Scaffolds Incorporated with Colloidal Gelatin Gels for Time- and Dose-Controlled Delivery of Dual Growth Factors. *Tissue Eng. - Part A* **2013**, *19*, 2605–2614.
- (236) Muir, V. G.; Qazi, T. H.; Weintraub, S.; Torres Maldonado, B. O.; Arratia, P. E.; Burdick, J. A. Sticking Together: Injectable Granular Hydrogels with Increased Functionality via Dynamic Covalent Interparticle Crosslinking. *Small* **2022**, 2201115.
- (237) Al-Helw, A. A.; Al-Angary, A. A.; Mahrous, G. M.; Al-Dardari, M. M. Preparation and Evaluation of Sustained Release Cross-Linked Chitosan Microspheres Containing Phenobarbitone. *J. Microencapsul.* **1998**, *15*, 373–382.
- (238) Prabakaran, M.; Mano, J. F. Chitosan-Based Particles as Controlled Drug Delivery Systems. *Drug Deliv.* **2004**, *12*, 41–57.
- (239) García Cruz, D. M.; Escobar Ivirico, J. L.; Gomes, M. M.; Gómez Ribelles, J. L.; Sánchez, M. S.; Reis, R. L.; Mano, J. F. Chitosan Microparticles as Injectable Scaffolds for Tissue Engineering. *J. Tissue Eng. Regen. Med.* **2008**, *2*, 378–380.
- (240) Klubthawee, N.; Bovone, G.; Marco-Dufort, B.; Guzzi, E. A.; Aunpad, R.; Tibbitt, M. W. Biopolymer Nano-Network for Antimicrobial Peptide Protection and Local Delivery. *Adv. Healthc. Mater.* **2022**, *11*, 2101426.
- (241) Appel, E. A.; Tibbitt, M. W.; Greer, J. M.; Fenton, O. S.; Kreuels, K.; Anderson, D. G.; Langer, R. Exploiting Electrostatic Interactions in Polymer-Nanoparticle Hydrogels. *ACS Macro Lett.* **2015**, *4*, 848–852.
- (242) Basu, S.; Pacelli, S.; Paul, A. Self-Healing DNA-Based Injectable Hydrogels with Reversible Covalent Linkages for Controlled Drug Delivery. *Acta Biomater.* **2020**, *105*, 159–169.
- (243) Appel, E. A.; Tibbitt, M. W.; Webber, M. J.; Mattix, B. A.; Veisoh, O.; Langer, R. Self-Assembled Hydrogels Utilizing Polymer-Nanoparticle Interactions. *Nat. Commun.* **2015**, *6*, 6295.
- (244) Rao, Z.; Inoue, M.; Matsuda, M.; Taguchi, T. Quick Self-Healing and Thermo-Reversible Liposome Gel. *Colloids Surfaces B Biointerfaces* **2011**, *82*, 196–202.
- (245) Shi, L.; Han, Y.; Hilborn, J.; Ossipov, D. Smart Drug Loaded Nanoparticle Delivery from a Self-Healing Hydrogel Enabled by Dynamic Magnesium-Biopolymer Chemistry. *Chem. Commun.* **2016**, *52*, 11151–11154.

- (246) Parisi-Amon, A.; Lo, D. D.; Montoro, D. T.; Dewi, R. E.; Longaker, M. T.; Heilshorn, S. C. Protein-Nanoparticle Hydrogels That Self-Assemble in Response to Peptide-Based Molecular Recognition. *ACS Biomater. Sci. Eng.* **2017**, *3*, 750–756.
- (247) Kong, Y.; Hou, Z.; Zhou, L.; Zhang, P.; Ouyang, Y.; Wang, P.; Chen, Y.; Luo, X. Injectable Self-Healing Hydrogels Containing CuS Nanoparticles with Abilities of Hemostasis, Antibacterial Activity, and Promoting Wound Healing. *ACS Biomater. Sci. Eng.* **2021**, *7*, 335–349.
- (248) Balavigneswaran, C. K.; Muthuvijayan, V. Nanohybrid-Reinforced Gelatin-Ureidopyrimidinone-Based Self-Healing Injectable Hydrogels for Tissue Engineering Applications. *ACS Appl. Bio Mater.* **2021**, *4*, 5362–5377.
- (249) Xu, J.; Wong, C. W.; Hsu, S. H. An Injectable, Electroconductive Hydrogel/Scaffold for Neural Repair and Motion Sensing. *Chem. Mater.* **2020**, *32*, 10407–10422.
- (250) Lin, T. W.; Hsu, S. H. Self-Healing Hydrogels and Cryogels from Biodegradable Polyurethane Nanoparticle Crosslinked Chitosan. *Adv. Sci.* **2020**, *7*, 1901388.
- (251) Pérez-Rafael, S.; Ivanova, K.; Stefanov, I.; Puiggalí, J.; del Valle, L. J.; Todorova, K.; Dimitrov, P.; Hinojosa-Caballero, D.; Tzanov, T. Nanoparticle-Driven Self-Assembling Injectable Hydrogels Provide a Multi-Factorial Approach for Chronic Wound Treatment. *Acta Biomater.* **2021**, *134*, 131–143.
- (252) Zengin, A.; Castro, J. P. O.; Habibovic, P.; Van Rijt, S. H. Injectable, Self-Healing Mesoporous Silica Nanocomposite Hydrogels with Improved Mechanical Properties. *Nanoscale* **2021**, *13*, 1144–1154.
- (253) Huang, W.; Qi, C.; Gao, Y. Injectable Self-Healable Nanocomposite Hydrogels with Mussel-Inspired Adhesive Properties for 3D Printing Ink. *ACS Appl. Nano Mater.* **2019**, *2*, 5000–5008.
- (254) Yanagioka, M.; Frank, C. W. Effect of Particle Distribution on Morphological and Mechanical Properties of Filled Hydrogel Composites. *Macromolecules* **2009**, *42*, 568–568.
- (255) Lin, L. J.; Larsson, M.; Liu, D. M. A Novel Dual-Structure, Self-Healable, Polysaccharide Based Hybrid Nanogel for Biomedical Uses. *Soft Matter* **2011**, *7*, 5816–5825.
- (256) Zhao, Q.; Mu, S.; Liu, X.; Qiu, G.; Astruc, D.; Gu, H. Gallol-Tethered Injectable AuNP Hydrogel with Desirable Self-Healing and Catalytic Properties. *Macromol. Chem. Phys.* **2019**, *220*, 1800427.
- (257) Zeng, Q.; Desai, M. S.; Jin, H. E.; Lee, J. H.; Chang, J.; Lee, S. W. Self-Healing Elastin-Bioglass Hydrogels. *Biomacromolecules* **2016**, *17*, 2619–2625.
- (258) Lee, S. C.; Gillispie, G.; Prim, P.; Lee, S. J. Physical and Chemical Factors Influencing the Printability of Hydrogel-Based Extrusion Bioinks. *Chem. Rev.* **2020**, *120*, 10834–10886.
- (259) Schwab, A.; Levato, R.; D'Este, M.; Piluso, S.; Eglín, D.; Malda, J. Printability and Shape Fidelity of Bioinks in 3D Bioprinting. *Chem. Rev.* **2020**, *120*, 11028–11055.
- (260) Amorim, P. A.; D'Ávila, M. A.; Anand, R.; Moldenaers, P.; Van Puyvelde, P.; Bloemen, V. Insights on Shear Rheology of Inks for Extrusion-Based 3D Bioprinting. *Bioprinting* **2021**, *22*, No. e00129.
- (261) Yan, C.; Altunbas, A.; Yucel, T.; Nagarkar, R. P.; Schneider, J. P.; Pochan, D. J. Injectable Solid Hydrogel: Mechanism of Shear-Thinning and Immediate Recovery of Injectable β -Hairpin Peptide Hydrogels. *Soft Matter* **2010**, *6*, 5143–5156.
- (262) Ewoldt, R. H.; Johnston, M. T.; Caretta, L. M. Experimental Challenges of Shear Rheology: How to Avoid Bad Data. In *Complex Fluids in Biological Systems: Experiment, Theory, and Computation*; Spagnolie, S. E., Ed.; Springer: New York, 2015; pp 207–241.
- (263) Barnes, H. A.; Walters, K. The Yield Stress Myth? *Rheol. Acta* **1985**, *24*, 323–326.
- (264) Bonn, D.; Denn, M. M.; Berthier, L.; Divoux, T.; Manneville, S. Yield Stress Materials in Soft Condensed Matter. *Rev. Mod. Phys.* **2017**, *89*, 035005.
- (265) Dinkgreve, M.; Paredes, J.; Denn, M. M.; Bonn, D. On Different Ways of Measuring “the” Yield Stress. *J. Nonnewton. Fluid Mech.* **2016**, *238*, 233–241.
- (266) Herschel, W. H.; Bulkley, R. Konsistenzmessungen von Gummi-Benzollösungen. *Colloid Polym. Sci.* **1926**, *39*, 291–300.
- (267) Paxton, N.; Smolan, W.; Böck, T.; Melchels, F.; Groll, J.; Jungst, T. Proposal to Assess Printability of Bioinks for Extrusion-Based Bioprinting and Evaluation of Rheological Properties Governing Bioprintability. *Biofabrication* **2017**, *9*, 044107.
- (268) Magnin, A.; Piau, J. M. Shear Rheometry of Fluids with a Yield Stress. *J. Nonnewton. Fluid Mech.* **1987**, *23*, 91–106.
- (269) Barnes, H. A.; Nguyen, Q. D. Rotating Vane Rheometry - a Review. *J. Nonnewton. Fluid Mech.* **2001**, *98*, 1–14.
- (270) Young, A. T.; White, O. C.; Daniele, M. A. Rheological Properties of Coordinated Physical Gelation and Chemical Cross-linking in Gelatin Methacryloyl (GelMA) Hydrogels. *Macromol. Biosci.* **2020**, *20*, 2000183.
- (271) Papanastasiou, T. C. Flows of Materials with Yield. *J. Rheol. (N. Y. N. Y.)* **1987**, *31*, 385–404.
- (272) Cox, W. P.; Merz, E. H. Correlation of Dynamic and Steady Flow Viscosities. *J. Polym. Sci.* **1958**, *28*, 619–622.
- (273) Ryl, A.; Owczarz, P. Injectability of Thermosensitive, Low-Concentrated Chitosan Colloids as Flow Phenomenon through the Capillary under High Shear Rate Conditions. *Polymers (Basel)*. **2020**, *12*, 2260.
- (274) Bertsch, P.; Isabettni, S.; Fischer, P. Ion-Induced Hydrogel Formation and Nematic Ordering of Nanocrystalline Cellulose Suspensions. *Biomacromolecules* **2017**, *18*, 4060–4066.
- (275) Olsen, B. D.; Kornfield, J. A.; Tirrell, D. A. Yielding Behavior in Injectable Hydrogels from Telechelic Proteins. *Macromolecules* **2010**, *43*, 9094–9099.
- (276) Yavitt, B. M.; Wiegart, L.; Salatto, D.; Huang, Z.; Endoh, M. K.; Poeller, S.; Petrash, S.; Koga, T. Structural Dynamics in UV Curable Resins Resolved by in Situ 3D Printing X-Ray Photon Correlation Spectroscopy. *ACS Appl. Polym. Mater.* **2020**, *2*, 4096–4108.
- (277) Esmaeili, M.; George, K.; Rezvan, G.; Taheri-Qazvini, N.; Zhang, R.; Sadati, M. Capillary Flow Characterizations of Chiral Nematic Cellulose Nanocrystal Suspensions. *Langmuir* **2022**, *38*, 2192–2204.
- (278) Swindle-Reilly, K. E.; Shah, M.; Hamilton, P. D.; Eskin, T. A.; Kaushal, S.; Ravi, N. Rabbit Study of an in Situ Forming Hydrogel Vitreous Substitute. *Investig. Ophthalmol. Vis. Sci.* **2009**, *50*, 4840–4846.
- (279) Lopez Hernandez, H.; Souza, J. W.; Appel, E. A. A Quantitative Description for Designing the Extrudability of Shear-Thinning Physical Hydrogels. *Macromol. Biosci.* **2021**, *21*, 2000295.
- (280) Lee, E.; Kim, B.; Choi, S. Hand-Held, Automatic Capillary Viscometer for Analysis of Newtonian and Non-Newtonian Fluids. *Sensors Actuators A Phys.* **2020**, *313*, 112176.
- (281) Srivastava, N.; Burns, M. A. Analysis of Non-Newtonian Liquids Using a Microfluidic Capillary Viscometer. *Anal. Chem.* **2006**, *78*, 1690–1696.
- (282) Coogan, T. J.; Kazmer, D. O. In-Line Rheological Monitoring of Fused Deposition Modeling. *J. Rheol. (N. Y. N. Y.)* **2019**, *63*, 141–155.
- (283) Allmendinger, A.; Fischer, S.; Huwyler, J.; Mahler, H. C.; Schwarb, E.; Zarraga, I. E.; Mueller, R. Rheological Characterization and Injection Forces of Concentrated Protein Formulations: An Alternative Predictive Model for Non-Newtonian Solutions. *Eur. J. Pharm. Biopharm.* **2014**, *87*, 318–328.
- (284) Liu, Q.; Zhang, N.; Wei, W.; Hu, X.; Tan, Y.; Yu, Y.; Deng, Y.; Bi, C.; Zhang, L.; Zhang, H. Assessing the Dynamic Extrusion-Based 3D Printing Process for Power-Law Fluid Using Numerical Simulation. *J. Food Eng.* **2020**, *275*, 109861.
- (285) Yu, H.; Liu, Y.; Yang, H.; Peng, K.; Zhang, X. An Injectable Self-Healing Hydrogel Based on Chain-Extended PEO-PPO-PEO Multi-block Copolymer. *Macromol. Rapid Commun.* **2016**, *37*, 1723–1728.
- (286) Chen, C. H.; Chen, S. H.; Mao, S. H.; Tsai, M. J.; Chou, P. Y.; Liao, C. H.; Chen, J. P. Injectable Thermosensitive Hydrogel Containing Hyaluronic Acid and Chitosan as a Barrier for Prevention of Postoperative Peritoneal Adhesion. *Carbohydr. Polym.* **2017**, *173*, 721–731.
- (287) Han, X.; Meng, X.; Wu, Z.; Wu, Z.; Qi, X. Dynamic Imine Bond Cross-Linked Self-Healing Thermosensitive Hydrogels for Sustained

Anticancer Therapy via Intratumoral Injection. *Mater. Sci. Eng., C* **2018**, *93*, 1064–1072.

(288) Wang, J.; Huang, L.; Huang, Y.; Jiang, Y.; Zhang, L.; Feng, G.; Liu, L. Therapeutic Effect of the Injectable Thermosensitive Hydrogel Loaded with SHP099 on Intervertebral Disc Degeneration. *Life Sci.* **2021**, *266*, 118891.

(289) Cao, Y.; Zhang, C.; Shen, W.; Cheng, Z.; Yu, L. L.; Ping, Q. Poly(N-Isopropylacrylamide)-Chitosan as Thermosensitive in Situ Gel-Forming System for Ocular Drug Delivery. *J. Controlled Release* **2007**, *120*, 186–194.

(290) Park, K. M.; Lee, S. Y.; Joung, Y. K.; Na, J. S.; Lee, M. C.; Park, K. D. Thermosensitive Chitosan-Pluronic Hydrogel as an Injectable Cell Delivery Carrier for Cartilage Regeneration. *Acta Biomater.* **2009**, *5*, 1956–1965.

(291) Lü, S.; Li, B.; Ni, B.; Sun, Z.; Liu, M.; Wang, Q. Thermoresponsive Injectable Hydrogel for Three-Dimensional Cell Culture: Chondroitin Sulfate Bioconjugated with Poly(N-Isopropylacrylamide) Synthesized by RAFT Polymerization. *Soft Matter* **2011**, *7*, 10763–10772.

(292) Chiesa, E.; Genta, I.; Dorati, R.; Modena, T.; Conti, B. Poly(Gamma-Glutamic Acid) Based Thermosetting Hydrogels for Injection: Rheology and Functional Parameters Evaluation. *React. Funct. Polym.* **2019**, *140*, 93–102.

(293) Besiri, I. N.; Goudoulas, T. B.; Germann, N. Custom-Made Rheological Setup for in Situ Real-Time Fast Alginate-Ca²⁺ Gelation. *Carbohydr. Polym.* **2020**, *246*, 116615.

(294) Diener, M.; Adamcik, J.; Bergfreund, J.; Catalini, S.; Fischer, P.; Mezzenga, R. Rigid, Fibrillar Quaternary Structures Induced by Divalent Ions in a Carboxylated Linear Polysaccharide. *ACS Macro Lett.* **2020**, *9*, 115–121.

(295) Xie, W.; Gao, Q.; Guo, Z.; Wang, D.; Gao, F.; Wang, X.; Wei, Y.; Zhao, L. Injectable and Self-Healing Thermosensitive Magnetic Hydrogel for Asynchronous Control Release of Doxorubicin and Docetaxel to Treat Triple-Negative Breast Cancer. *ACS Appl. Mater. Interfaces* **2017**, *9*, 33660–33673.

(296) Chen, W.; Zhang, Y.; Kumari, J.; Engelkamp, H.; Kouwer, P. H. J. Magnetic Stiffening in 3D Cell Culture Matrices. *Nano Lett.* **2021**, *21*, 6740–6747.

(297) Thakur, T.; Xavier, J. R.; Cross, L.; Jaiswal, M. K.; Mondragon, E.; Kaunas, R.; Gaharwar, A. K. Photocrosslinkable and Elastomeric Hydrogels for Bone Regeneration. *J. Biomed. Mater. Res. - Part A* **2016**, *104*, 879–888.

(298) Johnson, T. D.; Christman, K. L. Injectable Hydrogel Therapies and Their Delivery Strategies for Treating Myocardial Infarction. *Expert Opin. Drug Delivery* **2013**, *10*, 59–72.

(299) Hasan, A.; Khattab, A.; Islam, M. A.; Hweij, K. A.; Zeitouny, J.; Waters, R.; Sayegh, M.; Hossain, M. M.; Paul, A. Injectable Hydrogels for Cardiac Tissue Repair after Myocardial Infarction. *Adv. Sci.* **2015**, *2*, 1500122–18.

(300) Macaya, D.; Spector, M. Injectable Hydrogel Materials for Spinal Cord Regeneration: A Review. *Biomed. Mater.* **2012**, *7*, 012001.

(301) Lin, P. H.; Dong, Q.; Chew, S. Y. Injectable Hydrogels in Stroke and Spinal Cord Injury Treatment: A Review on Hydrogel Materials, Cell-Matrix Interactions and Glial Involvement. *Mater. Adv.* **2021**, *2*, 2561–2583.

(302) Kleinberg, T. T.; Tzekov, R. T.; Stein, L.; Ravi, N.; Kaushal, S. Vitreous Substitutes: A Comprehensive Review. *Surv. Ophthalmol.* **2011**, *56*, 300–323.

(303) Steele, A. N.; Stapleton, L. M.; Farry, J. M.; Lucian, H. J.; Paulsen, M. J.; Eskandari, A.; Hironaka, C. E.; Thakore, A. D.; Wang, H.; Yu, A. C.; Chan, D.; Appel, E. A.; Woo, Y. J. A Biocompatible Therapeutic Catheter-Deliverable Hydrogel for In Situ Tissue Engineering. *Adv. Healthc. Mater.* **2019**, *8*, 1801147.

(304) Wenk, J. F.; Wall, S. T.; Peterson, R. C.; Helgersson, S. L.; Sabbah, H. N.; Burger, M.; Stander, N.; Ratcliffe, M. B.; Guccione, J. M. A Method for Automatically Optimizing Medical Devices for Treating Heart Failure: Designing Polymeric Injection Patterns. *J. Biomech. Eng.* **2009**, *131*, 121011.

(305) Wang, H.; Rodell, C. B.; Lee, M. E.; Dusan, N. N.; Gorman, J. H.; Burdick, J. A.; Gorman, R. C.; Wenk, J. F. Computational Sensitivity Investigation of Hydrogel Injection Characteristics for Myocardial Support. *J. Biomech.* **2017**, *64*, 231–235.

(306) Li, D. S.; Avazmohammadi, R.; Merchant, S. S.; Kawamura, T.; Hsu, E. W.; Gorman, J. H.; Gorman, R. C.; Sacks, M. S. Insights into the Passive Mechanical Behavior of Left Ventricular Myocardium Using a Robust Constitutive Model Based on Full 3D Kinematics. *J. Mech. Behav. Biomed. Mater.* **2020**, *103*, 103508.

(307) Li, D. S.; Avazmohammadi, R.; Rodell, C. B.; Hsu, E. W.; Burdick, J. A.; Gorman, J. H.; Gorman, R. C.; Sacks, M. S. How Hydrogel Inclusions Modulate the Local Mechanical Response in Early and Fully Formed Post-Infarcted Myocardium. *Acta Biomater.* **2020**, *114*, 296–306.

(308) Tibbitt, M. W.; Dahlman, J. E.; Langer, R. Emerging Frontiers in Drug Delivery. *J. Am. Chem. Soc.* **2016**, *138*, 704–717.

(309) Serra, L.; Doménech, J.; Peppas, N. A. Drug Transport Mechanisms and Release Kinetics from Molecularly Designed Poly(Acrylic Acid-g-Ethylene Glycol) Hydrogels. *Biomaterials* **2006**, *27*, 5440–5451.

(310) Ritger, P. L.; Peppas, N. A. A Simple Equation for Description of Solute Release I. Fickian and Non-Fickian Release from Non-Swellable Devices in the Form of Slabs, Spheres, Cylinders or Discs. *J. Controlled Release* **1987**, *5*, 23–36.

(311) Ritger, P. L.; Peppas, N. A. A Simple Equation for Description of Solute Release II. Fickian and Anomalous Release from Swellable Devices. *J. Controlled Release* **1987**, *5*, 37–42.

(312) Jalili, N. A.; Jaiswal, M. K.; Peak, C. W.; Cross, L. M.; Gaharwar, A. K. Injectable Nanoengineered Stimuli-Responsive Hydrogels for on-Demand and Localized Therapeutic Delivery. *Nanoscale* **2017**, *9*, 15379–15389.

(313) Qu, J.; Zhao, X.; Ma, P. X.; Guo, B. Injectable Antibacterial Conductive Hydrogels with Dual Response to an Electric Field and pH for Localized “Smart” Drug Release. *Acta Biomater.* **2018**, *72*, 55–69.

(314) Zhao, J.; Liang, X.; Cao, H.; Tan, T. Preparation of Injectable Hydrogel with Near-Infrared Light Response and Photo-Controlled Drug Release. *Bioresour. Bioprocess.* **2020**, *7*, 1.

(315) Qian, C.; Zhang, T.; Gravesande, J.; Baysah, C.; Song, X.; Xing, J. Injectable and Self-Healing Polysaccharide-Based Hydrogel for pH-Responsive Drug Release. *Int. J. Biol. Macromol.* **2019**, *123*, 140–148.

(316) Brudno, Y.; Silva, E. A.; Kearney, C. J.; Lewin, S. A.; Miller, A.; Martinick, K. D.; Aizenberg, M.; Mooney, D. J. Refilling Drug Delivery Depots through the Blood. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, 12722–12727.

(317) Wu, J. P. J.; Cheng, B.; Roffler, S. R.; Lundy, D. J.; Yen, C. Y. T.; Chen, P.; Lai, J. J.; Pun, S. H.; Stayton, P. S.; Hsieh, P. C. H. Reloadable Multidrug Capturing Delivery System for Targeted Ischemic Disease Treatment. *Sci. Transl. Med.* **2016**, *8*, 365ra160.

(318) Chen, J.; Li, S.; Zhang, Y.; Wang, W.; Zhang, X.; Zhao, Y.; Wang, Y.; Bi, H. A Reloadable Self-Healing Hydrogel Enabling Diffusive Transport of C-Dots Across Gel-Gel Interface for Scavenging Reactive Oxygen Species. *Adv. Healthc. Mater.* **2017**, *6*, 1700746.

(319) Czuban, M.; Srinivasan, S.; Yee, N. A.; Agustin, E.; Koliszak, A.; Miller, E.; Khan, I.; Quinones, I.; Noory, H.; Motola, C.; Volkmer, R.; Di Luca, M.; Trampuz, A.; Royzen, M.; Mejia Oneto, J. M. Bio-Orthogonal Chemistry and Reloadable Biomaterial Enable Local Activation of Antibiotic Prodrugs and Enhance Treatments against *Staphylococcus Aureus* Infections. *ACS Cent. Sci.* **2018**, *4*, 1624–1632.

(320) Jia, Y. P.; Shi, K.; Yang, F.; Liao, J. F.; Han, R. X.; Yuan, L. P.; Hao, Y.; Pan, M.; Xiao, Y.; Qian, Z. Y.; Wei, X. W. Multifunctional Nanoparticle Loaded Injectable Thermoresponsive Hydrogel as NIR Controlled Release Platform for Local Photothermal Immunotherapy to Prevent Breast Cancer Postoperative Recurrence and Metastases. *Adv. Funct. Mater.* **2020**, *30*, 2001059.

(321) Wang, Z.; Zeng, W.; Chen, Z.; Suo, W.; Quan, H.; Tan, Z. J. An Intratumoral Injectable Nanozyme Hydrogel for Hypoxia-Resistant Thermoradiotherapy. *Colloids Surfaces B Biointerfaces* **2021**, *207*, 112026.

- (322) Schaal, J. L.; Li, X.; Mastria, E.; Bhattacharyya, J.; Zalutsky, M. R.; Chilkoti, A.; Liu, W. Injectable Polypeptide Micelles That Form Radiation Crosslinked Hydrogels in Situ for Intratumoral Radiotherapy. *J. Controlled Release* **2016**, *228*, 58–66.
- (323) Wolf, K.; te Lindert, M.; Krause, M.; Alexander, S.; te Riet, J.; Willis, A. L.; Hoffman, R. M.; Figdor, C. G.; Weiss, S. J.; Friedl, P. Physical Limits of Cell Migration: Control by ECM Space and Nuclear Deformation and Tuning by Proteolysis and Traction Force. *J. Cell Biol.* **2013**, *201*, 1069–1084.
- (324) Tang, S.; Richardson, B. M.; Anseth, K. S. Dynamic Covalent Hydrogels as Biomaterials to Mimic the Viscoelasticity of Soft Tissues. *Prog. Mater. Sci.* **2021**, *120*, 100738.
- (325) Salinas, C. N.; Anseth, K. S. The Enhancement of Chondrogenic Differentiation of Human Mesenchymal Stem Cells by Enzymatically Regulated RGD Functionalities. *Biomaterials* **2008**, *29*, 2370–2377.
- (326) Thakur, A.; Jaiswal, M. K.; Peak, C. W.; Carrow, J. K.; Gentry, J.; Dolatshahi-Pirouz, A.; Gaharwar, A. K. Injectable Shear-Thinning Nanoengineered Hydrogels for Stem Cell Delivery. *Nanoscale* **2016**, *8*, 12362–12372.
- (327) Lopez Hernandez, H.; Grosskopf, A. K.; Stapleton, L. M.; Agmon, G.; Appel, E. A. Non-Newtonian Polymer-Nanoparticle Hydrogels Enhance Cell Viability during Injection. *Macromol. Biosci.* **2019**, *19*, 1800275.
- (328) Wei, Z.; Gerecht, S. A Self-Healing Hydrogel as an Injectable Instructive Carrier for Cellular Morphogenesis. *Biomaterials* **2018**, *185*, 86–96.
- (329) Abruzzo, T.; Tun, T.; Sambanis, A. Efficient Transmicrocatheter Delivery of Functional Fibroblasts with a Bioengineered Collagen Gel-Platinum Microcoil Complex: Toward the Development of Endovascular Cell Therapy for Cerebral Aneurysms. *Am. J. Neuroradiol.* **2007**, *28*, 1586–1593.
- (330) Martens, T. P.; Godier, A. F. G.; Parks, J. J.; Wan, L. Q.; Koeckert, M. S.; Eng, G. M.; Hudson, B. I.; Sherman, W.; Vunjak-Novakovic, G. Percutaneous Cell Delivery into the Heart Using Hydrogels Polymerizing in Situ. *Cell Transplant.* **2009**, *18*, 297–304.
- (331) Lü, S.; Gao, C.; Xu, X.; Bai, X.; Duan, H.; Gao, N.; Feng, C.; Xiong, Y.; Liu, M. Injectable and Self-Healing Carbohydrate-Based Hydrogel for Cell Encapsulation. *ACS Appl. Mater. Interfaces* **2015**, *7*, 13029–13037.
- (332) Gao, Y.; Kong, W.; Li, B.; Ni, Y.; Yuan, T.; Guo, L.; Lin, H.; Fan, H.; Fan, Y.; Zhang, X. Fabrication and Characterization of Collagen-Based Injectable and Self-Crosslinkable Hydrogels for Cell Encapsulation. *Colloids Surfaces B Biointerfaces* **2018**, *167*, 448–456.
- (333) Pupkaite, J.; Rosenquist, J.; Hilborn, J.; Samanta, A. Injectable Shape-Holding Collagen Hydrogel for Cell Encapsulation and Delivery Cross-Linked Using Thiol-Michael Addition Click Reaction. *Biomacromolecules* **2019**, *20*, 3475–3484.
- (334) Parisi-Amon, A.; Mulyasasmita, W.; Chung, C.; Heilshorn, S. C. Protein-Engineered Injectable Hydrogel to Improve Retention of Transplanted Adipose-Derived Stem Cells. *Adv. Healthc. Mater.* **2013**, *2*, 428–432.
- (335) Seeto, W. J.; Tian, Y.; Winter, R. L.; Caldwell, F. J.; Wooldridge, A. A.; Lipke, E. A. Encapsulation of Equine Endothelial Colony Forming Cells in Highly Uniform, Injectable Hydrogel Microspheres for Local Cell Delivery. *Tissue Eng. - Part C Methods* **2017**, *23*, 815–825.
- (336) Miller, B.; Hansrisuk, A.; Highley, C. B.; Caliri, S. R. Guest-Host Supramolecular Assembly of Injectable Hydrogel Nanofibers for Cell Encapsulation. *ACS Biomater. Sci. Eng.* **2021**, *7*, 4164–4174.
- (337) Xu, Q.; A, S.; Gao, Y.; Guo, L.; Creagh-Flynn, J.; Zhou, D.; Greiser, U.; Dong, Y.; Wang, F.; Tai, H.; Liu, W.; Wang, W.; Wang, W. A Hybrid Injectable Hydrogel from Hyperbranched PEG Macromer as a Stem Cell Delivery and Retention Platform for Diabetic Wound Healing. *Acta Biomater.* **2018**, *75*, 63–74.
- (338) Kontturi, L. S.; Collin, E. C.; Murtomäki, L.; Pandit, A. S.; Yliperttula, M.; Urtti, A. Encapsulated Cells for Long-Term Secretion of Soluble VEGF Receptor 1: Material Optimization and Simulation of Ocular Drug Response. *Eur. J. Pharm. Biopharm.* **2015**, *95*, 387–397.
- (339) Wong, F. S. Y.; Tsang, K. K.; Chu, A. M. W.; Chan, B. P.; Yao, K. M.; Lo, A. C. Y. Injectable Cell-Encapsulating Composite Alginate-Collagen Platform with Inducible Termination Switch for Safer Ocular Drug Delivery. *Biomaterials* **2019**, *201*, 53–67.
- (340) Young, D. A.; Choi, Y. S.; Engler, A. J.; Christman, K. L. Stimulation of Adipogenesis of Adult Adipose-Derived Stem Cells Using Substrates That Mimic the Stiffness of Adipose Tissue. *Biomaterials* **2013**, *34*, 8581–8588.
- (341) Wang, H.; Mooney, D. J. Biomaterial-Assisted Targeted Modulation of Immune Cells in Cancer Treatment. *Nat. Mater.* **2018**, *17*, 761–772.
- (342) Whitaker, R.; Hernaez-Estrada, B.; Hernandez, R. M.; Santos-Vizcaino, E.; Spiller, K. L. Immunomodulatory Biomaterials for Tissue Repair. *Chem. Rev.* **2021**, *121*, 11305–11335.
- (343) Chao, Y.; Chen, Q.; Liu, Z. Smart Injectable Hydrogels for Cancer Immunotherapy. *Adv. Funct. Mater.* **2020**, *30*, 1902785.
- (344) Singh, A.; Peppas, N. A. Hydrogels and Scaffolds for Immunomodulation. *Adv. Mater.* **2014**, *26*, 6530–6541.
- (345) Øvrebo, Ø.; Perale, G.; Wojciechowski, J. P.; Echalié, C.; Jeffers, J. R. T.; Stevens, M. M.; Haugen, H. J.; Rossi, F. Design and Clinical Application of Injectable Hydrogels for Musculoskeletal Therapy. *Bioeng. Transl. Med.* **2022**, *7*, No. e10295.
- (346) Gheorghiadé, M.; Bonow, R. O. Chronic Heart Failure in the United States: A Manifestation of Coronary Artery Disease. *Circulation* **1998**, *97*, 282–289.
- (347) St. John Sutton, M. G.; Sharpe, N. Left Ventricular Remodeling after Myocardial Infarction: Pathophysiology and Therapy. *Circulation* **2000**, *101*, 2981–2988.
- (348) Weisman, H. F.; Healy, B. Myocardial Infarct Expansion, Infarct Extension, and Reinfarction: Pathophysiologic Concepts. *Prog. Cardiovasc. Dis.* **1987**, *30*, 73–110.
- (349) Pilla, J. J.; Blom, A. S.; Gorman, J. H.; Brockman, D. J.; Affuso, J.; Parish, L. M.; Sakamoto, H.; Jackson, B. M.; Acker, M. A.; Gorman, R. C. Early Postinfarction Ventricular Restraint Improves Borderzone Wall Thickening Dynamics during Remodeling. *Ann. Thorac. Surg.* **2005**, *80*, 2257–2262.
- (350) Kofidis, T.; Lebl, D. R.; Martinez, E. C.; Hoyt, G.; Tanaka, M.; Robbins, R. C. Novel Injectable Bioartificial Tissue Facilitates Targeted, Less Invasive, Large-Scale Tissue Restoration on the Beating Heart After Myocardial Injury. *Circulation* **2005**, *112*, 173–177.
- (351) Mukherjee, R.; Zavadzka, J. A.; Saunders, S. M.; McLean, J. E.; Jeffords, L. B.; Beck, C.; Stroud, R. E.; Leone, A. M.; Koval, C. N.; Rivers, W. T.; Basu, S.; Sheehy, A.; Michal, G.; Spinale, F. G. Targeted Myocardial Microinjections of a Biocomposite Material Reduces Infarct Expansion in Pigs. *Ann. Thorac. Surg.* **2008**, *86*, 1268–1276.
- (352) Fujimoto, K. L.; Ma, Z.; Nelson, D. M.; Hashizume, R.; Guan, J.; Tobita, K.; Wagner, W. R. Synthesis, Characterization and Therapeutic Efficacy of a Biodegradable, Thermoresponsive Hydrogel Designed for Application in Chronic Infarcted Myocardium. *Biomaterials* **2009**, *30*, 4357–4368.
- (353) Leor, J.; Tuvia, S.; Guetta, V.; Manczur, F.; Castel, D.; Willenz, U.; Petneházy, Ö.; Landa, N.; Feinberg, M. S.; Konen, E.; Goitein, O.; Tsur-Gang, O.; Shaul, M.; Klapper, L.; Cohen, S. Intracoronary Injection of In Situ Forming Alginate Hydrogel Reverses Left Ventricular Remodeling After Myocardial Infarction in Swine. *J. Am. Coll. Cardiol.* **2009**, *54*, 1014–1023.
- (354) Ryan, L. P.; Matsuzaki, K.; Noma, M.; Jackson, B. M.; Eperjesi, T. J.; Plappert, T. J.; St. John Sutton, M. G.; Gorman, J. H.; Gorman, R. C. Dermal Filler Injection: A Novel Approach for Limiting Infarct Expansion. *Ann. Thorac. Surg.* **2009**, *87*, 148–155.
- (355) Ifkovits, J. L.; Tous, E.; Minakawa, M.; Morita, M.; Robb, J. D.; Koomalsingh, K. J.; Gorman, J. H.; Gorman, R. C.; Burdick, J. A. Injectable Hydrogel Properties Influence Infarct Expansion and Extent of Postinfarction Left Ventricular Remodeling in an Ovine Model. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 11507–11512.
- (356) Bao, R.; Tan, B.; Liang, S.; Zhang, N.; Wang, W.; Liu, W. A π - π Conjugation-Containing Soft and Conductive Injectable Polymer Hydrogel Highly Efficiently Rebuilds Cardiac Function after Myocardial Infarction. *Biomaterials* **2017**, *122*, 63–71.

- (357) Rodell, C. B.; Lee, M. E.; Wang, H.; Takebayashi, S.; Takayama, T.; Kawamura, T.; Arkles, J. S.; Dusaj, N. N.; Dorsey, S. M.; Witschey, W. R. T.; Pilla, J. J.; Gorman, J. H.; Wenk, J. F.; Burdick, J. A.; Gorman, R. C. Injectable Shear-Thinning Hydrogels for Minimally Invasive Delivery to Infarcted Myocardium to Limit Left Ventricular Remodeling. *Circ. Cardiovasc. Interv.* **2016**, *9*, e004058.
- (358) Yoon, S. J.; Fang, Y. H.; Lim, C. H.; Kim, B. S.; Son, H. S.; Park, Y.; Sun, K. Regeneration of Ischemic Heart Using Hyaluronic Acid-Based Injectable Hydrogel. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2009**, *91B*, 163–171.
- (359) Plotkin, M.; Vaibavi, S. R.; Rufaihah, A. J.; Nithya, V.; Wang, J.; Shachaf, Y.; Kofidis, T.; Seliktar, D. The Effect of Matrix Stiffness of Injectable Hydrogels on the Preservation of Cardiac Function after a Heart Attack. *Biomaterials* **2014**, *35*, 1429–1438.
- (360) Wang, K.; Mitra, R. N.; Zheng, M.; Han, Z. Nanoceria-Loaded Injectable Hydrogels for Potential Age-Related Macular Degeneration Treatment. *J. Biomed. Mater. Res. - Part A* **2018**, *106*, 2795–2804.
- (361) Ding, J.; Yao, Y.; Li, J.; Duan, Y.; Nakkala, J. R.; Feng, X.; Cao, W.; Wang, Y.; Hong, L.; Shen, L.; Mao, Z.; Zhu, Y.; Gao, C. A Reactive Oxygen Species Scavenging and O₂ Generating Injectable Hydrogel for Myocardial Infarction Treatment In Vivo. *Small* **2020**, *16*, 2005038.
- (362) Li, C.; Nie, F.; Liu, X.; Chen, M.; Chi, D.; Li, S.; Pipinos, I. I.; Li, X. Antioxidative and Angiogenic Hyaluronic Acid-Based Hydrogel for the Treatment of Peripheral Artery Disease. *ACS Appl. Mater. Interfaces* **2021**, *13*, 45224–45235.
- (363) Liu, Y.; Guo, R.; Wu, T.; Lyu, Y.; Xiao, M.; He, B.; Fan, G.; Yang, J.; Liu, W. One Zwitterionic Injectable Hydrogel with Ion Conductivity Enables Efficient Restoration of Cardiac Function after Myocardial Infarction. *Chem. Eng. J.* **2021**, *418*, 129352.
- (364) Wang, H.; Zhang, X.; Li, Y.; Ma, Y.; Zhang, Y.; Liu, Z.; Zhou, J.; Lin, Q.; Wang, Y.; Duan, C.; Wang, C. Improved Myocardial Performance in Infarcted Rat Heart by Co-Injection of Basic Fibroblast Growth Factor with Temperature-Responsive Chitosan Hydrogel. *J. Hear. Lung Transplant.* **2010**, *29*, 881–887.
- (365) Wu, J.; Zeng, F.; Huang, X. P.; Chung, J. C. Y.; Konecny, F.; Weisel, R. D.; Li, R. K. Infarct Stabilization and Cardiac Repair with a VEGF-Conjugated, Injectable Hydrogel. *Biomaterials* **2011**, *32*, 579–586.
- (366) Steele, A. N.; Cai, L.; Truong, V. N.; Edwards, B. B.; Goldstone, A. B.; Eskandari, A.; Mitchell, A. C.; Marquardt, L. M.; Foster, A. A.; Cochran, J. R.; Heilshorn, S. C.; Woo, Y. J. A Novel Protein-Engineered Hepatocyte Growth Factor Analog Released via a Shear-Thinning Injectable Hydrogel Enhances Post-Infarction Ventricular Function. *Biotechnol. Bioeng.* **2017**, *114*, 2379–2389.
- (367) Koudstaal, S.; Bastings, M. M. C.; Feyen, D. A. M.; Waring, C. D.; Van Slochteren, F. J.; Dankers, P. Y. W.; Torella, D.; Sluijter, J. P. G.; Nadal-Ginard, B.; Doevendans, P. A.; Ellison, G. M.; Chamuleau, S. A. J. Sustained Delivery of Insulin-like Growth Factor-1/Hepatocyte Growth Factor Stimulates Endogenous Cardiac Repair in the Chronic Infarcted Pig Heart. *J. Cardiovasc. Transl. Res.* **2014**, *7*, 232–241.
- (368) Steele, A. N.; Paulsen, M. J.; Wang, H.; Stapleton, L. M.; Lucian, H. J.; Eskandari, A.; Hironaka, C. E.; Farry, J. M.; Baker, S. W.; Thakore, A. D.; Jaatinen, K. J.; Tada, Y.; Hollander, M. J.; Williams, K. M.; Seymour, A. J.; Tothorow, K. P.; Yu, A. C.; Cochran, J. R.; Appel, E. A.; Woo, Y. J. Multi-Phase Catheter-Injectable Hydrogel Enables Dual-Stage Protein-Engineered Cytokine Release to Mitigate Adverse Left Ventricular Remodeling Following Myocardial Infarction in a Small Animal Model and a Large Animal Model. *Cytokine* **2020**, *127*, 154974.
- (369) Song, M.; Jang, H.; Lee, J.; Kim, J. H.; Kim, S. H.; Sun, K.; Park, Y. Regeneration of Chronic Myocardial Infarction by Injectable Hydrogels Containing Stem Cell Homing Factor SDF-1 and Angiogenic Peptide Ac-SDKP. *Biomaterials* **2014**, *35*, 2436–2445.
- (370) Wang, L. L.; Liu, Y.; Chung, J. J.; Wang, T.; Gaffey, A. C.; Lu, M.; Cavanaugh, C. A.; Zhou, S.; Kanade, R.; Atluri, P.; Morrissey, E. E.; Burdick, J. A. Sustained miRNA Delivery from an Injectable Hydrogel Promotes Cardiomyocyte Proliferation and Functional Regeneration after Ischaemic Injury. *Nat. Biomed. Eng.* **2017**, *1*, 983–992.
- (371) Garbern, J. C.; Minami, E.; Stayton, P. S.; Murry, C. E. Delivery of Basic Fibroblast Growth Factor with a pH-Responsive, Injectable Hydrogel to Improve Angiogenesis in Infarcted Myocardium. *Biomaterials* **2011**, *32*, 2407–2416.
- (372) Yuan, Z.; Tsou, Y. H.; Zhang, X. Q.; Huang, S.; Yang, Y.; Gao, M.; Ho, W.; Zhao, Q.; Ye, X.; Xu, X. Injectable Citrate-Based Hydrogel as an Angiogenic Biomaterial Improves Cardiac Repair after Myocardial Infarction. *ACS Appl. Mater. Interfaces* **2019**, *11*, 38429–38439.
- (373) Burgess, K. A.; Frati, C.; Meade, K.; Gao, J.; Castillo Diaz, L.; Madeddu, D.; Graiani, G.; Cavalli, S.; Miller, A. F.; Oceandy, D.; Quaini, F.; Saiani, A. Functionalised Peptide Hydrogel for the Delivery of Cardiac Progenitor Cells. *Mater. Sci. Eng., C* **2021**, *119*, 111539.
- (374) Li, Y.; Chen, X.; Jin, R.; Chen, L.; Dang, M.; Cao, H.; Dong, Y.; Cai, B.; Bai, G.; Gooding, J. J.; Liu, S.; Zou, D.; Zhang, Z.; Yang, C. Injectable Hydrogel with MSNs/MicroRNA-21–Sp Delivery Enables Both Immunomodification and Enhanced Angiogenesis for Myocardial Infarction Therapy in Pigs. *Sci. Adv.* **2021**, *7*, 101227.
- (375) Zhu, D.; Li, Z.; Huang, K.; Caranasos, T. G.; Rossi, J. S.; Cheng, K. Minimally Invasive Delivery of Therapeutic Agents by Hydrogel Injection into the Pericardial Cavity for Cardiac Repair. *Nat. Commun.* **2021**, *12*, 1412.
- (376) Li, Z.; Zhu, D.; Hui, Q.; Bi, J.; Yu, B.; Huang, Z.; Hu, S.; Wang, Z.; Caranasos, T.; Rossi, J.; Li, X.; Cheng, K.; Wang, X. Injection of ROS-Responsive Hydrogel Loaded with Basic Fibroblast Growth Factor into the Pericardial Cavity for Heart Repair. *Adv. Funct. Mater.* **2021**, *31*, 2004377.
- (377) Frey, N.; Linke, A.; Süselbeck, T.; Müller-Ehmsen, J.; Vermeersch, P.; Schoors, D.; Rosenberg, M.; Bea, F.; Tuvia, S.; Leor, J. Intracoronary Delivery of Injectable Bioabsorbable Scaffold (IK-5001) to Treat Left Ventricular Remodeling After ST-Elevation Myocardial Infarction. *Circ. Cardiovasc. Interv.* **2014**, *7*, 806–812.
- (378) Anker, S. D.; Coats, A. J. S.; Cristian, G.; Dragomir, D.; Pusineri, E.; Piredda, M.; Bettari, L.; Dowling, R.; Volterrani, M.; Kirwan, B.-A.; Filippatos, G.; Mas, J.-L.; Danchin, N.; Solomon, S. D.; Lee, R. J.; Ahmann, F.; Hinson, A.; Sabbah, H. N.; Mann, D. L. A Prospective Comparison of Alginate-Hydrogel with Standard Medical Therapy to Determine Impact on Functional Capacity and Clinical Outcomes in Patients with Advanced Heart Failure (AUGMENT-HF Trial). *Eur. Heart J.* **2015**, *36*, 2297–2309.
- (379) Li, L.; Gu, J.; Zhang, J.; Xie, Z.; Lu, Y.; Shen, L.; Dong, Q.; Wang, Y. Injectable and Biodegradable pH-Responsive Hydrogels for Localized and Sustained Treatment of Human Fibrosarcoma. *ACS Appl. Mater. Interfaces* **2015**, *7*, 8033–8040.
- (380) Fenton, O. S.; Tibbitt, M. W.; Appel, E. A.; Jhunjunwala, S.; Webber, M. J.; Langer, R. Injectable Polymer-Nanoparticle Hydrogels for Local Immune Cell Recruitment. *Biomacromolecules* **2019**, *20*, 4430–4436.
- (381) Du, X.; Liu, Y.; Wang, X.; Yan, H.; Wang, L.; Qu, L.; Kong, D.; Qiao, M.; Wang, L. Injectable Hydrogel Composed of Hydrophobically Modified Chitosan/Oxidized-Dextran for Wound Healing. *Mater. Sci. Eng., C* **2019**, *104*, 109930.
- (382) Darnell, M.; Young, S.; Gu, L.; Shah, N.; Lippens, E.; Weaver, J.; Suda, G.; Mooney, D. Substrate Stress-Relaxation Regulates Scaffold Remodeling and Bone Formation In Vivo. *Adv. Healthc. Mater.* **2017**, *6*, 1601185.
- (383) Wang, S.; Chi, J.; Jiang, Z.; Hu, H.; Yang, C.; Liu, W.; Han, B. A Self-Healing and Injectable Hydrogel Based on Water-Soluble Chitosan and Hyaluronic Acid for Vitreous Substitute. *Carbohydr. Polym.* **2021**, *256*, 117519.
- (384) Tukmachiev, D.; Forostyak, S.; Koci, Z.; Zaviskova, K.; Vackova, I.; Vyborny, K.; Sandvig, I.; Sandvig, A.; Medberry, C. J.; Badylak, S. F.; Sykova, E.; Kubinova, S. Injectable Extracellular Matrix Hydrogels as Scaffolds for Spinal Cord Injury Repair. *Tissue Eng. - Part A* **2016**, *22*, 306–317.
- (385) Hong, L. T. A.; Kim, Y.-M.; Park, H. H.; Hwang, D. H.; Cui, Y.; Lee, E. M.; Yahn, S.; Lee, J. K.; Song, S.-C.; Kim, B. G. An Injectable Hydrogel Enhances Tissue Repair after Spinal Cord Injury by Promoting Extracellular Matrix Remodeling. *Nat. Commun.* **2017**, *8*, 533.
- (386) Chen, S.; Liu, S.; Zhang, L.; Han, Q.; Liu, H.; Shen, J.; Li, G.; Zhang, L.; Yang, Y. Construction of Injectable Silk Fibroin/Polydop-

amine Hydrogel for Treatment of Spinal Cord Injury. *Chem. Eng. J.* **2020**, *399*, 125795.

(387) Cigognini, D.; Satta, A.; Colleoni, B.; Silva, D.; Donegà, M.; Antonini, S.; Gelain, F. Evaluation of Early and Late Effects into the Acute Spinal Cord Injury of an Injectable Functionalized Self-Assembling Scaffold. *PLoS One* **2011**, *6*, No. e19782.

(388) Cigognini, D.; Silva, D.; Paloppi, S.; Gelain, F. Evaluation of Mechanical Properties and Therapeutic Effect of Injectable Self-Assembling Hydrogels for Spinal Cord Injury. *J. Biomed. Nanotechnol.* **2014**, *10*, 309–323.

(389) King, V. R.; Alovskaya, A.; Wei, D. Y. T.; Brown, R. A.; Priestley, J. V. The Use of Injectable Forms of Fibrin and Fibronectin to Support Axonal Ingrowth after Spinal Cord Injury. *Biomaterials* **2010**, *31*, 4447–4456.

(390) Gupta, D.; Tator, C. H.; Shoichet, M. S. Fast-Gelling Injectable Blend of Hyaluronan and Methylcellulose for Intrathecal, Localized Delivery to the Injured Spinal Cord. *Biomaterials* **2006**, *27*, 2370–2379.

(391) Führmann, T.; Tam, R. Y.; Ballarin, B.; Coles, B.; Elliott Donaghue, I.; van der Kooy, D.; Nagy, A.; Tator, C. H.; Morshead, C. M.; Shoichet, M. S. Injectable Hydrogel Promotes Early Survival of Induced Pluripotent Stem Cell-Derived Oligodendrocytes and Attenuates Longterm Teratoma Formation in a Spinal Cord Injury Model. *Biomaterials* **2016**, *83*, 23–36.

(392) Cornelison, R. C.; Gonzalez-Rothi, E. J.; Porvasnik, S. L.; Wellman, S. M.; Park, J. H.; Fuller, D. D.; Schmidt, C. E. Injectable Hydrogels of Optimized Acellular Nerve for Injection in the Injured Spinal Cord. *Biomed. Mater.* **2018**, *13*, 034110.

(393) Comolli, N.; Neuhuber, B.; Fischer, I.; Lowman, A. In Vitro Analysis of PNIPAAm-PEG, a Novel, Injectable Scaffold for Spinal Cord Repair. *Acta Biomater.* **2009**, *5*, 1046–1055.

(394) Piantino, J.; Burdick, J. A.; Goldberg, D.; Langer, R.; Benowitz, L. I. An Injectable, Biodegradable Hydrogel for Trophic Factor Delivery Enhances Axonal Rewiring and Improves Performance after Spinal Cord Injury. *Exp. Neurol.* **2006**, *201*, 359–367.

(395) Kang, C. E.; Baumann, M. D.; Tator, C. H.; Shoichet, M. S. Localized and Sustained Delivery of Fibroblast Growth Factor-2 from a Nanoparticle-Hydrogel Composite for Treatment of Spinal Cord Injury. *Cells Tissues Organs* **2012**, *197*, 55–63.

(396) Ansorena, E.; De Berdt, P.; Ucakar, B.; Simón-Yarza, T.; Jacobs, D.; Schakman, O.; Jankovski, A.; Deumens, R.; Blanco-Prieto, M. J.; Pr  at, V.; des Rieux, A. Injectable Alginate Hydrogel Loaded with GDNF Promotes Functional Recovery in a Hemisection Model of Spinal Cord Injury. *Int. J. Pharm.* **2013**, *455*, 148–158.

(397) Lindsey, S.; Piatt, J. H.; Worthington, P.; S  nmez, C.; Satheye, S.; Schneider, J. P.; Pochan, D. J.; Langhans, S. A. Beta Hairpin Peptide Hydrogels as an Injectable Solid Vehicle for Neurotrophic Growth Factor Delivery. *Biomacromolecules* **2015**, *16*, 2672–2683.

(398) Des Rieux, A.; De Berdt, P.; Ansorena, E.; Ucakar, B.; Damien, J.; Schakman, O.; Audouard, E.; Bouzin, C.; Auhl, D.; Sim  n-Yarza, T.; Feron, O.; Blanco-Prieto, M. J.; Carmeliet, P.; Bailly, C.; Clotman, F.; Pr  at, V. Vascular Endothelial Growth Factor-Loaded Injectable Hydrogel Enhances Plasticity in the Injured Spinal Cord. *J. Biomed. Mater. Res. - Part A* **2014**, *102*, 2345–2355.

(399) Liu, S.; Sandner, B.; Schackel, T.; Nicholson, L.; Chtarto, A.; Tenenbaum, L.; Puttagunta, R.; M  ller, R.; Weidner, N.; Blesch, A. Regulated Viral BDNF Delivery in Combination with Schwann Cells Promotes Axonal Regeneration through Capillary Alginate Hydrogels after Spinal Cord Injury. *Acta Biomater.* **2017**, *60*, 167–180.

(400) Zhao, T.; Sellers, D. L.; Cheng, Y.; Horner, P. J.; Pun, S. H. Tunable, Injectable Hydrogels Based on Peptide-Cross-Linked, Cyclized Polymer Nanoparticles for Neural Progenitor Cell Delivery. *Biomacromolecules* **2017**, *18*, 2723–2731.

(401) Hassannejad, Z.; Zadeegan, S. A.; Vaccaro, A. R.; Rahimi-Movaghar, V.; Sabzevari, O. Biofunctionalized Peptide-Based Hydrogel as an Injectable Scaffold for BDNF Delivery Can Improve Regeneration after Spinal Cord Injury. *Injury* **2019**, *50*, 278–285.

(402) Rose, J. C.; C  mara-Torres, M.; Rahimi, K.; K  hler, J.; M  ller, M.; De Laporte, L. Nerve Cells Decide to Orient inside an Injectable

Hydrogel with Minimal Structural Guidance. *Nano Lett.* **2017**, *17*, 3782–3791.

(403) Omidinia-Anarkoli, A.; Boesveld, S.; Tuvshindorj, U.; Rose, J. C.; Haraszti, T.; De Laporte, L. An Injectable Hybrid Hydrogel with Oriented Short Fibers Induces Unidirectional Growth of Functional Nerve Cells. *Small* **2017**, *13*, 1702207.

(404) Ghaderinejad, P.; Najmoddin, N.; Bagher, Z.; Saeed, M.; Karimi, S.; Simorgh, S.; Pezeshki-Modaress, M. An Injectable Anisotropic Alginate Hydrogel Containing Oriented Fibers for Nerve Tissue Engineering. *Chem. Eng. J.* **2021**, *420*, 130465.

(405) Nerger, B. A.; Brun, P. T.; Nelson, C. M. Microextrusion Printing Cell-Laden Networks of Type I Collagen with Patterned Fiber Alignment and Geometry. *Soft Matter* **2019**, *15*, 5728–5738.

(406) Zhang, K.; Li, J.; Jin, J.; Dong, J.; Li, L.; Xue, B.; Wang, W.; Jiang, Q.; Cao, Y. Injectable, Anti-Inflammatory and Conductive Hydrogels Based on Graphene Oxide and Diacerein-Terminated Four-Armed Polyethylene Glycol for Spinal Cord Injury Repair. *Mater. Des.* **2020**, *196*, 109092.

(407) Luo, Y.; Fan, L.; Liu, C.; Wen, H.; Wang, S.; Guan, P.; Chen, D.; Ning, C.; Zhou, L.; Tan, G. An Injectable, Self-Healing, Electroconductive Extracellular Matrix-Based Hydrogel for Enhancing Tissue Repair after Traumatic Spinal Cord Injury. *Bioact. Mater.* **2022**, *7*, 98–111.

(408) Pan, Z.; Sun, H.; Xie, B.; Xia, D.; Zhang, X.; Yu, D.; Li, J.; Xu, Y.; Wang, Z.; Wu, Y.; Zhang, X.; Wang, Y.; Fu, Q.; Hu, W.; Yang, Y.; Bunpetch, V.; Shen, W.; Heng, B. C.; Zhang, S.; Ouyang, H. Therapeutic Effects of Gefitinib-Encapsulated Thermosensitive Injectable Hydrogel in Intervertebral Disc Degeneration. *Biomaterials* **2018**, *160*, 56–68.

(409) Frith, J. E.; Cameron, A. R.; Menzies, D. J.; Ghosh, P.; Whitehead, D. L.; Gronthos, S.; Zannettino, A. C. W.; Cooper-White, J. J. An Injectable Hydrogel Incorporating Mesenchymal Precursor Cells and Pentosan Polysulphate for Intervertebral Disc Regeneration. *Biomaterials* **2013**, *34*, 9430–9440.

(410) Thorpe, A. A.; Boyes, V. L.; Sammon, C.; Le Maitre, C. L. Thermally Triggered Injectable Hydrogel, Which Induces Mesenchymal Stem Cell Differentiation to Nucleus Pulposus Cells: Potential for Regeneration of the Intervertebral Disc. *Acta Biomater.* **2016**, *36*, 99–111.

(411) Wang, F.; Nan, L.; Zhou, S.; Liu, Y.; Wang, Z.; Wang, J.; Feng, X.; Zhang, L. Injectable Hydrogel Combined with Nucleus Pulposus-Derived Mesenchymal Stem Cells for the Treatment of Degenerative Intervertebral Disc in Rats. *Stem Cells Int.* **2019**, *2019*, 8496025.

(412) Ligorio, C.; Zhou, M.; Wychowanec, J. K.; Zhu, X.; Bartlam, C.; Miller, A. F.; Vijayaraghavan, A.; Hoyland, J. A.; Saiani, A. Graphene Oxide Containing Self-Assembling Peptide Hybrid Hydrogels as a Potential 3D Injectable Cell Delivery Platform for Intervertebral Disc Repair Applications. *Acta Biomater.* **2019**, *92*, 92–103.

(413) Emerich, D. F.; Mooney, D. J.; Storrie, H.; Babu, R. S.; Kordower, J. H. Injectable Hydrogels Providing Sustained Delivery of Vascular Endothelial Growth Factor Are Neuroprotective in a Rat Model of Huntington's Disease. *Neurotox. Res.* **2010**, *17*, 66–74.

(414) Li, J.; Darabi, M.; Gu, J.; Shi, J.; Xue, J.; Huang, L.; Liu, Y.; Zhang, L.; Liu, N.; Zhong, W.; Zhang, L.; Xing, M.; Zhang, L. A Drug Delivery Hydrogel System Based on Activin B for Parkinson's Disease. *Biomaterials* **2016**, *102*, 72–86.

(415) Ren, Y.; Zhao, X.; Liang, X.; Ma, P. X.; Guo, B. Injectable Hydrogel Based on Quaternized Chitosan, Gelatin and Dopamine as Localized Drug Delivery System to Treat Parkinson's Disease. *Int. J. Biol. Macromol.* **2017**, *105*, 1079–1087.

(416) Xue, J.; Liu, Y.; Darabi, M. A.; Tu, G.; Huang, L.; Ying, L.; Xiao, B.; Wu, Y.; Xing, M.; Zhang, L.; Zhang, L. An Injectable Conductive Gelatin-PANI Hydrogel System Serves as a Promising Carrier to Deliver BMSCs for Parkinson's Disease Treatment. *Mater. Sci. Eng., C* **2019**, *100*, 584–597.

(417) Akhtar, A.; Andleeb, A.; Waris, T. S.; Bazzar, M.; Moradi, A. R.; Awan, N. R.; Yar, M. Neurodegenerative Diseases and Effective Drug Delivery: A Review of Challenges and Novel Therapeutics. *J. Controlled Release* **2021**, *330*, 1152–1167.

- (418) Khaing, Z. Z.; Ehsanipour, A.; Hofstetter, C. P.; Seidlits, S. K. Injectable Hydrogels for Spinal Cord Repair: A Focus on Swelling and Intraspinal Pressure. *Cells Tissues Organs* **2016**, *202*, 67–84.
- (419) Carmichael, S. T. The 3 Rs of Stroke Biology: Radial, Relayed, and Regenerative. *Neurotherapeutics* **2016**, *13*, 348–359.
- (420) Emerich, D. F.; Silva, E.; Ali, O.; Mooney, D.; Bell, W.; Yu, S. J.; Kaneko, Y.; Borlongan, C. Injectable VEGF Hydrogels Produce near Complete Neurological and Anatomical Protection Following Cerebral Ischemia in Rats. *Cell Transplant.* **2010**, *19*, 1063–1071.
- (421) Wang, Y.; Cooke, M. J.; Morshead, C. M.; Shoichet, M. S. Hydrogel Delivery of Erythropoietin to the Brain for Endogenous Stem Cell Stimulation after Stroke Injury. *Biomaterials* **2012**, *33*, 2681–2692.
- (422) Wang, Y.; Cooke, M. J.; Sachewsky, N.; Morshead, C. M.; Shoichet, M. S. Bioengineered Sequential Growth Factor Delivery Stimulates Brain Tissue Regeneration after Stroke. *J. Controlled Release* **2013**, *172*, 1–11.
- (423) Lam, J.; Lowry, W. E.; Carmichael, S. T.; Segura, T. Delivery of IPS-NPCs to the Stroke Cavity within a Hyaluronic Acid Matrix Promotes the Differentiation of Transplanted Cells. *Adv. Funct. Mater.* **2014**, *24*, 7053–7062.
- (424) Nih, L. R.; Gojgini, S.; Carmichael, S. T.; Segura, T. Dual-Function Injectable Angiogenic Biomaterial for the Repair of Brain Tissue Following Stroke. *Nat. Mater.* **2018**, *17*, 642–651.
- (425) Tuladhar, A.; Obermeyer, J. M.; Payne, S. L.; Siu, R. C. W.; Zand, S.; Morshead, C. M.; Shoichet, M. S. Injectable Hydrogel Enables Local and Sustained Co-Delivery to the Brain: Two Clinically Approved Biomolecules, Cyclosporine and Erythropoietin, Accelerate Functional Recovery in Rat Model of Stroke. *Biomaterials* **2020**, *235*, 119794.
- (426) Corrie, P. G. Cytotoxic Chemotherapy: Clinical Aspects. *Medicine (Baltimore)*. **2008**, *36*, 24–28.
- (427) de Lázaro, I.; Mooney, D. J. A Nanoparticle's Pathway into Tumours. *Nat. Mater.* **2020**, *19*, 486–487.
- (428) Sindhvani, S.; Syed, A. M.; Ngai, J.; Kingston, B. R.; Maiorino, L.; Rothschild, J.; MacMillan, P.; Zhang, Y.; Rajesh, N. U.; Hoang, T.; Wu, J. L. Y.; Wilhelm, S.; Zilman, A.; Gadde, S.; Sulaiman, A.; Ouyang, B.; Lin, Z.; Wang, L.; Egeblad, M.; Chan, W. C. W. The Entry of Nanoparticles into Solid Tumours. *Nat. Mater.* **2020**, *19*, 566–575.
- (429) Al-Abd, A. M.; Hong, K. Y.; Song, S. C.; Kuh, H. J. Pharmacokinetics of Doxorubicin after Intratumoral Injection Using a Thermosensitive Hydrogel in Tumor-Bearing Mice. *J. Controlled Release* **2010**, *142*, 101–107.
- (430) Seo, H. W.; Kim, D. Y.; Kwon, D. Y.; Kwon, J. S.; Jin, L. M.; Lee, B.; Kim, J. H.; Min, B. H.; Kim, M. S. Injectable Intratumoral Hydrogel as 5-Fluorouracil Drug Depot. *Biomaterials* **2013**, *34*, 2748–2757.
- (431) Kim, D. Y.; Kwon, D. Y.; Kwon, J. S.; Park, J. H.; Park, S. H.; Oh, H. J.; Kim, J. H.; Min, B. H.; Park, K.; Kim, M. S. Synergistic Anti-Tumor Activity through Combinational Intratumoral Injection of an in-Situ Injectable Drug Depot. *Biomaterials* **2016**, *85*, 232–245.
- (432) Park, S. H.; Kim, D. Y.; Panta, P.; Heo, J. Y.; Lee, H. Y.; Kim, J. H.; Min, B. H.; Kim, M. S. An Intratumoral Injectable, Electrostatic, Cross-Linkable Curcumin Depot and Synergistic Enhancement of Anticancer Activity. *NPG Asia Mater.* **2017**, *9*, No. e397.
- (433) Gao, Q.; Tang, S.; Chen, H.; Chen, H.; Li, X. J.; Jiang, Y. Q.; Fu, S. Z.; Lin, S. Intratumoral Injection of Anlotinib Hydrogel Enhances Antitumor Effects and Reduces Toxicity in Mouse Model of Lung Cancer. *Drug Delivery* **2020**, *27*, 1524–1534.
- (434) Xu, K.; Yao, H.; Fan, D.; Zhou, L.; Wei, S. Hyaluronic Acid Thiol Modified Injectable Hydrogel: Synthesis, Characterization, Drug Release, Cellular Drug Uptake and Anticancer Activity. *Carbohydr. Polym.* **2021**, *254*, 117286.
- (435) Fiorica, C.; Palumbo, F. S.; Pitarresi, G.; Puleio, R.; Condorelli, L.; Collura, G.; Giammona, G. A Hyaluronic Acid/Cyclodextrin Based Injectable Hydrogel for Local Doxorubicin Delivery to Solid Tumors. *Int. J. Pharm.* **2020**, *589*, 119879.
- (436) Ruel-Gariépy, E.; Shive, M.; Bichara, A.; Berrada, M.; Le Garrec, D.; Chenite, A.; Leroux, J. C. A Thermosensitive Chitosan-Based Hydrogel for the Local Delivery of Paclitaxel. *Eur. J. Pharm. Biopharm.* **2004**, *57*, 53–63.
- (437) Xu, L.; Cooper, R. C.; Wang, J.; Yeudall, W. A.; Yang, H. Synthesis and Application of Injectable Bioorthogonal Dendrimer Hydrogels for Local Drug Delivery. *ACS Biomater. Sci. Eng.* **2017**, *3*, 1641–1653.
- (438) Ahsan, A.; Farooq, M. A.; Parveen, A. Thermosensitive Chitosan-Based Injectable Hydrogel as an Efficient Anticancer Drug Carrier. *ACS Omega* **2020**, *5*, 20450–20460.
- (439) Zhang, C.; Shi, G.; Zhang, J.; Song, H.; Niu, J.; Shi, S.; Huang, P.; Wang, Y.; Wang, W.; Li, C.; Kong, D. Targeted Antigen Delivery to Dendritic Cell via Functionalized Alginate Nanoparticles for Cancer Immunotherapy. *J. Controlled Release* **2017**, *256*, 170–181.
- (440) Liu, H.; Shi, X.; Wu, D.; Kahsay Khshen, F.; Deng, L.; Dong, A.; Wang, W.; Zhang, J. Injectable, Biodegradable, Thermosensitive Nanoparticles-Aggregated Hydrogel with Tumor-Specific Targeting, Penetration, and Release for Efficient Postsurgical Prevention of Tumor Recurrence. *ACS Appl. Mater. Interfaces* **2019**, *11*, 19700–19711.
- (441) Qian, H.; Qian, K.; Cai, J.; Yang, Y.; Zhu, L.; Liu, B. Therapy for Gastric Cancer with Peritoneal Metastasis Using Injectable Albumin Hydrogel Hybridized with Paclitaxel-Loaded Red Blood Cell Membrane Nanoparticles. *ACS Biomater. Sci. Eng.* **2019**, *5*, 1100–1112.
- (442) Thakur, S.; Singh, H.; Singh, A.; Kaur, S.; Sharma, A.; Singh, S. K.; Kaur, S.; Kaur, G.; Jain, S. K. Thermosensitive Injectable Hydrogel Containing Carboplatin Loaded Nanoparticles: A Dual Approach for Sustained and Localized Delivery with Improved Safety and Therapeutic Efficacy. *J. Drug Delivery Sci. Technol.* **2020**, *58*, 101817.
- (443) Sabino, I. J.; Lima-Sousa, R.; Alves, C. G.; Melo, B. L.; Moreira, A. F.; Correia, I. J.; de Melo-Diogo, D. Injectable in Situ Forming Hydrogels Incorporating Dual-Nanoparticles for Chemo-Photothermal Therapy of Breast Cancer Cells. *Int. J. Pharm.* **2021**, *600*, 120510.
- (444) Leng, Q. Q.; Li, Y.; Zhou, P.; Xiong, K.; Lu, Y.; Cui, Y. X.; Wang, B. Q.; Wu, Z. X.; Zhao, L.; Fu, S. Z. Injectable Hydrogel Loaded with Paclitaxel and Epirubicin to Prevent Postoperative Recurrence and Metastasis of Breast Cancer. *Mater. Sci. Eng., C* **2021**, *129*, 112390.
- (445) Zhang, X.; Zhang, Y.; Zhang, C.; Yang, C.; Tian, R.; Sun, T.; Zhang, W.; Chang, J.; Wang, H. An Injectable Hydrogel Co-Loading with Cyanobacteria and Upconversion Nanoparticles for Enhanced Photodynamic Tumor Therapy. *Colloids Surfaces B Biointerfaces* **2021**, *201*, 111640.
- (446) Zhou, L.; Chen, F.; Hou, Z.; Chen, Y.; Luo, X. Injectable Self-Healing CuS Nanoparticle Complex Hydrogels with Antibacterial, Anti-Cancer, and Wound Healing Properties. *Chem. Eng. J.* **2021**, *409*, 128224.
- (447) Zhao, L.; Zhu, L.; Liu, F.; Liu, C.; Dan, S.; Wang, Q.; Zhang, C.; Li, J.; Liu, J.; Qu, X.; Yang, Z. pH Triggered Injectable Amphiphilic Hydrogel Containing Doxorubicin and Paclitaxel. *Int. J. Pharm.* **2011**, *410*, 83–91.
- (448) Qu, J.; Zhao, X.; Ma, P. X.; Guo, B. pH-Responsive Self-Healing Injectable Hydrogel Based on N-Carboxyethyl Chitosan for Hepatocellular Carcinoma Therapy. *Acta Biomater.* **2017**, *58*, 168–180.
- (449) Zhan, J.; Wu, Y.; Wang, H.; Liu, J.; Ma, Q.; Xiao, K.; Li, Z.; Li, J.; Luo, F.; Tan, H. An Injectable Hydrogel with pH-Sensitive and Self-Healing Properties Based on 4armPEGDA and N-Carboxyethyl Chitosan for Local Treatment of Hepatocellular Carcinoma. *Int. J. Biol. Macromol.* **2020**, *163*, 1208–1222.
- (450) Wu, M.; Chen, J.; Huang, W.; Yan, B.; Peng, Q.; Liu, J.; Chen, L.; Zeng, H. Injectable and Self-Healing Nanocomposite Hydrogels with Ultrasensitive pH-Responsiveness and Tunable Mechanical Properties: Implications for Controlled Drug Delivery. *Biomacromolecules* **2020**, *21*, 2409–2420.
- (451) Shi, J.; Guobao, W.; Chen, H.; Zhong, W.; Qiu, X.; Xing, M. M. Q. Schiff Based Injectable Hydrogel for in Situ pH-Triggered Delivery of Doxorubicin for Breast Tumor Treatment. *Polym. Chem.* **2014**, *5*, 6180–6189.
- (452) Zhang, W.; Jin, X.; Li, H.; Zhang, R. R.; Wu, C. W. Injectable and Body Temperature Sensitive Hydrogels Based on Chitosan and Hyaluronic Acid for pH Sensitive Drug Release. *Carbohydr. Polym.* **2018**, *186*, 82–90.
- (453) Fathi, M.; Alami-Milani, M.; Geranmayeh, M. H.; Barar, J.; Erfan-Niya, H.; Omid, Y. Dual Thermo-and pH-Sensitive Injectable

Hydrogels of Chitosan/(Poly(N-Isopropylacrylamide-Co-Itaconic Acid)) for Doxorubicin Delivery in Breast Cancer. *Int. J. Biol. Macromol.* **2019**, *128*, 957–964.

(454) Fong, Y.; Chen, C.-H.; Chen, J.-P. Intratumoral Delivery of Doxorubicin on Folate-Conjugated Graphene Oxide by In-Situ Forming Thermo-Sensitive Hydrogel for Breast Cancer Therapy. *Nanomaterials* **2017**, *7*, 388.

(455) Mukerji, R.; Schaal, J.; Li, X.; Bhattacharyya, J.; Asai, D.; Zalutsky, M. R.; Chilkoti, A.; Liu, W. Spatiotemporally Photoradiation-Controlled Intratumoral Depot for Combination of Brachytherapy and Photodynamic Therapy for Solid Tumor. *Biomaterials* **2016**, *79*, 79–87.

(456) Hou, M.; Liu, W.; Zhang, L.; Zhang, L.; Xu, Z.; Cao, Y.; Kang, Y.; Xue, P. Responsive Agarose Hydrogel Incorporated with Natural Humic Acid and MnO₂ Nanoparticles for Effective Relief of Tumor Hypoxia and Enhanced Photo-Induced Tumor Therapy. *Biomater. Sci.* **2020**, *8*, 353–369.

(457) Le Renard, P. E.; Jordan, O.; Faes, A.; Petri-Fink, A.; Hofmann, H.; Rüfenacht, D.; Bosman, F.; Buchegger, F.; Doelker, E. The in Vivo Performance of Magnetic Particle-Loaded Injectable, in Situ Gelling, Carriers for the Delivery of Local Hyperthermia. *Biomaterials* **2010**, *31*, 691–705.

(458) Zhu, X.; Zhang, H.; Huang, H.; Zhang, Y.; Hou, L.; Zhang, Z. Functionalized Graphene Oxide-Based Thermosensitive Hydrogel for Magnetic Hyperthermia Therapy on Tumors. *Nanotechnology* **2015**, *26*, 365103.

(459) Wu, H.; Liu, L.; Song, L.; Ma, M.; Gu, N.; Zhang, Y. Enhanced Tumor Synergistic Therapy by Injectable Magnetic Hydrogel Mediated Generation of Hyperthermia and Highly Toxic Reactive Oxygen Species. *ACS Nano* **2019**, *13*, 14013–14023.

(460) Qian, K. Y.; Song, Y.; Yan, X.; Dong, L.; Xue, J.; Xu, Y.; Wang, B.; Cao, B.; Hou, Q.; Peng, W.; Hu, J.; Jiang, K.; Chen, S.; Wang, H.; Lu, Y. Injectable Ferrimagnetic Silk Fibroin Hydrogel for Magnetic Hyperthermia Ablation of Deep Tumor. *Biomaterials* **2020**, *259*, 120299.

(461) Zheng, Y.; Wang, W.; Zhao, J.; Wu, C.; Ye, C.; Huang, M.; Wang, S. Preparation of Injectable Temperature-Sensitive Chitosan-Based Hydrogel for Combined Hyperthermia and Chemotherapy of Colon Cancer. *Carbohydr. Polym.* **2019**, *222*, 115039.

(462) Puente, P. de la; Fettig, N.; Luderer, M. J.; Jin, A.; Shah, S.; Muz, B.; Kapoor, V.; Goddu, S. M.; Salama, N. N.; Tsien, C.; Thotala, D.; Shoghi, K.; Rogers, B.; Azab, A. K. Injectable Hydrogels for Localized Chemotherapy and Radiotherapy in Brain Tumors. *J. Pharm. Sci.* **2018**, *107*, 922–933.

(463) Kim, S.; Yim, S. G.; Chandrasekharan, A.; Seong, K. Y.; Lee, T. W.; Kim, B.; Kim, K.; Choi, S.; Yang, S. Y. On-Site Fabrication of Injectable 131I-Labeled Microgels for Local Radiotherapy. *J. Controlled Release* **2020**, *322*, 337–345.

(464) De Souza Lawrence, L.; Ford, E.; Gilbert, C.; Yarmus, L.; Meneshian, A.; Feller-Kopman, D.; Hales, R. Novel Applications of an Injectable Radiopaque Hydrogel Tissue Marker for Management of Thoracic Malignancies. *Chest* **2013**, *143*, 1635–1641.

(465) Patel, H.; Goyal, S.; Kim, L. Using Injectable Hydrogel Markers to Assess Resimulation for Boost Target Volume Definition in a Patient Undergoing Whole-Breast Radiotherapy. *Med. Dosim.* **2015**, *40*, 352–354.

(466) Bair, R. J.; Bair, E.; Viswanathan, A. N. A Radiopaque Polymer Hydrogel Used as a Fiducial Marker in Gynecologic-Cancer Patients Receiving Brachytherapy. *Brachytherapy* **2015**, *14*, 876–880.

(467) Beydoun, N.; Bucci, J. A.; Chin, Y. S.; Malouf, D.; Enari, E.; Painter, S. D. First Report of Transperineal Polyethylene Glycol Hydrogel Spacer Use to Curtail Rectal Radiation Dose after Permanent Iodine-125 Prostate Brachytherapy. *Brachytherapy* **2013**, *12*, 368–374.

(468) Damato, A. L.; Kassick, M.; Viswanathan, A. N. Rectum and Bladder Spacing in Cervical Cancer Brachytherapy Using a Novel Injectable Hydrogel Compound. *Brachytherapy* **2017**, *16*, 949–955.

(469) Hepp, R.; Eggert, T.; Schabl, G.; Herberholz, L.; Petry, T.; Galalae, R. Salvage High-Dose-Rate Brachytherapy for Prostate Cancer

Persistence after Brachytherapy: Repeated Use of a Polyethylene Glycol Hydrogel Spacer. *J. Contemp. Brachytherapy* **2018**, *10*, 169–173.

(470) Kahn, J.; Dahman, B.; McLaughlin, C.; Kapoor, P.; Kapoor, R.; Harris, E.; Sharma, M.; Schutzer, M.; Moghanaki, D. Rectal Spacing, Prostate Coverage, and Periprocedural Outcomes after Hydrogel Spacer Injection during Low-Dose-Rate Brachytherapy Implantation. *Brachytherapy* **2020**, *19*, 228–233.

(471) Postow, M. A.; Callahan, M. K.; Wolchok, J. D. Immune Checkpoint Blockade in Cancer Therapy. *J. Clin. Oncol.* **2015**, *33*, 1974–1982.

(472) Srivastava, S.; Riddell, S. R. Chimeric Antigen Receptor T Cell Therapy: Challenges to Bench-to-Bedside Efficacy. *J. Immunol.* **2018**, *200*, 459–468.

(473) Song, H.; Yang, P.; Huang, P.; Zhang, C.; Kong, D.; Wang, W. Injectable Polypeptide Hydrogel-Based Co-Delivery of Vaccine and Immune Checkpoint Inhibitors Improves Tumor Immunotherapy. *Theranostics* **2019**, *9*, 2299–2314.

(474) Chen, M.; Tan, Y.; Dong, Z.; Lu, J.; Han, X.; Jin, Q.; Zhu, W.; Shen, J.; Cheng, L.; Liu, Z.; Chen, Q. Injectable Anti-Inflammatory Nanofiber Hydrogel to Achieve Systemic Immunotherapy Post Local Administration. *Nano Lett.* **2020**, *20*, 6763–6773.

(475) Liu, M.; Cao, Z.; Zhang, R.; Chen, Y.; Yang, X. Injectable Supramolecular Hydrogel for Locoregional Immune Checkpoint Blockade and Enhanced Cancer Chemo-Immunotherapy. *ACS Appl. Mater. Interfaces* **2021**, *13*, 33874–33884.

(476) Qin, X.; He, L.; Feng, C.; Fan, D.; Liang, W.; Wang, Q.; Fang, J. Injectable Micelle-Incorporated Hydrogels for the Localized Chemo-Immunotherapy of Breast Tumors. *ACS Appl. Mater. Interfaces* **2021**, *13*, 46270–46281.

(477) Ren, X.; Wang, N.; Zhou, Y.; Song, A.; Jin, G.; Li, Z.; Luan, Y. An Injectable Hydrogel Using an Immunomodulating Gelator for Amplified Tumor Immunotherapy by Blocking the Arginase Pathway. *Acta Biomater.* **2021**, *124*, 179–190.

(478) Atik, A. F.; Suryadevara, C. M.; Schweller, R. M.; West, J. L.; Healy, P.; Herndon II, J. E.; Congdon, K. L.; Sanchez-Perez, L.; McLendon, R. E.; Archer, G. E.; Fecci, P.; Sampson, J. H. Hyaluronic Acid Based Low Viscosity Hydrogel as a Novel Carrier for Convection Enhanced Delivery of CAR T Cells. *J. Clin. Neurosci.* **2018**, *56*, 163–168.

(479) Luo, Z.; Liu, Z.; Liang, Z.; Pan, J.; Xu, J.; Dong, J.; Bai, Y.; Deng, H.; Wei, S. Injectable Porous Microchips with Oxygen Reservoirs and an Immune-Niche Enhance the Efficacy of CAR T Cell Therapy in Solid Tumors. *ACS Appl. Mater. Interfaces* **2020**, *12*, 56712–56722.

(480) Ogunnaike, E. A.; Valdivia, A.; Yazdimaghani, M.; Leon, E.; Nandi, S.; Hudson, H.; Du, H.; Khagi, S.; Gu, Z.; Savoldo, B.; Ligler, F. S.; Hingtgen, S.; Dotti, G. Fibrin Gel Enhances the Antitumor Effects of Chimeric Antigen Receptor T Cells in Glioblastoma. *Sci. Adv.* **2021**, *7*, No. eabg5841.

(481) Cao, Y.; Zhou, Y.; Chen, Z.; Zhang, Z.; Chen, X.; He, C. Localized Chemotherapy Based on Injectable Hydrogel Boosts the Antitumor Activity of Adoptively Transferred T Lymphocytes In Vivo. *Adv. Healthc. Mater.* **2021**, *10*, 2100814.

(482) Grosskopf, A. K.; Labanieh, L.; Klysz, D. D.; Roth, G. A.; Xu, P.; Adebawale, O.; Gale, E. C.; Jons, C. K.; Klich, J. H.; Yan, J.; Maikawa, C. L.; Correa, S.; Ou, B. S.; D'Aquino, A. I.; Cochran, J. R.; Chaudhuri, O.; Mackall, C. L.; Appel, E. A. Delivery of CAR-T Cells in a Transient Injectable Stimulatory Hydrogel Niche Improves Treatment of Solid Tumors. *Sci. Adv.* **2022**, *8*, No. eabn8264.

(483) Song, H.; Huang, P.; Niu, J.; Shi, G.; Zhang, C.; Kong, D.; Wang, W. Injectable Polypeptide Hydrogel for Dual-Delivery of Antigen and TLR3 Agonist to Modulate Dendritic Cells in Vivo and Enhance Potent Cytotoxic T-Lymphocyte Response against Melanoma. *Biomaterials* **2018**, *159*, 119–129.

(484) Korupalli, C.; Pan, W.-Y.; Yeh, C.-Y.; Chen, P.-M.; Mi, F.-L.; Tsai, H.-W.; Chang, Y.; Wei, H.-J.; Sung, H.-W. Single-Injecting, Bioinspired Nanocomposite Hydrogel That Can Recruit Host Immune Cells in Situ to Elicit Potent and Long-Lasting Humoral Immune Responses. *Biomaterials* **2019**, *216*, 119268.

- (485) Hou, X. L.; Dai, X.; Yang, J.; Zhang, B.; Zhao, D. H.; Li, C. Q.; Yin, Z. Y.; Zhao, Y. Di; Liu, B. Injectable Polypeptide-Engineered Hydrogel Depot for Amplifying the Anti-Tumor Immune Effect Induced by Chemo-Photothermal Therapy. *J. Mater. Chem. B* **2020**, *8*, 8623–8633.
- (486) Cao, Y.; Zhou, Y.; Pan, J.; Zhong, X.; Ding, J.; Jing, X.; Sun, S. K. A General Strategy towards an Injectable Microwave-Sensitive Immune Hydrogel for Combined Percutaneous Microwave Ablation and Immunotherapy. *Chem. Eng. J.* **2021**, *422*, 130111.
- (487) Dai, X.; Meng, J.; Deng, S.; Zhang, L.; Wan, C.; Lu, L.; Huang, J.; Hu, Y.; Zhang, Z.; Li, Y.; Lovell, J. F.; Wu, G.; Yang, K.; Jin, H. Targeting CAMKII to Reprogram Tumor-Associated Macrophages and Inhibit Tumor Cells for Cancer Immunotherapy with an Injectable Hybrid Peptide Hydrogel. *Theranostics* **2020**, *10*, 3049–3063.
- (488) Yang, Y.; Yang, Y.; Chen, M.; Chen, J.; Wang, J.; Ma, Y.; Qian, H. Injectable Shear-Thinning Polylysine Hydrogels for Localized Immunotherapy of Gastric Cancer through Repolarization of Tumor-Associated Macrophages. *Biomater. Sci.* **2021**, *9*, 6597–6608.
- (489) Wang, H.; Najibi, A. J.; Sobral, M. C.; Seo, B. R.; Lee, J. Y.; Wu, D.; Li, A. W.; Verbeke, C. S.; Mooney, D. J. Biomaterial-Based Scaffold for In Situ Chemo-Immunotherapy to Treat Poorly Immunogenic Tumors. *Nat. Commun.* **2020**, *11*, 5696.
- (490) Sadeghzadeh, M.; Bornehdeli, S.; Mohamammadrezakhani, H.; Abolghasemi, M.; Poursaei, E.; Asadi, M.; Zafari, V.; Aghebati-Maleki, L.; Shانهbandi, D. Dendritic Cell Therapy in Cancer Treatment; the State-of-the-Art. *Life Sci.* **2020**, *254*, 117580.
- (491) Steinman, R. M.; Banchereau, J. Taking Dendritic Cells into Medicine. *Nature* **2007**, *449*, 419–426.
- (492) Hori, Y.; Winans, A. M.; Huang, C. C.; Horrigan, E. M.; Irvine, D. J. Injectable Dendritic Cell-Carrying Alginate Gels for Immunization and Immunotherapy. *Biomaterials* **2008**, *29*, 3671–3682.
- (493) Yang, P.; Song, H.; Qin, Y.; Huang, P.; Zhang, C.; Kong, D.; Wang, W. Engineering Dendritic-Cell-Based Vaccines and PD-1 Blockade in Self-Assembled Peptide Nanofibrous Hydrogel to Amplify Antitumor T-Cell Immunity. *Nano Lett.* **2018**, *18*, 4377–4385.
- (494) Ali, O. A.; Huebsch, N.; Cao, L.; Dranoff, G.; Mooney, D. J. Infection-Mimicking Materials to Program Dendritic Cells in Situ. *Nat. Mater.* **2009**, *8*, 151–158.
- (495) Kim, J.; Li, W. A.; Choi, Y.; Lewin, S. A.; Verbeke, C. S.; Dranoff, G.; Mooney, D. J. Injectable, Spontaneously Assembling, Inorganic Scaffolds Modulate Immune Cells in Vivo and Increase Vaccine Efficacy. *Nat. Biotechnol.* **2015**, *33*, 64–72.
- (496) Wang, H.; Sobral, M. C.; Zhang, D. K. Y.; Cartwright, A. N.; Li, A. W.; Dellacherie, M. O.; Tringides, C. M.; Koshy, S. T.; Wucherpfennig, K. W.; Mooney, D. J. Metabolic Labeling and Targeted Modulation of Dendritic Cells. *Nat. Mater.* **2020**, *19*, 1244–1252.
- (497) Wang, C.; Adrianus, G. N.; Sheng, N.; Toh, S.; Gong, Y.; Wang, D. A. In Vitro Performance of an Injectable Hydrogel/Microsphere Based Immunocyte Delivery System for Localised Anti-Tumour Activity. *Biomaterials* **2009**, *30*, 6986–6995.
- (498) Liu, Y.; Xiao, L.; Joo, K. I.; Hu, B.; Fang, J.; Wang, P. In Situ Modulation of Dendritic Cells by Injectable Thermosensitive Hydrogels for Cancer Vaccines in Mice. *Biomacromolecules* **2014**, *15*, 3836–3845.
- (499) Verbeke, C. S.; Mooney, D. J. Injectable, Pore-Forming Hydrogels for In Vivo Enrichment of Immature Dendritic Cells. *Adv. Healthc. Mater.* **2015**, *4*, 2677–2687.
- (500) Jin, H.; Wan, C.; Zou, Z.; Zhao, G.; Zhang, L.; Geng, Y.; Chen, T.; Huang, A.; Jiang, F.; Feng, J. P.; Lovell, J. F.; Chen, J.; Wu, G.; Yang, K. Tumor Ablation and Therapeutic Immunity Induction by an Injectable Peptide Hydrogel. *ACS Nano* **2018**, *12*, 3295–3310.
- (501) Duong, H. T. T.; Thambi, T.; Yin, Y.; Kim, S. H.; Nguyen, T. L.; Phan, V. H. G.; Kim, J.; Jeong, J. H.; Lee, D. S. Degradation-Regulated Architecture of Injectable Smart Hydrogels Enhances Humoral Immune Response and Potentiates Antitumor Activity in Human Lung Carcinoma. *Biomaterials* **2020**, *230*, 119599.
- (502) He, T.; Liang, X.; Li, L.; Gong, S.; Li, X.; Zhang, M.; Zhu, S.; Xiao, H.; Wu, Q.; Gong, C. A Spontaneously Formed and Self-Adjuvanted Hydrogel Vaccine Triggers Strong Immune Responses. *Mater. Des.* **2021**, *197*, 109232.
- (503) Broughton, G.; Janis, J. E.; Attinger, C. E. The Basic Science of Wound Healing. *Plast. Reconstr. Surg.* **2006**, *117*, 12S–34S.
- (504) Hoque, J.; Prakash, R. G.; Paramanandham, K.; Shome, B. R.; Haldar, J. Biocompatible Injectable Hydrogel with Potent Wound Healing and Antibacterial Properties. *Mol. Pharmaceutics* **2017**, *14*, 1218–1230.
- (505) Zhao, X.; Wu, H.; Guo, B.; Dong, R.; Qiu, Y.; Ma, P. X. Antibacterial Anti-Oxidant Electroactive Injectable Hydrogel as Self-Healing Wound Dressing with Hemostasis and Adhesiveness for Cutaneous Wound Healing. *Biomaterials* **2017**, *122*, 34–47.
- (506) Chen, H.; Cheng, J.; Ran, L.; Yu, K.; Lu, B.; Lan, G.; Dai, F.; Lu, F. An Injectable Self-Healing Hydrogel with Adhesive and Antibacterial Properties Effectively Promotes Wound Healing. *Carbohydr. Polym.* **2018**, *201*, 522–531.
- (507) Kong, L.; Wu, Z.; Zhao, H.; Cui, H.; Shen, J.; Chang, J.; Li, H.; He, Y. Bioactive Injectable Hydrogels Containing Desferrioxamine and Bioglass for Diabetic Wound Healing. *ACS Appl. Mater. Interfaces* **2018**, *10*, 30103–30114.
- (508) Qu, J.; Zhao, X.; Liang, Y.; Xu, Y.; Ma, P. X.; Guo, B. Degradable Conductive Injectable Hydrogels as Novel Antibacterial, Anti-Oxidant Wound Dressings for Wound Healing. *Chem. Eng. J.* **2019**, *362*, 548–560.
- (509) Mao, X.; Cheng, R.; Zhang, H.; Bae, J.; Cheng, L.; Zhang, L.; Deng, L.; Cui, W.; Zhang, Y.; Santos, H. A.; Sun, X. Self-Healing and Injectable Hydrogel for Matching Skin Flap Regeneration. *Adv. Sci.* **2019**, *6*, 1801555.
- (510) Liu, H.; Zhu, X.; Guo, H.; Huang, H.; Huang, S.; Huang, S.; Xue, W.; Zhu, P.; Guo, R. Nitric Oxide Released Injectable Hydrogel Combined with Synergistic Photothermal Therapy for Antibacterial and Accelerated Wound Healing. *Appl. Mater. Today* **2020**, *20*, 100781.
- (511) Wang, S.; Zheng, H.; Zhou, L.; Cheng, F.; Liu, Z.; Zhang, H.; Wang, L.; Zhang, Q. Nanoenzyme-Reinforced Injectable Hydrogel for Healing Diabetic Wounds Infected with Multidrug Resistant Bacteria. *Nano Lett.* **2020**, *20*, 5149–5158.
- (512) Qiu, W.; Han, H.; Li, M.; Li, N.; Wang, Q.; Qin, X.; Wang, X.; Yu, J.; Zhou, Y.; Li, Y.; Li, F.; Wu, D. Nanofibers Reinforced Injectable Hydrogel with Self-Healing, Antibacterial, and Hemostatic Properties for Chronic Wound Healing. *J. Colloid Interface Sci.* **2021**, *596*, 312–323.
- (513) Ma, Z.; Song, W.; He, Y.; Li, H. Multilayer Injectable Hydrogel System Sequentially Delivers Bioactive Substances for Each Wound Healing Stage. *ACS Appl. Mater. Interfaces* **2020**, *12*, 29787–29806.
- (514) Kim, M. H.; Park, H.; Nam, H. C.; Park, S. R.; Jung, J. Y.; Park, W. H. Injectable Methylcellulose Hydrogel Containing Silver Oxide Nanoparticles for Burn Wound Healing. *Carbohydr. Polym.* **2018**, *181*, 579–586.
- (515) Xuan, X.; Zhou, Y.; Chen, A.; Zheng, S.; An, Y.; He, H.; Huang, W.; Chen, Y.; Yang, Y.; Li, S.; Xuan, T.; Xiao, J.; Li, X.; Wu, J. Silver Crosslinked Injectable BFGF-Eluting Supramolecular Hydrogels Speed up Infected Wound Healing. *J. Mater. Chem. B* **2020**, *8*, 1359–1370.
- (516) Niu, Y.; Guo, T.; Yuan, X.; Zhao, Y.; Ren, L. An Injectable Supramolecular Hydrogel Hybridized with Silver Nanoparticles for Antibacterial Application. *Soft Matter* **2018**, *14*, 1227–1234.
- (517) Zhang, H.; Sun, X.; Wang, J.; Zhang, Y.; Dong, M.; Bu, T.; Li, L.; Liu, Y.; Wang, L. Multifunctional Injectable Hydrogel Dressings for Effectively Accelerating Wound Healing: Enhancing Biomineralization Strategy. *Adv. Funct. Mater.* **2021**, *31*, 2100093.
- (518) Andrabi, S. M.; Majumder, S.; Gupta, K. C.; Kumar, A. Dextran Based Amphiphilic Nano-Hybrid Hydrogel System Incorporated with Curcumin and Cerium Oxide Nanoparticles for Wound Healing. *Colloids Surfaces B Biointerfaces* **2020**, *195*, 111263.
- (519) Chen, Y.-H.; Rao, Z.-F.; Liu, Y.-J.; Liu, X.-S.; Liu, Y.-F.; Xu, L.-J.; Wang, Z.-Q.; Guo, J.-Y.; Zhang, L.; Dong, Y.-S.; Qi, C.-X.; Yang, C.; Wang, S.-F. Multifunctional Injectable Hydrogel Loaded with Cerium-Containing Bioactive Glass Nanoparticles for Diabetic Wound Healing. *Biomolecules* **2021**, *11*, 702.

- (520) Mao, Y.; Pan, M.; Yang, H.; Lin, X.; Yang, L. Injectable Hydrogel Wound Dressing Based on Strontium Ion Cross-Linked Starch. *Front. Mater. Sci.* **2020**, *14*, 232–241.
- (521) Zhou, W.; Zi, L.; Cen, Y.; You, C.; Tian, M. Copper Sulfide Nanoparticles-Incorporated Hyaluronic Acid Injectable Hydrogel With Enhanced Angiogenesis to Promote Wound Healing. *Front. Bioeng. Biotechnol.* **2020**, *8*, 417.
- (522) Boffito, M.; Pontremoli, C.; Fiorilli, S.; Laurano, R.; Ciardelli, G.; Vitale-Brovarene, C. Injectable Thermosensitive Formulation Based on Polyurethane Hydrogel/Mesoporous Glasses for Sustained Co-Delivery of Functional Ions and Drugs. *Pharmaceutics* **2019**, *11*, 501.
- (523) Liu, S.; Yu, J.; Zhang, Q.; Lu, H.; Qiu, X.; Zhou, D.; Qi, Y.; Huang, Y. Dual Cross-Linked HHA Hydrogel Supplies and Regulates M ϕ 2 for Synergistic Improvement of Immunocompromise and Impaired Angiogenesis to Enhance Diabetic Chronic Wound Healing. *Biomacromolecules* **2020**, *21*, 3795–3806.
- (524) Sheng, L.; Zhang, Z.; Zhang, Y.; Wang, E.; Ma, B.; Xu, Q.; Ma, L.; Zhang, M.; Pei, G.; Chang, J. A Novel “Hot Spring”-Mimetic Hydrogel with Excellent Angiogenic Properties for Chronic Wound Healing. *Biomaterials* **2021**, *264*, 120414.
- (525) Yang, R.; Huang, J.; Zhang, W.; Xue, W.; Jiang, Y.; Li, S.; Wu, X.; Xu, H.; Ren, J.; Chi, B. Mechanoadaptive Injectable Hydrogel Based on Poly(γ -Glutamic Acid) and Hyaluronic Acid Regulates Fibroblast Migration for Wound Healing. *Carbohydr. Polym.* **2021**, *273*, 118607.
- (526) Wang, K.; Dong, R.; Tang, J.; Li, H.; Dang, J.; Zhang, Z.; Yu, Z.; Guo, B.; Yi, C. Exosomes Laden Self-Healing Injectable Hydrogel Enhances Diabetic Wound Healing via Regulating Macrophage Polarization to Accelerate Angiogenesis. *Chem. Eng. J.* **2022**, *430*, 132664.
- (527) Li, J.; Chen, G.; Xu, X.; Abdou, P.; Jiang, Q.; Shi, D.; Gu, Z. Advances of Injectable Hydrogel-Based Scaffolds for Cartilage Regeneration. *Regen. Biomater.* **2019**, *6*, 129–140.
- (528) Kwon, J. S.; Yoon, S. M.; Shim, S. W.; Park, J. H.; Min, K. J.; Oh, H. J.; Kim, J. H.; Kim, Y. J.; Yoon, J. J.; Choi, B. H.; Kim, M. S. Injectable Extracellular Matrix Hydrogel Developed Using Porcine Articular Cartilage. *Int. J. Pharm.* **2013**, *454*, 183–191.
- (529) Chen, W.; Li, C.; Peng, M.; Xie, B.; Zhang, L.; Tang, X. Autologous Nasal Chondrocytes Delivered by Injectable Hydrogel for in Vivo Articular Cartilage Regeneration. *Cell Tissue Bank.* **2018**, *19*, 35–46.
- (530) Cipriani, F.; Krüger, M.; De Torre, I. G.; Sierra, L. Q.; Rodrigo, M. A.; Kock, L.; Rodríguez-Cabello, J. C. Cartilage Regeneration in Preactivated Silk Elastin-Like Co-Recombinamers Injectable Hydrogel Embedded with Mature Chondrocytes in an Ex Vivo Culture Platform. *Biomacromolecules* **2018**, *19*, 4333–4347.
- (531) Li, X.; A, S.; Xu, Q.; Alshehri, F.; Zeng, M.; Zhou, D.; Li, J.; Zhou, G.; Wang, W. Cartilage-Derived Progenitor Cell-Laden Injectable Hydrogel-An Approach for Cartilage Tissue Regeneration. *ACS Appl. Bio Mater.* **2020**, *3*, 4756–4765.
- (532) Li, X.; Xu, Q.; Johnson, M.; Wang, X.; Lyu, J.; Li, Y.; McMahon, S.; Greiser, U.; A, S.; Wang, W. A Chondroitin Sulfate Based Injectable Hydrogel for Delivery of Stem Cells in Cartilage Regeneration. *Biomater. Sci.* **2021**, *9*, 4139–4148.
- (533) Dai, M.; Sui, B.; Xue, Y.; Liu, X.; Sun, J. Cartilage Repair in Degenerative Osteoarthritis Mediated by Squid Type II Collagen via Immunomodulating Activation of M2 Macrophages, Inhibiting Apoptosis and Hypertrophy of Chondrocytes. *Biomaterials* **2018**, *180*, 91–103.
- (534) Ji, X.; Lei, Z.; Yuan, M.; Zhu, H.; Yuan, X.; Liu, W.; Pu, H.; Jiang, J.; Zhang, Y.; Jiang, X.; Xiao, J. Cartilage Repair Mediated by Thermosensitive Photocrosslinkable TGF β 1-Loaded GM-HPCH via Immunomodulating Macrophages, Recruiting MSCs and Promoting Chondrogenesis. *Theranostics* **2020**, *10*, 2872–2887.
- (535) Yu, W.; Zhu, Y.; Li, H.; He, Y. Injectable Quercetin-Loaded Hydrogel with Cartilage-Protection and Immunomodulatory Properties for Articular Cartilage Repair. *ACS Appl. Bio Mater.* **2020**, *3*, 761–771.
- (536) Mhanna, R.; Kashyap, A.; Palazzolo, G.; Vallmajo-Martin, Q.; Becher, J.; Möller, S.; Schnabelrauch, M.; Zenobi-Wong, M. Chondrocyte Culture in Three Dimensional Alginate Sulfate Hydrogels Promotes Proliferation While Maintaining Expression of Chondrogenic Markers. *Tissue Eng. - Part A* **2014**, *20*, 1454–1464.
- (537) Mhanna, R.; Öztürk, E.; Vallmajo-Martin, Q.; Millan, C.; Müller, M.; Zenobi-Wong, M. GFOGER-Modified MMP-Sensitive Polyethylene Glycol Hydrogels Induce Chondrogenic Differentiation of Human Mesenchymal Stem Cells. *Tissue Eng. - Part A* **2014**, *20*, 1165–1174.
- (538) Wang, L. S.; Du, C.; Toh, W. S.; Wan, A. C. A.; Gao, S. J.; Kurisawa, M. Modulation of Chondrocyte Functions and Stiffness-Dependent Cartilage Repair Using an Injectable Enzymatically Crosslinked Hydrogel with Tunable Mechanical Properties. *Biomaterials* **2014**, *35*, 2207–2217.
- (539) Loebel, C.; Szczesny, S. E.; Cosgrove, B. D.; Alini, M.; Zenobi-Wong, M.; Mauck, R. L.; Eglin, D. Cross-Linking Chemistry of Tyramine-Modified Hyaluronan Hydrogels Alters Mesenchymal Stem Cell Early Attachment and Behavior. *Biomacromolecules* **2017**, *18*, 855–864.
- (540) Park, Y.; Lutolf, M. P.; Hubbell, J. A.; Hunziker, E. B.; Wong, M. Bovine Primary Chondrocyte Culture in Synthetic Matrix Metalloproteinase-Sensitive Poly(Ethylene Glycol)-Based Hydrogels as a Scaffold for Cartilage Repair. *Tissue Eng.* **2004**, *10*, 515–522.
- (541) Jin, Y.; Koh, R. H.; Kim, S. H.; Kim, K. M.; Park, G. K.; Hwang, N. S. Injectable Anti-Inflammatory Hyaluronic Acid Hydrogel for Osteoarthritic Cartilage Repair. *Mater. Sci. Eng., C* **2020**, *115*, 111096.
- (542) Koh, R. H.; Jin, Y.; Kim, J.; Hwang, N. S. Inflammation-Modulating Hydrogels for Osteoarthritis Cartilage Tissue Engineering. *Cells* **2020**, *9*, 419.
- (543) García-Fernández, L.; Olmeda-Lozano, M.; Benito-Garzón, L.; Pérez-Caballer, A.; San Román, J.; Vázquez-Lasa, B. Injectable Hydrogel-Based Drug Delivery System for Cartilage Regeneration. *Mater. Sci. Eng., C* **2020**, *110*, 110702.
- (544) Fuoco, C.; Salvatori, M. L.; Biondo, A.; Shapira-Schweitzer, K.; Santoleri, S.; Antonini, S.; Bernardini, S.; Tedesco, F. S.; Cannata, S.; Seliktar, D.; Cossu, G.; Gargioli, C. Injectable Polyethylene Glycol-Fibrinogen Hydrogel Adjuvant Improves Survival and Differentiation of Transplanted Mesoangioblasts in Acute and Chronic Skeletal Muscle Degeneration. *Skeletal Muscle* **2012**, *2*, 24.
- (545) Shan, H.; Gao, X.; Zhang, M.; Huang, M.; Fang, X.; Chen, H.; Tian, B.; Wang, C.; Zhou, C.; Bai, J.; Zhou, X. Injectable ROS-Scavenging Hydrogel with MSCs Promoted the Regeneration of Damaged Skeletal Muscle. *J. Tissue Eng.* **2021**, *12*, 20417314211031378.
- (546) DeQuach, J.; Lin, J.; Cam, C.; Hu, D.; Salvatore, M.; Sheikh, F.; Christman, K. Injectable Skeletal Muscle Matrix Hydrogel Promotes Neovascularization and Muscle Cell Infiltration in a Hindlimb Ischemia Model. *Eur. Cells Mater.* **2012**, *23*, 400–412.
- (547) Zhang, K.; Zhao, X.; Chen, X.; Wei, Y.; Du, W.; Wang, Y.; Liu, L.; Zhao, W.; Han, Z.; Kong, D.; Zhao, Q.; Guo, Z.; Han, Z.; Liu, N.; Ma, F.; Li, Z. Enhanced Therapeutic Effects of Mesenchymal Stem Cell-Derived Exosomes with an Injectable Hydrogel for Hindlimb Ischemia Treatment. *ACS Appl. Mater. Interfaces* **2018**, *10*, 30081–30091.
- (548) Borselli, C.; Storrie, H.; Benesch-Lee, F.; Shvartsman, D.; Cezar, C.; Lichtman, J. W.; Vandenburgh, H. H.; Mooney, D. J. Functional Muscle Regeneration with Combined Delivery of Angiogenesis and Myogenesis Factors. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 3287–3292.
- (549) Chang, L.; Li, Y.; Li, M.; Liu, S.; Han, J.; Zhao, G.; Ji, C.; Lyu, Y.; Genin, G. M.; Bai, B.; Xu, F. An Injectable, Biodegradable Magnetic Hydrogel System for Exogenous Promotion of Muscle Mass and Regeneration. *Chem. Eng. J.* **2021**, *420*, 130398.
- (550) Van Nieuwenhove, I.; Tytgat, L.; Ryx, M.; Blondeel, P.; Stillaert, F.; Thienpont, H.; Ottevaere, H.; Dubrue, P.; Van Vlierberghe, S. Soft Tissue Fillers for Adipose Tissue Regeneration: From Hydrogel Development toward Clinical Applications. *Acta Biomater.* **2017**, *63*, 37–49.

- (551) Manafi, A.; Emami, A. H.; Pooli, A. H.; Habibi, M.; Saidian, L. Unacceptable Results with an Accepted Soft Tissue Filler: Polyacrylamide Hydrogel. *Aesthetic Plast. Surg.* **2010**, *34*, 413–422.
- (552) AMIN, S. P.; MARMUR, E. S.; GOLDBERG, D. J. Complications from Injectable Polyacrylamide Gel, a New Non-biodegradable Soft Tissue Filler. *Dermatologic Surg.* **2004**, *30*, 1507–1509.
- (553) Gold, G. T.; Varma, D. M.; Harbottle, D.; Gupta, M. S.; Stalling, S. S.; Taub, P. J.; Nicoll, S. B. Injectable Redox-Polymerized Methylcellulose Hydrogels as Potential Soft Tissue Filler Materials. *J. Biomed. Mater. Res.: A* **2014**, *102*, 4536–4544.
- (554) Varma, D. M.; Gold, G. T.; Taub, P. J.; Nicoll, S. B. Injectable Carboxymethylcellulose Hydrogels for Soft Tissue Filler Applications. *Acta Biomater.* **2014**, *10*, 4996–5004.
- (555) Hong, B. M.; Hong, G. L.; Gwak, M. A.; Kim, K. H.; Jeong, J. E.; Jung, J. Y.; Park, S. A.; Park, W. H. Self-Crosslinkable Hyaluronate-Based Hydrogels as a Soft Tissue Filler. *Int. J. Biol. Macromol.* **2021**, *185*, 98–110.
- (556) Koons, G. L.; Diba, M.; Mikos, A. G. Materials Design for Bone-Tissue Engineering. *Nat. Rev. Mater.* **2020**, *5*, 584–603.
- (557) Schemitsch, E. H. Size Matters: Defining Critical in Bone Defect Size! *J. Orthop. Trauma* **2017**, *31*, S20–S22.
- (558) Short, A. R.; Koralla, D.; Deshmukh, A.; Wissel, B.; Stocker, B.; Calhoun, M.; Dean, D.; Winter, J. O. Hydrogels That Allow and Facilitate Bone Repair, Remodeling, and Regeneration. *J. Mater. Chem. B* **2015**, *3*, 7818–7830.
- (559) Liu, W.; Zhan, J.; Su, Y.; Wu, T.; Ramakrishna, S.; Liao, S.; Mo, X. Injectable Hydrogel Incorporating with Nanoyarn for Bone Regeneration. *J. Biomater. Sci. Polym. Ed.* **2014**, *25*, 168–180.
- (560) Thorpe, A. A.; Freeman, C.; Farthing, P.; Callaghan, J.; Hatton, P. V.; Brook, I. M.; Sammon, C.; Le Maitre, C. L. In Vivo Safety and Efficacy Testing of a Thermally Triggered Injectable Hydrogel Scaffold for Bone Regeneration and Augmentation in a Rat Model. *Oncotarget* **2018**, *9*, 18277–18295.
- (561) Hou, S.; Wang, X.; Park, S.; Jin, X.; Ma, P. X. Rapid Self-Integrating, Injectable Hydrogel for Tissue Complex Regeneration. *Adv. Healthc. Mater.* **2015**, *4*, 1491–1495.
- (562) Cheng, W.; Ding, Z.; Zheng, X.; Lu, Q.; Kong, X.; Zhou, X.; Lu, G.; Kaplan, D. L. Injectable Hydrogel Systems with Multiple Biophysical and Biochemical Cues for Bone Regeneration. *Biomater. Sci.* **2020**, *8*, 2537–2548.
- (563) Dyondi, D.; Webster, T. J.; Banerjee, R. A Nanoparticulate Injectable Hydrogel as a Tissue Engineering Scaffold for Multiple Growth Factor Delivery for Bone Regeneration. *Int. J. Nanomedicine* **2012**, *8*, 47–59.
- (564) Ning, Z.; Tan, B.; Chen, B.; Lau, D. S. A.; Wong, T. M.; Sun, T.; Peng, S.; Li, Z.; Lu, W. W. Precisely Controlled Delivery of Abaloparatide through Injectable Hydrogel to Promote Bone Regeneration. *Macromol. Biosci.* **2019**, *19*, 1900020.
- (565) Seo, B. B.; Koh, J. T.; Song, S. C. Tuning Physical Properties and BMP-2 Release Rates of Injectable Hydrogel Systems for an Optimal Bone Regeneration Effect. *Biomaterials* **2017**, *122*, 91–104.
- (566) Tommasi, G.; Perni, S.; Prokopovich, P. An Injectable Hydrogel as Bone Graft Material with Added Antimicrobial Properties. *Tissue Eng. Part A* **2016**, *22*, 862–872.
- (567) Wu, J.; Li, G.; Ye, T.; Lu, G.; Li, R.; Deng, L.; Wang, L.; Cai, M.; Cui, W. Stem Cell-Laden Injectable Hydrogel Microspheres for Cancellous Bone Regeneration. *Chem. Eng. J.* **2020**, *393*, 124715.
- (568) Gan, M.; Zhou, Q.; Ge, J.; Zhao, J.; Wang, Y.; Yan, Q.; Wu, C.; Yu, H.; Xiao, Q.; Wang, W.; Yang, H.; Zou, J. Precise In-Situ Release of MicroRNA from an Injectable Hydrogel Induces Bone Regeneration. *Acta Biomater.* **2021**, *135*, 289–303.
- (569) Pan, Y.; Zhao, Y.; Kuang, R.; Liu, H.; Sun, D.; Mao, T.; Jiang, K.; Yang, X.; Watanabe, N.; Mayo, K. H.; Lin, Q.; Li, J. Injectable Hydrogel-Loaded Nano-Hydroxyapatite That Improves Bone Regeneration and Alveolar Ridge Promotion. *Mater. Sci. Eng., C* **2020**, *116*, 111158.
- (570) Van, T. D.; Tran, N. Q.; Nguyen, D. H.; Nguyen, C. K.; Tran, D. L.; Nguyen, P. T. Injectable Hydrogel Composite Based Gelatin-PEG and Biphasic Calcium Phosphate Nanoparticles for Bone Regeneration. *J. Electron. Mater.* **2016**, *45*, 2415–2422.
- (571) Yao, S.; Xu, Y.; Zhou, Y.; Shao, C.; Liu, Z.; Jin, B.; Zhao, R.; Cao, H.; Pan, H.; Tang, R. Calcium Phosphate Nanocluster-Loaded Injectable Hydrogel for Bone Regeneration. *ACS Appl. Bio Mater.* **2019**, *2*, 4408–4417.
- (572) Andersson, Ö. H.; Karlsson, K. H.; Kangasniemi, K. Calcium Phosphate Formation at the Surface of Bioactive Glass in Vivo. *J. Non. Cryst. Solids* **1990**, *119*, 290–296.
- (573) Day, R. M. Bioactive Glass Stimulates the Secretion of Angiogenic Growth Factors and Angiogenesis in Vitro. *Tissue Eng.* **2005**, *11*, 768–777.
- (574) Leppäranta, O.; Vaahtio, M.; Peltola, T.; Zhang, D.; Hupa, L.; Hupa, M.; Ylänen, H.; Salonen, J. I.; Viljanen, M. K.; Eerola, E. Antibacterial Effect of Bioactive Glasses on Clinically Important Anaerobic Bacteria in Vitro. *J. Mater. Sci. Mater. Med.* **2008**, *19*, 547–551.
- (575) Gkioni, K.; Leeuwenburgh, S. C. G.; Douglas, T. E. L.; Mikos, A. G.; Jansen, J. A. Mineralization of Hydrogels for Bone Regeneration. *Tissue Eng. - Part B Rev.* **2010**, *16*, 577–585.
- (576) Lee, H.; Stowers, R.; Chaudhuri, O. Volume Expansion and TRPV4 Activation Regulate Stem Cell Fate in Three-Dimensional Microenvironments. *Nat. Commun.* **2019**, *10*, 529.
- (577) Thompson, J. T. Advantages and Limitations of Small Gauge Vitrectomy. *Surv. Ophthalmol.* **2011**, *56*, 162–172.
- (578) Su, W. Y.; Chen, K. H.; Chen, Y. C.; Lee, Y. H.; Tseng, C. L.; Lin, F. H. An Injectable Oxidated Hyaluronic Acid/Adipic Acid Dihydrazide Hydrogel as a Vitreous Substitute. *J. Biomater. Sci. Polym. Ed.* **2011**, *22*, 1777–1797.
- (579) Annaka, M.; Mortensen, K.; Vigild, M. E.; Matsuura, T.; Tsuji, S.; Ueda, T.; Tsujinaka, H. Design of an Injectable in Situ Gelation Biomaterials for Vitreous Substitute. *Biomacromolecules* **2011**, *12*, 4011–4021.
- (580) Feng, S.; Chen, H.; Liu, Y.; Huang, Z.; Sun, X.; Zhou, L.; Lu, X.; Gao, Q. A Novel Vitreous Substitute of Using a Foldable Capsular Vitreous Body Injected with Polyvinylalcohol Hydrogel. *Sci. Rep.* **2013**, *3*, 1838.
- (581) Tao, Y.; Tong, X.; Zhang, Y.; Lai, J.; Huang, Y.; Jiang, Y. R.; Guo, B. H. Evaluation of an in Situ Chemically Crosslinked Hydrogel as a Long-Term Vitreous Substitute Material. *Acta Biomater.* **2013**, *9*, 5022–5030.
- (582) Xue, K.; Liu, Z.; Jiang, L.; Kai, D.; Li, Z.; Su, X.; Loh, X. J. A New Highly Transparent Injectable PHA-Based Thermogelling Vitreous Substitute. *Biomater. Sci.* **2020**, *8*, 926–936.
- (583) Tram, N. K.; Jiang, P.; Torres-Flores, T. C.; Jacobs, K. M.; Chandler, H. L.; Swindle-Reilly, K. E. A Hydrogel Vitreous Substitute That Releases Antioxidant. *Macromol. Biosci.* **2020**, *20*, 1900305.
- (584) Bertsch, P.; Bergfreund, J.; Windhab, E. J.; Fischer, P. Physiological Fluid Interfaces: Functional Microenvironments, Drug Delivery Targets, and First Line of Defense. *Acta Biomater.* **2021**, *130*, 32–53.
- (585) Wang, K.; Chen, Y.; Ahn, S.; Zheng, M.; Landoni, E.; Dotti, G.; Savoldo, B.; Han, Z. GD2-Specific CAR T Cells Encapsulated in an Injectable Hydrogel Control Retinoblastoma and Preserve Vision. *Nat. Cancer* **2020**, *1*, 990–997.
- (586) Gao, Y.; Sun, Y.; Ren, F.; Gao, S. PLGA-PEG-PLGA Hydrogel for Ocular Drug Delivery of Dexamethasone Acetate. *Drug Dev. Ind. Pharm.* **2010**, *36*, 1131–1138.
- (587) Chen, X.; Li, X.; Zhou, Y.; Wang, X.; Zhang, Y.; Fan, Y.; Huang, Y.; Liu, Y. Chitosan-Based Thermosensitive Hydrogel as a Promising Ocular Drug Delivery System: Preparation, Characterization, and in Vivo Evaluation. *J. Biomater. Appl.* **2012**, *27*, 391–402.
- (588) Xu, X.; Weng, Y.; Xu, L.; Chen, H. Sustained Release of Avastin® from Polysaccharides Cross-Linked Hydrogels for Ocular Drug Delivery. *Int. J. Biol. Macromol.* **2013**, *60*, 272–276.
- (589) Yu, J.; Xu, X.; Yao, F.; Luo, Z.; Jin, L.; Xie, B.; Shi, S.; Ma, H.; Li, X.; Chen, H. In Situ Covalently Cross-Linked PEG Hydrogel for Ocular Drug Delivery Applications. *Int. J. Pharm.* **2014**, *470*, 151–157.

- (590) Lu, C.; Zahedi, P.; Forman, A.; Allen, C. Multi-Arm PEG/Silica Hydrogel for Sustained Ocular Drug Delivery. *J. Pharm. Sci.* **2014**, *103*, 216–226.
- (591) Song, Y.; Nagai, N.; Saijo, S.; Kaji, H.; Nishizawa, M.; Abe, T. In Situ Formation of Injectable Chitosan-Gelatin Hydrogels through Double Crosslinking for Sustained Intraocular Drug Delivery. *Mater. Sci. Eng., C* **2018**, *88*, 1–12.
- (592) Chegini, S. P.; Varshosaz, J.; Sadeghi, H. M.; Dehghani, A.; Minaian, M. Shear Sensitive Injectable Hydrogels of Cross-Linked Tragacanthic Acid for Ocular Drug Delivery: Rheological and Biological Evaluation. *Int. J. Biol. Macromol.* **2020**, *165*, 2789–2804.
- (593) Campochiaro, P. A. Ocular Neovascularization. *J. Mol. Med. (Berl.)* **2013**, *91*, 311–321.
- (594) Iyer, S.; Radwan, A. E.; Hafezi-Moghadam, A.; Malyala, P.; Amiji, M. Long-Acting Intraocular Delivery Strategies for Biological Therapy of Age-Related Macular Degeneration. *J. Controlled Release* **2019**, *296*, 140–149.
- (595) Osswald, C. R.; Kang-Mieler, J. J. Controlled and Extended Release of a Model Protein from a Microsphere-Hydrogel Drug Delivery System. *Ann. Biomed. Eng.* **2015**, *43*, 2609–2617.
- (596) Osswald, C. R.; Guthrie, M. J.; Avila, A.; Valio, J. A.; Mieler, W. F.; Kang-Mieler, J. J. In Vivo Efficacy of an Injectable Microsphere-Hydrogel Ocular Drug Delivery System. *Curr. Eye Res.* **2017**, *42*, 1293–1301.
- (597) Liu, W.; Lee, B. S.; Mieler, W. F.; Kang-Mieler, J. J. Biodegradable Microsphere-Hydrogel Ocular Drug Delivery System for Controlled and Extended Release of Bioactive Aflibercept In Vitro. *Curr. Eye Res.* **2019**, *44*, 264–274.
- (598) Liu, W.; Borrell, M. A.; Venerus, D. C.; Mieler, W. F.; Kang-Mieler, J. J. Characterization of Biodegradable Microsphere-Hydrogel Ocular Drug Delivery System for Controlled and Extended Release of Ranibizumab. *Transl. Vis. Sci. Technol.* **2019**, *8*, 12.
- (599) Wang, K.; Zheng, M.; Lester, K. L.; Han, Z. Light-Induced Nrf2^{-/-} Mice as Atrophic Age-Related Macular Degeneration Model and Treatment with Nanoceria Laden Injectable Hydrogel. *Sci. Rep.* **2019**, *9*, 14573.
- (600) Ballios, B. G.; Cooke, M. J.; van der Kooy, D.; Shoichet, M. S. A Hydrogel-Based Stem Cell Delivery System to Treat Retinal Degenerative Diseases. *Biomaterials* **2010**, *31*, 2555–2564.
- (601) Ballios, B. G.; Cooke, M. J.; Donaldson, L.; Coles, B. L. K.; Morshead, C. M.; Van Der Kooy, D.; Shoichet, M. S. A Hyaluronan-Based Injectable Hydrogel Improves the Survival and Integration of Stem Cell Progeny Following Transplantation. *Stem Cell Reports* **2015**, *4*, 1031–1045.
- (602) Jiang, F.; Tang, Z.; Zhang, Y.; Ju, Y.; Gao, H.; Sun, N.; Liu, F.; Gu, P.; Zhang, W. Enhanced Proliferation and Differentiation of Retinal Progenitor Cells through a Self-Healing Injectable Hydrogel. *Biomater. Sci.* **2019**, *7*, 2335–2347.
- (603) Shin, E. Y.; Park, J. H.; Shin, M. E.; Song, J. E.; Thangavelu, M.; Carlomagno, C.; Motta, A.; Migliaresi, C.; Khang, G. Injectable Taurine-Loaded Alginate Hydrogels for Retinal Pigment Epithelium (RPE) Regeneration. *Mater. Sci. Eng., C* **2019**, *103*, 109787.
- (604) Groll, J.; Burdick, J. A.; Cho, D.-W.; Derby, B.; Gelinsky, M.; Heilshorn, S. C.; Jüngst, T.; Malda, J.; Mironov, V. A.; Nakayama, K.; Ovsianikov, A.; Sun, W.; Takeuchi, S.; Yoo, J. J.; Woodfield, T. B. F. A Definition of Bioinks and Their Distinction from Biomaterial Inks. *Biofabrication* **2019**, *11*, 013001.
- (605) Schaffner, M.; Rühls, P. A.; Coulter, F.; Kilcher, S.; Studart, A. R. 3D Printing of Bacteria into Functional Complex Materials. *Sci. Adv.* **2017**, *3*, No. eaao6804.
- (606) Wu, W.; DeConinck, A.; Lewis, J. A. Omnidirectional Printing of 3D Microvascular Networks. *Adv. Mater.* **2011**, *23*, H178–H183.
- (607) Stanton, M. M.; Samitier, J.; Sánchez, S. Bioprinting of 3D Hydrogels. *Lab Chip* **2015**, *15*, 3111–3115.
- (608) Jang, T.; Jung, H.; Pan, H. M.; Han, W. T.; Chen, S.; Song, J. 3D Printing of Hydrogel Composite Systems: Recent Advances in Technology for Tissue Engineering. *Int. J. Bioprint.* **2018**, *4*, 126.
- (609) Daly, A. C.; Prendergast, M. E.; Hughes, A. J.; Burdick, J. A. Bioprinting for the Biologist. *Cell* **2021**, *184*, 18–32.
- (610) Zhang, Y. S.; Haghighashtiani, G.; Hübscher, T.; Kelly, D. J.; Lee, J. M.; Lutolf, M.; McAlpine, M. C.; Yeong, W. Y.; Zenobi-Wong, M.; Malda, J. 3D Extrusion Bioprinting. *Nat. Rev. Methods Prim.* **2021**, *1*, 75.
- (611) Kirchmayer, D. M.; Gorkin, R.; In Het Panhuis, M. An Overview of the Suitability of Hydrogel-Forming Polymers for Extrusion-Based 3D-Printing. *J. Mater. Chem. B* **2015**, *3*, 4105–4117.
- (612) Ouyang, L.; Yao, R.; Zhao, Y.; Sun, W. Effect of Bioink Properties on Printability and Cell Viability for 3D Bioplotting of Embryonic Stem Cells. *Biofabrication* **2016**, *8*, 035020.
- (613) Soltan, N.; Ning, L.; Mohabattpour, F.; Papagerakis, P.; Chen, X. Printability and Cell Viability in Bioprinting Alginate Dialdehyde-Gelatin Scaffolds. *ACS Biomater. Sci. Eng.* **2019**, *5*, 2976–2987.
- (614) Jessop, Z. M.; Al-Sabah, A.; Gao, N.; Kyle, S.; Thomas, B.; Badiei, N.; Hawkins, K.; Whitaker, I. S. Printability of Pulp Derived Crystal, Fibril and Blend Nanocellulose-Alginate Bioinks for Extrusion 3D Bioprinting. *Biofabrication* **2019**, *11*, 045006.
- (615) Nolan, M. C.; Fuentes Caparrós, A. M.; Dietrich, B.; Barrow, M.; Cross, E. R.; Bleuel, M.; King, S. M.; Adams, D. J. Optimising Low Molecular Weight Hydrogels for Automated 3D Printing. *Soft Matter* **2017**, *13*, 8426–8432.
- (616) Yang, F.; Guo, C.; Zhang, M.; Bhandari, B.; Liu, Y. Improving 3D Printing Process of Lemon Juice Gel Based on Fluid Flow Numerical Simulation. *LWT* **2019**, *102*, 89–99.
- (617) Yi, H.-G.; Lee, H.; Cho, D.-W. 3D Printing of Organs-On-Chips. *Bioengineering* **2017**, *4*, 10.
- (618) Ning, L.; Guillemot, A.; Zhao, J.; Kipourous, G.; Chen, X. Influence of Flow Behavior of Alginate-Cell Suspensions on Cell Viability and Proliferation. *Tissue Eng. Part C Methods* **2016**, *22*, 652–662.
- (619) Rutz, A. L.; Lewis, P. L.; Shah, R. N. Toward Next-Generation Bioinks: Tuning Material Properties Pre- and Post-Printing to Optimize Cell Viability. *MRS Bull.* **2017**, *42*, S63–S70.
- (620) Zhang, B.; Li, S.; Hingorani, H.; Serjouei, A.; Larush, L.; Pawar, A. A.; Goh, W. H.; Sakhaei, A. H.; Hashimoto, M.; Kowsari, K.; Magdassi, S.; Ge, Q. Highly Stretchable Hydrogels for UV Curing Based High-Resolution Multimaterial 3D Printing. *J. Mater. Chem. B* **2018**, *6*, 3246–3253.
- (621) Sodupe-Ortega, E.; Sanz-Garcia, A.; Pernia-Espinoza, A.; Escobedo-Lucea, C. Accurate Calibration in Multi-Material 3D Bioprinting for Tissue Engineering. *Materials (Basel)* **2018**, *11*, 1402.
- (622) Nadernezhad, A.; Khani, N.; Skvortsov, G. A.; Toprakhisar, B.; Bakirci, E.; Menciloglu, Y.; Unal, S.; Koc, B. Multifunctional 3D Printing of Heterogeneous Hydrogel Structures. *Sci. Rep.* **2016**, *6*, 33178.
- (623) Ruiz-Cantu, L.; Gleadall, A.; Faris, C.; Segal, J.; Shakesheff, K.; Yang, J. Multi-Material 3D Bioprinting of Porous Constructs for Cartilage Regeneration. *Mater. Sci. Eng., C* **2020**, *109*, 110578.
- (624) Tavafoghi, M.; Darabi, M. A.; Mahmoodi, M.; Tutar, R.; Xu, C.; Mirjafari, A.; Billi, F.; Swieszkowski, W.; Nasrollahi, F.; Ahadian, S.; Hosseini, V.; Khademhosseini, A.; Ashammakhi, N. Multimaterial Bioprinting and Combination of Processing Techniques towards the Fabrication of Biomimetic Tissues and Organs. *Biofabrication* **2021**, *13*, 042002.
- (625) Hamid, O. A.; Eltaher, H. M.; Sottile, V.; Yang, J. 3D Bioprinting of a Stem Cell-Laden, Multi-Material Tubular Composite: An Approach for Spinal Cord Repair. *Mater. Sci. Eng., C* **2021**, *120*, 111707.
- (626) Hockaday, L. A.; Kang, K. H.; Colangelo, N. W.; Cheung, P. Y. C.; Duan, B.; Malone, E.; Wu, J.; Girardi, L. N.; Bonassar, L. J.; Lipson, H.; Chu, C. C.; Butcher, J. T. Rapid 3D Printing of Anatomically Accurate and Mechanically Heterogeneous Aortic Valve Hydrogel Scaffolds. *Biofabrication* **2012**, *4*, 035005.
- (627) Rutz, A. L.; Hyland, K. E.; Jakus, A. E.; Burghardt, W. R.; Shah, R. N. A Multimaterial Bioink Method for 3D Printing Tunable, Cell-Compatible Hydrogels. *Adv. Mater.* **2015**, *27*, 1607–1614.
- (628) Jung, J. W.; Lee, J.-S.; Cho, D.-W. Computer-Aided Multiple-Head 3D Printing System for Printing of Heterogeneous Organ/Tissue Constructs. *Sci. Rep.* **2016**, *6*, 21685.

- (629) Bakarich, S. E.; Gorkin, R.; Gately, R.; Naficy, S.; in het Panhuis, M.; Spinks, G. M. 3D Printing of Tough Hydrogel Composites with Spatially Varying Materials Properties. *Addit. Manuf.* **2017**, *14*, 24–30.
- (630) Tarafder, S.; Koch, A.; Jun, Y.; Chou, C.; Awadallah, M. R.; Lee, C. H. Micro-Precise Spatiotemporal Delivery System Embedded in 3D Printing for Complex Tissue Regeneration. *Biofabrication* **2016**, *8*, 025003.
- (631) Bittner, S. M.; Guo, J. L.; Mikos, A. G. Spatiotemporal Control of Growth Factors in Three-Dimensional Printed Scaffolds. *Bioprinting* **2018**, *12*, No. e00032.
- (632) Pati, F.; Shim, J. H.; Lee, J. S.; Cho, D. W. 3D Printing of Cell-Laden Constructs for Heterogeneous Tissue Regeneration. *Manuf. Lett.* **2013**, *1*, 49–53.
- (633) Kolesky, D. B.; Truby, R. L.; Gladman, A. S.; Busbee, T. A.; Homan, K. A.; Lewis, J. A. 3D Bioprinting of Vascularized, Heterogeneous Cell-Laden Tissue Constructs. *Adv. Mater.* **2014**, *26*, 3124–3130.
- (634) Freeman, F. E.; Pitacco, P.; van Dommelen, L. H. A.; Nulty, J.; Browe, D. C.; Shin, J.-Y.; Alsberg, E.; Kelly, D. J. 3D Bioprinting Spatiotemporally Defined Patterns of Growth Factors to Tightly Control Tissue Regeneration. *Sci. Adv.* **2020**, *6*, eabbb5093.
- (635) Kant, R. J.; Coulombe, K. L. K. Integrated Approaches to Spatiotemporally Directing Angiogenesis in Host and Engineered Tissues. *Acta Biomater.* **2018**, *69*, 42–62.
- (636) Hinton, T. J.; Jallerat, Q.; Palchesko, R. N.; Park, J. H.; Grodzicki, M. S.; Shue, H. J.; Ramadan, M. H.; Hudson, A. R.; Feinberg, A. W. Three-Dimensional Printing of Complex Biological Structures by Freeform Reversible Embedding of Suspended Hydrogels. *Sci. Adv.* **2015**, *1*, No. e1500758.
- (637) Bhattacharjee, T.; Zehnder, S. M.; Rowe, K. G.; Jain, S.; Nixon, R. M.; Sawyer, W. G.; Angelini, T. E. Writing in the Granular Gel Medium. *Sci. Adv.* **2015**, *1*, No. e1500655.
- (638) Patrício, S. G.; Sousa, L. R.; Correia, T. R.; Gaspar, V. M.; Pires, L. S.; Luís, J. L.; Oliveira, J. M.; Mano, J. F. Freeform 3D Printing Using a Continuous Viscoelastic Supporting Matrix. *Biofabrication* **2020**, *12*, 035017.
- (639) Noor, N.; Shapira, A.; Edri, R.; Gal, I.; Wertheim, L.; Dvir, T. 3D Printing of Personalized Thick and Perfusable Cardiac Patches and Hearts. *Adv. Sci.* **2019**, *6*, 1900344.
- (640) Sousa, C. F. V.; Saraiva, C. A.; Correia, T. R.; Pesqueira, T.; Patrício, S. G.; Rial-Hermida, M. I.; Borges, J.; Mano, J. F. Bioinstructive Layer-by-Layer-Coated Customizable 3D Printed Perfusable Microchannels Embedded in Photocrosslinkable Hydrogels for Vascular Tissue Engineering. *Biomolecules* **2021**, *11*, 863.
- (641) Vyas, C.; Pereira, R.; Huang, B.; Liu, F.; Wang, W.; Bartolo, P. Engineering the Vasculature with Additive Manufacturing. *Curr. Opin. Biomed. Eng.* **2017**, *2*, 1–13.
- (642) Suntornnond, R.; Tan, E. Y. S.; An, J.; Chua, C. K. A Highly Printable and Biocompatible Hydrogel Composite for Direct Printing of Soft and Perfusable Vasculature-like Structures. *Sci. Rep.* **2017**, *7*, 16902.
- (643) Liu, S.; Hu, Q.; Shen, Z.; Krishnan, S.; Zhang, H.; Ramalingam, M. 3D Printing of Self-standing and Vascular Supportive Multimaterial Hydrogel Structures for Organ Engineering. *Biotechnol. Bioeng.* **2022**, *119*, 118–133.
- (644) Kinstlinger, I. S.; Miller, J. S. 3D-Printed Fluidic Networks as Vasculature for Engineered Tissue. *Lab Chip* **2016**, *16*, 2025–2043.
- (645) Lei, D.; Yang, Y.; Liu, Z.; Yang, B.; Gong, W.; Chen, S.; Wang, S.; Sun, L.; Song, B.; Xuan, H.; Mo, X.; Sun, B.; Li, S.; Yang, Q.; Huang, S.; Chen, S.; Ma, Y.; Liu, W.; He, C.; Zhu, B.; Jeffries, E. M.; Qing, F. L.; Ye, X.; Zhao, Q.; You, Z. 3D Printing of Biomimetic Vasculature for Tissue Regeneration. *Mater. Horizons* **2019**, *6*, 1197–1206.
- (646) Guzzi, E. A.; Bovone, G.; Tibbitt, M. W. Universal Nanocarrier Ink Platform for Biomaterials Additive Manufacturing. *Small* **2019**, *15*, 1905421.
- (647) Kinstlinger, I. S.; Saxton, S. H.; Calderon, G. A.; Ruiz, K. V.; Yalacki, D. R.; Deme, P. R.; Rosenkrantz, J. E.; Louis-Rosenberg, J. D.; Johansson, F.; Janson, K. D.; Sazer, D. W.; Panchavati, S. S.; Bissig, K. D.; Stevens, K. R.; Miller, J. S. Generation of Model Tissues with Dendritic Vascular Networks via Sacrificial Laser-Sintered Carbohydrate Templates. *Nat. Biomed. Eng.* **2020**, *4*, 916–932.
- (648) Greenwood, T. E.; Hatch, S. E.; Colton, M. B.; Thomson, S. L. 3D Printing Low-Stiffness Silicone within a Curable Support Matrix. *Addit. Manuf.* **2021**, *37*, 101681.
- (649) Hua, W.; Mitchell, K.; Raymond, L.; Godina, B.; Zhao, D.; Zhou, W.; Jin, Y. Fluid Bath-Assisted 3D Printing for Biomedical Applications: From Pre- to Postprinting Stages. *ACS Biomater. Sci. Eng.* **2021**, *7*, 4736–4756.
- (650) Grosskopf, A. K.; Truby, R. L.; Kim, H.; Perazzo, A.; Lewis, J. A.; Stone, H. A. Viscoplastic Matrix Materials for Embedded 3D Printing. *ACS Appl. Mater. Interfaces* **2018**, *10*, 23353–23361.
- (651) Cooke, M. E.; Rosenzweig, D. H. The Rheology of Direct and Suspended Extrusion Bioprinting. *APL Bioeng.* **2021**, *5*, 011502.
- (652) Prendergast, M. E.; Burdick, J. A. Computational Modeling and Experimental Characterization of Extrusion Printing into Suspension Baths. *Adv. Healthc. Mater.* **2022**, *11*, 2101679.
- (653) Jakab, K.; Neagu, A.; Mironov, V.; Markwald, R. R.; Forgacs, G. Engineering Biological Structures of Prescribed Shape Using Self-Assembling Multicellular Systems. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 2864–2869.
- (654) Daly, A. C.; Davidson, M. D.; Burdick, J. A. 3D Bioprinting of High Cell-Density Heterogeneous Tissue Models through Spheroid Fusion within Self-Healing Hydrogels. *Nat. Commun.* **2021**, *12*, 753.
- (655) Ma, X.; Qu, X.; Zhu, W.; Li, Y. S.; Yuan, S.; Zhang, H.; Liu, J.; Wang, P.; Lai, C. S. E.; Zanella, F.; Feng, G. S.; Sheikh, F.; Chien, S.; Chen, S. Deterministically Patterned Biomimetic Human iPSC-Derived Hepatic Model via Rapid 3D Bioprinting. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, 2206–2211.
- (656) Ashammakhi, N.; Ahadian, S.; Pountos, I.; Hu, S.-K.; Tellisi, N.; Bandaru, P.; Ostrovidov, S.; Dokmeci, M. R.; Khademhosseini, A. In Situ Three-Dimensional Printing for Reparative and Regenerative Therapy. *Biomed. Microdevices* **2019**, *21*, 42.
- (657) Urciuolo, A.; Poli, I.; Brandolino, L.; Raffa, P.; Scattolini, V.; Laterza, C.; Giobbe, G. G.; Zambaiti, E.; Selmin, G.; Magnussen, M.; Brigo, L.; De Coppi, P.; Salmaso, S.; Giomo, M.; Elvassore, N. Intravital Three-Dimensional Bioprinting. *Nat. Biomed. Eng.* **2020**, *4*, 901–915.
- (658) Tibbitt, M. W. Bioprinting within Live Animals. *Nat. Biomed. Eng.* **2020**, *4*, 851–852.