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Nanoparticle–hydrogel superstructures for biomedical applications

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Abstract

The incorporation of nanoparticles into hydrogels yields novel superstructures that have become increasingly popular in biomedical research. Each component of these nanoparticle–hydrogel superstructures can be easily modified, resulting in platforms that are highly tunable and inherently multifunctional. The advantages of the nanoparticle and hydrogel constituents can be synergistically combined, enabling these superstructures to excel in scenarios where employing each component separately may have suboptimal outcomes. In this review, the synthesis and fabrication of different nanoparticle–hydrogel superstructures are discussed, followed by an overview of their use in a range of applications, including drug delivery, detoxification, immune modulation, and tissue engineering. Overall, these platforms hold significant clinical potential, and it is envisioned that future development along these lines will lead to unique solutions for addressing areas of pressing medical need.

Graphical Abstract

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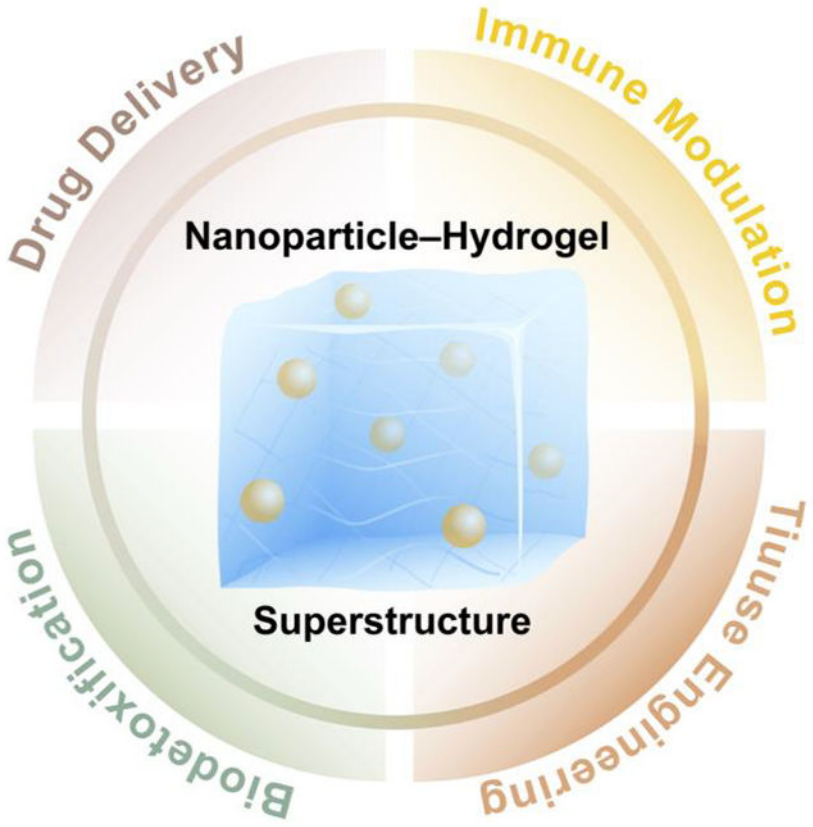
Author Contributions:

R.H.F. and L.Z. design the structure of the manuscript. Y.J., N.K., J.H., R.H.F., and L.Z. write the manuscript together.



Keywords

nanomedicine; nanoparticle–hydrogel hybrid; drug delivery; detoxification; immune modulation; tissue engineering

1. Introduction

Over the past several decades, nanotechnology has enabled new ways of addressing challenges in various fields. The ability to custom tailor nanomaterials that can interact in different ways with biological systems is particularly attractive in the biomedical sciences, where nanotechnology platforms hold significant potential for improving how we diagnose, prevent, and treat human disease [1–3]. Nanoparticle–hydrogel superstructures represent an emerging class of nanomaterial and are generally composed of hydrated, crosslinked polymeric networks incorporated with nanoparticles. Significant advances have been made in both nanoparticle and hydrogel platforms in recent years [4–8], and combining the advantages of these individual technologies into a single platform has yielded hybrid superstructures that can be applied towards drug delivery, immune modulation, detoxification, and tissue engineering.

Nanoparticles have excelled as drug delivery vehicles that can encapsulate one or multiple payloads, including small molecules, peptides, proteins, and nucleic acids, among others [9–13]. Nanoformulations can be used to overcome some of the inherent limitations of

conventional drugs by improving drug localization, enhancing drug solubility, and allowing for controlled release of encapsulated payloads [14–16]. The unique characteristics of nanocarriers can be attributed to their size, shape, material composition, and surface properties. For example, their small size has been widely utilized for cancer drug delivery, as nanoparticles can passively extravasate through leaky vasculature via the enhanced permeation and retention effect, leading to preferential tumor accumulation [17]. Active targeted delivery systems can also be designed by functionalizing nanoparticles with a variety of moieties such as antibodies, aptamers, peptides, small molecules, and cell membrane [18, 19]. *In vitro* and *in vivo* studies have demonstrated that actively targeted nanoparticles can exhibit significantly higher activity when compared to conventional drugs, thus improving treatment efficacy and safety [20]. Besides drug delivery, nanotechnology-based immune modulation has recently been garnering increased attention [21–23]. As an immunotherapy, nanoparticles offer many benefits, including the ability to deliver antigen and adjuvant payloads together, enhanced lymphatic transport, and targeted delivery to the appropriate immune cell subsets [24, 25]. More recently, biomimetic nanotechnology has become a major topic of study, where nanoscale platforms are designed by taking inspiration from nature [26–28]. This approach has yielded exciting new platforms that have excelled in a number of areas, including biodetoxification, antibacterial and anticancer vaccination, and sensing [29–32]. Despite considerable advancement in nanoparticle technology, there are still limitations that need to be addressed. For example, unwanted systemic exposure can lead to toxicity in certain organs [33], thus compromising safety. Even when locally administered, nanoparticles are subject to bulk drainage and cell-mediated transport away from the injection site. Drug-loaded nanoparticles may also suffer from premature release of their payloads depending on nanomaterial properties and exposure to the local tissue microenvironment [34–36].

Hydrogels are three-dimensional (3D) networks of polymers that have the capacity to absorb and retain large quantities of water [37–41]. The high amounts of water in hydrogels allow for excellent biocompatibility, physical similarities with tissues, and the encapsulation of hydrophilic drugs [42]. Crosslinking of the polymer network allows for tunability of the hydrogel's mechanical properties [43, 44], as well as offering the ability to protect and control the release of therapeutics [42]. These qualities have made hydrogels suitable for a variety of applications, including immune modulation, drug delivery, and tissue engineering [38, 39]. A hydrogel's properties can be highly dependent on its polymer composition, and this can also determine the application for which it is best suited [45]. For example, chitosan, a naturally derived cationic polymer, can be degraded by human enzymes into a product that mimics the extracellular matrix, making it a widely used component of hydrogel formulations [46]. Synthetic hydrogels based on polyethylene glycol (PEG) display desirable properties such as biocompatibility and low immunogenicity [47]. The addition of functional groups to PEG allows for the mechanical strength and degradability of the resulting hydrogel to be varied depending on the desired application [48]. There are also examples of hydrogels made from natural components that have been synthetically modified to enable crosslinking, as is the case with gelatin (GelMA) [49]. Despite their many benefits, some hydrogel platforms still have a number of limitations that can limit their utility for therapeutic applications. Pure hydrogels oftentimes have limited mechanical performance,

leading to suboptimal strength, compressibility, and elasticity characteristics [50]. Additionally, it can be difficult to achieve high loading and sustained release of certain drug payloads due to the inherently hydrophilic nature of hydrogels [51, 52].

Various nanoparticle–hydrogel superstructures, which combine both nanoparticles and hydrogels into a signal platform, can be fabricated by altering each component (Fig. 1). For drug delivery applications, variations in the nanoparticle component can be used to modify release characteristics from the hydrogel [53, 54]. Encapsulation of drug-loaded nanoparticles within a hydrogel matrix is also a strategy that has been used to prevent rapid drug release [55]. For localized administration to an affected area, nanoparticle–hydrogels provide a promising approach for the delivery of both hydrophobic and hydrophilic payloads [56]. These platforms can also be designed with components that enable selective release under certain stimuli, such as chitosan/alginate hydrogels that degrade in response to pH conditions or metallic nanoparticles that generate heat in response to near-infrared (NIR) irradiation [57, 58]. Moving away from drug delivery, nanoparticle–hydrogels have been used as detoxification platforms, and the inclusion of cell membrane-coated nanoparticles has proven highly useful for this purpose [59, 60]. For tissue engineering applications, nanocomposite hydrogels can offer improved mechanical strength over hydrogels alone and enhanced payload retention over nanoparticles alone [50]. Other variations in either the nanoparticle or hydrogel component of these superstructures have yielded platforms that can be used for immune modulation, allowing for improved efficacy [61–63]. Overall, nanoparticle–hydrogel systems have the potential to greatly improve upon current solutions for addressing human disease in a number of different areas.

2. Synthesis of Nanoparticle–Hydrogel Superstructures

2.1 Physical Crosslinking

Physically crosslinked hydrogels are formed based on the noncovalent interactions of the components within the structure [64, 65]. Overall, physical crosslinking does not require the use of initiators, which may provide benefits such as lower drug degradation during synthesis and reduced toxicity. For pure hydrogel systems, polymers can interact with themselves or other polymers to create a crosslinked structure. Similarly, nanoparticle–hydrogels can be formed through the interaction between nanoparticles and polymer chains. Furthermore, nanoparticles have been engineered to interact with each other to form gel-like structures. There has been a trend towards applying these platforms in stimuli-responsive applications, where therapeutics can be released on-demand based on an external trigger [66]. In the future, it will be necessary to identify methods for further improving the stability of physically crosslinked platforms while preserving their ability to be facilely administered for *in vivo* applications.

Hydrogels formed due to the physical interactions between polymers can also provide a useful scaffold into which nanoparticles are subsequently loaded. In such a scenario, the nanoparticles do not play a role in maintaining structural integrity, but are leveraged for their drug encapsulation and release characteristics to improve the therapeutic effect of the overall platform. In a simple yet versatile delivery platform, a hydrogel made of poly(vinyl alcohol) was physically crosslinked through several freeze-thaw cycles [67]. This process caused the

polymers to crystallize into 3D structures [68]. After this synthesis, insulin-loaded nanoparticles were embedded into the structure, improving the release kinetics of the therapeutic compared to nanoparticles alone.

DNA-based hydrogels are formed due to physical crosslinking and have gained more popularity in recent years for biomedical applications due to their tunable mechanical properties, responsiveness to outside stimuli, and facile functionalization [69]. These DNA biopolymers can be easily manipulated by confining enzymes and ligases at specific sites within the structure, allowing for fine control over hydrogel degradation and the release kinetics of therapeutic payloads. The incorporation of different functional elements into DNA hydrogels can facilitate their response to external stimuli [69, 70], and this has been leveraged to improve gene and drug delivery. A self-assembling DNA-based hydrogel was synthesized through the complementary binding between multi-armed DNA monomer units with three sticky ends and a DNA-based linker with two sticky ends [71]. The platform was engineered to respond to glutathione, recognize specific targets through aptamer functionalization, and deliver a therapeutic gene payload. In a similar approach, multi-armed DNA building blocks with specific binding sequences were used to crosslink human serum albumin conjugated to both single-stranded DNA and PEG to form a 3D hydrogel [72]. Through interactions with naturally occurring enzymes such as DNase and trypsin, this hydrogel could degrade and release loaded therapeutics into the surrounding environment without introducing any toxic byproducts. To respond to light stimuli, a DNA hydrogel was incorporated with gold nanorods, and this platform was used for the delivery of doxorubicin [73]. The DNA-based hydrogel proved to be an effective system for the stable incorporation of positively charged gold nanorods due to the highly negative charge of the DNA backbone. With exposure to light, the gold nanorods induced photothermal melting of the DNA components and the hydrogel released doxorubicin into the surrounding environment.

Nanoparticle–hydrogels can be formed solely based on the interaction between nanoparticles and polymer chains. Like other physically crosslinked structures, this synthesis technique does not require the use of additional crosslinking agents, which are often toxic [54]. With the diffusion, degradation, and clearance of the nanoparticles from the hydrogel, the overall structure begins to degrade and clear from the body. In one example, a hydrogel was fabricated based on the interactions between hydrophobically modified cellulose (HPMC) derivatives and PEG-poly(lactic acid) nanoparticles, both of which are biocompatible and biodegradable [53]. In order to prepare these gels, the HPMC polymers were dissolved in water and mixed by vortexing with the nanoparticles to facilitate noncovalent, transient, and reversible interactions driven by hydrophobic forces that are labile under applied stress. Using polystyrene nanoparticles as a basis to characterize the properties of the gel, it was seen that modifying the properties of both the HPMC polymer and the nanoparticles affected the physical characteristics of combined structure. Nanoparticle size played a significant role in the formation of the gel, as nanoparticles greater than 100 nm in diameter failed to produce gels, while those smaller than 100 nm formed robust gels. It was also seen that an increase in diameter caused a corresponding decrease in elasticity, storage modulus, and loss modulus. The number of nanoparticles incorporated into hydrogels also affected mechanical properties of the structure, with a decrease in the number of particles causing fewer polymer–nanoparticle interactions and thus a decreased storage modulus. In terms of

polymer modifications, gels fabricated from C12-modified HPMC were seen to be three times stronger than gels formed from C6-modified, adamantyl-modified, and unmodified versions of the polymer. C12-modified polymer-based gels also showed a wide processing regime and shear-thinning behavior. The hydrogel scaffold, without nanoparticles, was broken down by macrophages within one week, indicating that it possessed a favorable biocompatibility profile.

Colloidal gels depend on the interactions between individual nanoparticles to provide crosslinking [74]. For this approach, charge-based attraction has been used to retain the structure of the gel. In one particular example, negatively charged red blood cell membrane-coated nanoparticles (RBC-NPs) were combined with positively charged chitosan-functionalized poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles (Chi-NPs) [59]. With mixing, these two nanoparticles formed a cohesive colloidal network via electrostatic forces. At higher RBC-NP concentrations, the hydrogels displayed weak shear-shinning properties and were too viscous for injection. Hydrogels made up of 30% or 50% RBC-NPs displayed high viscosity and strong shear-shinning properties, making them suitable for injectable applications. By forming a strong and cohesive interparticle network, the gels managed to maintain their shape for several days. In another approach, thermally responsive colloidal hydrogels were developed based on a network of monodispersed nanoparticles synthesized of polyacrylic acid (PAA) and poly-isopropylacrylamide (PNIPAM) [75]. The mixture of nanoparticles was found to abruptly form a gel at 33 °C due to the temperature-dependent physical interactions of PNIPAM. The PAA within each nanoparticle contributed ionic charges that helped to prevent the collapse of the gel. By building a hydrogel superstructure that is comprised exclusively of nanoparticles, exceptionally high loading ratios can be achieved, which could benefit a number of applications, including drug delivery and biodetoxification.

2.2 Covalent Crosslinking

Hydrogels can also be synthesized using chemical crosslinkers that promote gelation during the polymerization of precursor building blocks [64]. Chemically induced crosslinking can be initiated by mechanisms such as free-radical polymerization, enzymatic activity, Michael-type addition, and Schiff base formation, all of which provide certain advantages. Compared to physically crosslinked hydrogels, those based on chemical crosslinking oftentimes exhibit improved *in vivo* stability, enhanced mechanical properties, and tunable degradation behavior based on crosslinker concentration. Like with physically crosslinked platforms, there has been an increasing emphasis on environmentally sensitive crosslinking to provide additional layers of control for drug release [66]. In the future, it will be necessary to further improve synthesis techniques to minimize the unwanted degradation of drug payloads and to explore methods for improving the ease of administration for downstream clinical translation [76].

Biological gels based on natural components have also been leveraged for the formation of nanoparticle-incorporated superstructures. Commonly seen as a product of enzymatic crosslinking, such hydrogels allow for strong covalent bonding, rapid gelation under physiological conditions, and control over the kinetics of gel formation through variations in

enzyme concentration [65]. In one such scenario, the interaction between thrombin and fibrinogen has been leveraged for a variety of applications, including wound healing and tissue engineering [77]. This enzymatically crosslinked gel forms through the interaction of fibrinogen, a glycoprotein complex, with Factor XIII, a transglutaminase. First, the protease thrombin releases the end peptides of fibrinogen to produce fibrin monomers, which then coalesce and are eventually crosslinked by Factor XIII [78]. This mechanism has been adapted for *in situ* formation by spraying two components, fibrinogen and thrombin together over a surgical site [62]. In this platform, antibody-loaded $CaCO_3$ nanoparticles were easily incorporated into the hydrogel by including them within either of the precursor solutions. Due to the inherent pH-responsiveness of the $CaCO_3$ nanoparticles, the payload exhibited more release at a slightly acidic pH 6.5 compared with a neutral pH 7.4. When administered *in vivo*, the nanoparticle–hydrogel formulation enabled enhanced payload retention at the site of administration, whereas free antibody and nanoparticle-loaded antibody were more rapidly cleared. Besides application by spraying, fibrin glues have been developed that can be administered by a dual-syringe system [79]. In this case, fibrin and Factor XIII were loaded into one syringe, while thrombin and protein-loaded chitosan nanoparticles were loaded into the other. The two were then placed into a delivery system containing a common plunger where both solutions were passed through a common outlet for gel formation. It was demonstrated that the protein payload released from the gel in a more sustained manner compared with protein loaded inside either a fibrin gel or chitosan nanoparticles only. These characteristics could also be fine-tuned by adjusting the concentrations of the thrombin and fibrinogen precursors.

The use of methacrylated precursors is one of the most common ways of achieving chemical crosslinking. The carbon double bonds enable these reagents to undergo free-radical polymerization, leading to the formation of hydrogels [80]. Free-radical polymerization allows for facile and rapid synthesis, yielding heterogeneous network structures [81]. In one such scenario, dextran, a polysaccharide, was functionalized with glycidyl methacrylate (GMA) [82]. This dextran–GMA complex rapidly polymerized in the aqueous phase of hydroxyapatite-stabilized oil/water emulsions to form a porous hydrogel, which could potentially be leveraged for a variety of applications. Methacrylate can also be used in conjunction with other polymers to form stimuli-responsive hydrogels. For example, a hydrogel of poly(2-hydroxyethyl methacrylate) fabricated using a disulfide group-containing crosslinker was shown to degrade in response to reducing agents, resulting in the slow release of loaded therapeutics [83]. Against colon cancer, poly(methyl methacrylate) (PMMA) nanoparticles were incorporated into a hydrophilic PMMA structure grafted with PEG, forming a pH-responsive hydrogel [84]. In order to form this hydrogel, the two precursors, methacrylic acid and PEG monomethyl ether monomethacrylate, were combined with the crosslinker tetraethylene glycol dimethacrylate and exposed to ultraviolet (UV) light, thus initiating free-radical polymerization. Incorporated prior to gelation, the PMMA nanoparticles helped the hydrogel to reduce water uptake and slowed drug release in low pH conditions due to increased hydrophobicity.

PEG-modified constructs have been leveraged in a number of different reaction types for the fabrication of hydrogel formulations. Commonly, PEG that has been modified with methacrylate functional groups is used in free-radical polymerization reactions [65]. In one

example of this usage scenario, ammonium persulfate and tetramethylethylenediamine (TEMED) were used as initiators for the polymerization of acrylamide in the presence of PEG dimethacrylate (PEGDMA) as a crosslinker [85]. The nanoparticle–hydrogel was formulated so that the particles could eventually migrate out of the gel to interact with the surrounding environment. It was demonstrated that the PEGDMA concentration played a significant role in determining the final properties of the system. By varying the concentration from 0.6% to 0.8%, the crosslinked solution turned from a free-flowing viscous fluid into a gel structure. This also had a major impact on the release kinetics of nanoparticles from the gel, which were greatly accelerated in the fluid formulation compared with the gel-like formulation. Rather than depending on spontaneous chemical crosslinking, hydrogels can also be designed to form only in the presence of an external stimulus. This allows for benefits in administration, as well as more controlled incorporation of nanoparticles within the hydrogel. In another example of a nanoparticle-containing acrylamide gel with PEGDMA as a crosslinker, lithium phenyl-2,4,6-trimethylbenzoylphosphinate was employed as a photoinitiator that was responsive to UV light [86]. It was shown that nanoparticle retention within the gel was greatly enhanced with increasing crosslinker concentrations. When a model antibiotic was loaded into the hydrogel via nanoparticle encapsulation, drug release was significantly prolonged compared with free drug incorporated into the gel alone. A methacrylated dopamine derivative was also included into the formulation to provide tissue adhesion properties. Many other responsive hydrogels, including those using light, pH, temperature, and shear stress as the stimulus, have been reported [87].

Multi-arm PEG constructs have been widely used for fabricating hydrogels, and various formulations have been developed for tissue engineering applications [88–90]. These constructs are frequently used in conjunction with simple and biocompatible chemistries such as Michael addition or Schiff base reactions. Hybrid systems formed from the mixture multi-arm PEG and modified hyaluronic acid have been reported, and the resulting hydrogels showed promise as injectable scaffolds for supporting stem cell growth [91]. Hydrogels synthesized by a Schiff base reaction possess the ability to uncouple and recouple among the linkages, thus creating a highly flexible and self-healing structure ideal for tissue engineering applications [65]. In another example, where polydopamine nanoparticles were used as a crosslinking agent, the functional groups on the particles were oxidized and then reacted with the thiol groups on 4-arm-PEG-SH to form a biocompatible hydrogel [54]. This crosslinking mechanism was facilitated through either a Schiff base reaction, as discussed above, or Michael addition, which can be carried out with favorable reaction rates and high specificity under mild reaction conditions [65]. Upon mixing the individual components, followed by a short incubation at room temperature, the resulting nanoparticle–hydrogel could be directly injected or molded into different shapes. It was confirmed that the PDA retained its photothermal capabilities after gelation, significantly raising the temperature of the surrounding solution when irradiated with NIR light. When a model drug was loaded into the system, there was minimal leakage of the payload over the course of 6 days in physiological media under normal conditions. In contrast, the drug could be quickly released while under irradiation.

Utilizing irradiation-induced crosslinking, a novel rapid 3D printing technique was developed for the high-resolution fabrication of hydrogels [92–94]. This microscale continuous optical printing (μCOP) technique is capable of constructing high-resolution hydrogels based on PEG diacrylate (PEGDA) and loaded with a variety of nanoparticles for different applications. The μCOP system modulates UV light to project the desired optical pattern onto a polymer solution, specifically crosslinking the light-exposed areas. Rapidly, a polymer scaffold can be built with high efficiency and resolution, which could prove useful for constructing molded hybrid structures to be used in applications such as tissue engineering and detoxification. Within this system, nanoparticles can easily be incorporated through surface modification or simple addition prior to UV light exposure. For example, acrylamide-modified polydiacetylene nanoparticles have been incorporated into a PEGDA hydrogel by this type of approach [92]. Piezoelectric polymers have also been fabricated by incorporating barium titanate nanoparticles into the photolabile polymer solution [93]. For this platform, to achieve enhanced piezoelectric coefficients, the nanoparticles were modified with photosensitive surface groups that enabled them to form covalent linkages with the polymer matrices. In a later work, 3D microfish hydrogels loaded with different types of nanoparticles were fabricated by alternating the nanoparticle component of the polymer solution and polymerizing the desired area of the structure [94]. 3D-printed microfish containing iron oxide or platinum nanoparticles in specific portions of the head or tail enabled propulsion in the presence of a magnetic field or hydrogen peroxide, respectively.

3. Biomedical Applications of Nanoparticle–Hydrogel Superstructures

One of the most notable advantages of nanoparticle–hydrogel platforms is their ability to promote the enhanced local delivery of therapeutic payloads. When administered into the body, both the hydrogel and nanoparticle components can be modulated to achieve controlled drug release, thus improving the bioavailability of the payload at the delivery site while minimizing systemic toxicity. In this section, we discuss the application of nanoparticle–hydrogels in a number of important biomedical areas, including drug delivery, detoxification, immune modulation, and tissue engineering, specifically focusing on the advantages of these hybrid systems (Table 1).

3.1 Drug Delivery

Both nanoparticle and hydrogel systems have been extensively investigated for drug delivery applications in the last several decades [1, 95]. Drug delivery refers to a method or process for transporting a pharmaceutical compound to attain its desired therapeutic effects [96]. Nanoparticle-based delivery can be used to improve the therapeutic efficacy of drugs by altering their pharmacokinetic and biodistribution profiles, and many nanoformulations have been successfully translated for clinical use [14, 97, 98]. The advantages of these platforms include the ability to enable targeted delivery, reduced toxicity, enhanced drug solubility, and tunable circulation half-life, among others [15, 99, 100]. There are many ways to tailor drug release kinetics, including by modulating nanoparticle composition, structure, and size [101]. Not only can the drug be released as a result of physical diffusion, but nanoparticles can also be engineered to be responsive to various stimuli [102]. Such systems have the

potential to further enhance the specificity of the encapsulated drug, leading to treatments that are more effective and safer [103]. Hydrogels also have unique characteristics that can be leveraged for drug delivery applications. They have a porous structure that can be modulated through the use of porogens, gas foaming, or freeze drying, as well as by adjusting the density of crosslinkers within the gel matrix [104]. Due to their porosity, it is possible to encapsulate drugs into hydrogels, and drug release generally occurs via diffusion of the payload through the gel network [52]. Hydrogel platforms can also be environmentally sensitive, where certain triggers are used to degrade the polymeric network of the gel, leading to on-demand drug release [42]. Moreover, many hydrogel platforms are considered to be biocompatible, making them highly attractive for use in biomedical applications [52].

More recently, therapeutic nanoparticles have been increasingly incorporated into hydrogels to form a single superstructure capable of enhanced drug delivery [105]. This concept centers around the creation of a hierarchical delivery system with multiple components, which are arranged in a manner that enables exceptional versatility that is difficult to achieve by either nanoparticles or hydrogels independently [56]. Conventional drug delivery systems often require high dosages or repeated administration to achieve a therapeutic effect, which is highly reliant on patient compliance and may result in side effects or toxicity [42, 106]. By combining the two systems of nanoparticles and hydrogels together, the resulting nanoparticle–hydrogel hybrids have drug release profiles that can be fine-tuned, making them particularly useful for localized applications that require prolonged exposure.

3.1.1 Controlled drug release—By encapsulating nanoparticles within hydrogel structures, it is possible to further enhance the stability of drug payloads, as well as to prevent their premature release. For example, porous silicon nanoparticles have been employed as biocompatible drug carriers with high loading capacities [107]; however, the utility of the platform can be limited by fast and uncontrollable drug release [108]. To address this challenge, porous silicon nanoparticles were conjugated with gold nanorods and encapsulated within a calcium alginate hydrogel shell that helped to prevent drug leakage, enabling the platform to exhibit controlled release characteristics [55]. In another example, drug-loaded metal-organic framework (MOF) nanoparticles were incorporated into acrylamide/DNA hydrogels (Fig. 2) [34]. For this platform, the crosslinking of polyacrylamide chains functionalized with DNA hairpin structures drove hydrogel formation. The hydrogel-coated MOF nanoparticles showed reduced leakage of a model drug, as well as enhanced drug loading efficiency compared to duplex DNA-capped MOF nanoparticles. Hydrogels have also been used to protect encapsulated biological compounds from degradation and elimination, promoting enhanced bioavailability [42]. It was previously demonstrated that the stability of small interfering RNA (siRNA) encapsulated into nanoparticles could be enhanced within a hydrogel scaffold, and release kinetics could be controlled by tuning the hydrogel degradation rate [36]. A later work demonstrated the development of a self-assembled nanoparticle–hydrogel that could be used to enhance the activity of microRNA [35]. The platform was fabricated by complexing an RNA triple-helix structure with positively charged dendrimer nanoparticles, which together could form an adhesive hydrogel scaffold after the addition of dextran aldehyde. The scaffolds adhered to

tumor tissue and were used to facilitate the local delivery of microRNA, resulting in significant tumor reduction after two weeks of treatment in a breast tumor xenograft model.

Hydrogel-based platforms excel at local drug delivery to tumors by providing elevated concentration of drug in the surrounding areas [52], and the inclusion of a nanoparticle component can further boost the utility of this therapeutic strategy. In one study, drug-loaded mesoporous silica nanoparticles coated around gold nanobipyramids were conjugated with azobenzene and α-cyclodextrin-functionalized hyaluronic acid (Fig. 3) [109]. For this platform, the photothermal transformation of the azobenzene into the trans isomer upon NIR irradiation of the gold acted as the trigger for hydrogel formation. Notably, the hyaluronic acid moiety, which can target the CD44 antigen overexpressed on cancer cells, aided in localizing the nanoparticle–hydrogel formation around tumor tissue. After gelation, the hydrogel network could eventually be degraded due to the upregulation of hyaluronidase in the surrounding tumor microenvironment, resulting in sustained drug release. In another example, cisplatin-loaded gelatin/poly(acrylic acid) nanoparticles were integrated into gelatin hydrogels and surgically implanted onto tumors [110]. In an *in vivo* biodistribution assay, it was shown that the nanoparticle-loaded hydrogels enabled a higher concentration and improved retention of cisplatin within the tumor, as well as lower drug accumulation in other organs, compared with intravenously injected nanoparticles.

Delivering therapeutics to the brain is challenging due to the blood-brain barrier and cerebrospinal fluid flow [111, 112]. To locally deliver DNA nanocomplexes for the treatment of post-surgery residual glioblastoma, a DNA nanocomplex-loaded GelMA scaffold for implantation was developedTo locally deliver DNA nanocomplexes for the treatment of post-surgery residual glioblastoma, a DNA nanocomplex-loaded GelMA scaffold for implantation was developed [113]. Fabricated by 3D printing, the implant could be shaped to match postoperative tumor cavities, which enabled localized release of the nanocomplexes to induce apoptosis of residual glioma cells. Nanoparticle–hydrogel drug delivery systems have also shown potential for use in other immune-privileged organs, including for glaucoma therapy. Due to precorneal tear clearance and the permi-selective corneal epithelium, glaucoma treatment through eye drops has limitations such as low bioavailability and short duration of activity [114]. To address this issue, it is necessary to develop treatments that can release drugs for an extended period of time to reduce dosing frequency [115]. Along these lines, a hybrid dendrimer hydrogel/PLGA nanoparticle platform was fabricated and shown to maintain significantly higher concentrations of a glaucoma medication in the aqueous humor and cornea compared to PLGA nanoparticles alone [116]. Fabricated by 3D printing, the implant could be shaped to match postoperative tumor cavities, which enabled localized release of the nanocomplexes to induce apoptosis of residual glioma cells. Nanoparticle–hydrogel drug delivery systems have also shown potential for use in other immune-privileged organs, including for glaucoma therapy. Due to precorneal tear clearance and the permi-selective corneal epithelium, glaucoma treatment through eye drops has limitations such as low bioavailability and short duration of activity [114]. To address this issue, it is necessary to develop treatments that can release drugs for an extended period of time to reduce dosing frequency [115]. Along these lines, a hybrid dendrimer hydrogel/PLGA nanoparticle platform was fabricated and shown to maintain

significantly higher concentrations of a glaucoma medication in the aqueous humor and cornea compared to PLGA nanoparticles alone [116].

The localized delivery of antibacterial agents using hydrogels has shown potential in reducing bacterial infection and improving would healing [117]. Silver nanoparticles are well-known for their activity against multidrug-resistant bacteria and have been explored extensively as antibacterial agents to prevent infection [118]. The fabrication of silver–hydrogel composites has been achieved by a variety of methods, including the reduction of silver nitrate by sodium borohydride, photolysis, or encapsulation into preformed hydrogel scaffolds [119–122]. Inspired by mussels that utilize catechol as an adhesive [123], an antibacterial silver-releasing covalent polymer hydrogel was fabricated [119]. The nanoparticle–hydrogel achieved sustained silver release for two weeks in physiological buffer and showed the ability to inhibit bacterial growth without affecting mammalian cell viability. In another study inspired by marine mussels, an adhesive nanoparticle–hydrogel hybrid system was again developed for localized antimicrobial drug delivery [86]. Ciprofloxacin, an antibiotic, was encapsulated into PLGA nanoparticles for controlled and sustained release. By integrating the mussel-inspired catechol into the hydrogel, the resulting platform exhibited enhanced tissue adhesion and was effective at locally delivering the antibiotic payload. The nanoparticle–hydrogel composite remained intact on a bacterial film, a mammalian cell monolayer, and mouse skin tissue. Under flow conditions, it demonstrated the ability to inhibit the formation of *Escherichia coli* films.

3.1.2 Stimuli-triggered release—Polymers that change their properties upon exposure to physical, chemical, and biological stimuli have attracted significant attention in the field of biomedical engineering [42, 95, 124]. Stimuli-responsive hydrogels can experience volume or phase transitions in responding to external and internal stimuli such as temperature, pH, electric field, magnetic field, light, and chemical triggers [125]. In hybrid systems, stimuli-responsive hydrogels are often used for on-demand drug delivery, and the incorporation of nanoparticles can enable more complex and tunable drug release kinetics. These properties can be highly useful for medical applications where off-target effects need to be minimized, and strategies employing chemical and biological stimulus to trigger release have been investigated [126]. One approach has been to take advantage of the pH-responsive property of chitosan/alginate hydrogels to enable degradation in the colon [57]. In order to treat inflammatory bowel disease, nanoparticles loaded with an anti-inflammatory tripeptide were encapsulated into the hydrogel structure. The nanoparticle–hydrogel, which was shown to break down in intestinal fluid at pH 5 or 6, reduced both intestinal inflammation and minimized weight loss in a mouse model of colitis. In colon cancer treatment, oral administration of chemotherapeutic drugs often results in limited efficacy due to the lack of specificity and various side effects [127]. To address these challenges, another multifunctional hybrid system based on chitosan/alginate hydrogels was developed (Fig. 4) [128]. A chemotherapeutic drug and siRNA were co-loaded into Fab'-functionalized nanoparticles targeting CD98, which is found to be upregulated during the progression of human colon cancer, and these nanoparticles were then encapsulated into the hydrogel. The pH-responsive property of the platform protected the nanoparticles during

transport through the gastrointestinal tract, enabling eventual delivery to the colonic lumen after oral administration.

Nanoparticles possess unique electronic, optical, and physicochemical properties that are different from bulk material [129]. For example, metallic nanoparticles such as silver and gold exhibit surface plasmon resonance [130]. The light absorption property of these nanoparticles are often employed in applications such as photothermal therapy, where the heat generated after irradiation can induce hyperthermia for cancer treatment [131, 132]. There are several examples of NIR-responsive nanoparticle–hydrogel systems that take advantage of this phenomenon to achieve control of tumor growth *in vivo* [54, 55, 133]. In one such hybrid system, PDA nanoparticles were used due to their photothermal effect and high drug loading capability (Fig. 5) [54]. Incorporation of PDA nanoparticles rendered hydrogels amenable to the photothermal effect for tumor ablation. Upon NIR irradiation, an anticancer drug loaded on the PDA nanoparticles via $\pi-\pi$ stacking could also be released in an on-demand manner. It was confirmed that, without irradiation, there was minimal drug leakage from the hydrogels. The photothermal properties of nanoparticles can also be employed to depolymerize specific types of hydrogels [133]. In one case, superparamagnetic iron oxide nanoparticles were able to trigger the release of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) through temperature-sensitive hydrogel dissolution. Taking advantage of this magnetic hyperthermia, the tumor temperatures could be significantly elevated in mice treated with the composite material. It was also demonstrated that TRAIL release could be controlled by the number of hyperthermia cycles.

3.2 Detoxification

Another application in which nanoparticle–hydrogel superstructures can be applied is biodetoxification, and these platforms have shown great promise in neutralizing biological toxins, particularly virulence factors secreted from bacteria. For these types of applications, the ability to confine the detoxification agent to a specific area can maximize its therapeutic effect, particularly in the case of local infections [134]. As such, the use of hydrogels, which excel at local delivery and exhibit prolonged retention, can be highly beneficial. Nanoparticles have also been investigated for their detoxification properties. In particular, RBC-NPs are part of a rising class of cell membrane-coated nanoparticle platforms that have become increasingly popular over the past decade [135]. These nanoparticles are fabricated by coating membrane purified from a source cell such as RBCs, platelets, white blood cells, cancer cells, or stem cells around a synthetic core. This represents a facile strategy for generating new nanoformulations with unique properties that would be difficult to replicate using existing strategies. Cell membrane-coated nanoparticles have demonstrated considerable utility for detoxification applications, where they act as decoys that bind and neutralize toxins based on their affinity to cell membrane [136].

A novel nanoparticle–hydrogel superstructure for detoxification leveraged RBC-NPs for antibacterial therapy (Fig. 6) [134]. For hydrogel formation, RBC-NPs were combined with acrylamide as a monomer, PEGDMA as a crosslinker, and TEMED and ammonium persulfate as the initiators. While free RBC-NPs generally show significant therapeutic effect against pore-forming toxins by irreversibly binding with and diverting the toxins away

from healthy cells, the particles are subject to diffusing away from injection sites, thus limiting their potency over time for local infections [137]. However, upon incorporation into a nanoparticle–hydrogel superstructure and subcutaneous administration, 80% of the RBC-NPs remained at the site of injection after 48 hours [134]. Using this platform to treat a mouse model of methicillin-resistant *Staphylococcus aureus* skin infection, the nanoparticle–hydrogel platform yielded significantly better efficacy compared to an empty hydrogel [134]. Colloidal gels utilize interactions between nanoparticle components to form a cohesive structure [59]. This concept has been applied to develop a superstructure comprised of negatively charged RBC-NPs and cationic Chi-NPs (Fig. 7) [59]. Similar to the previous example, the RBC-NP component was leveraged for its ability to neutralize secreted bacterial toxins, effectively hindering the progress of local infections. The Chi-NPs, with their positive charge, facilitated assembly of a cohesive network upon mixing with the negatively charged RBC-NPs. One of the advantages of this colloidal network is its shear-thinning properties, allowing for direct injection and recovery of gel-like properties afterwards.

Another commonly used hydrogel base consists of acrylamide and PEGDMA, and these gels have been incorporated with nanoparticle-stabilized liposomes for antimicrobial therapy [85]. While liposomes generally exhibit high biocompatibility and high drug loading capabilities, their tendency to nonspecifically fuse with membranous structures limits their specificity [138]. With the addition of small charged nanoparticles to their surface, liposomes exhibit reduced fusion due to steric repulsion, reduced surface tension, and enhanced liposome stability [139]. In an example of a superstructure platform utilizing this phenomenon, carboxyl-modified gold nanoparticles were used for liposome stabilization and enabled triggered fusion with *S. aureus* under low pH conditions [85]. As a similar gold nanoparticle-stabilized liposome platform has shown the ability to bind staphylococcal toxins for on-demand drug release [140], this nanoparticle–hydrogel superstructure could eventually be used for dual antibacterial therapy that combines toxin neutralization with antibiotic delivery.

Recently developed, the incorporation of nanoparticles into hydrogels synthesized by 3D printing has been an approach for designing detoxification platforms. In one such example, a hydrogel microfish encapsulating toxin-neutralizing PDA nanoparticles was synthesized through μCOP [94]. The body of the microfish consisted of PEGDA, which is photopolymerizable upon exposure to UV light. The PDA nanoparticles, which can mimic cell membranes, were incorporated into the hydrogel body of the microfish as a means to capture and neutralize pore-forming toxins. These particles also served another purpose as a toxin sensor, as the binding of toxins to the nanoparticle surface led to fluorescence emission. Along with the PDA nanoparticles, platinum nanoparticles were also incorporated into the tails of the functionalized microfish, enabling chemical propulsion upon exposure to hydrogen peroxide. While the majority of nanoparticle-based detoxification platforms rely on passive diffusion to achieve interaction with toxins, this new 3D-printed superstructure was able to utilize an active approach based on directed propulsion. It was demonstrated that the mobile, functionalized microfish had significantly increased toxin binding and neutralization when compared to a control microfish without any particles or a stationary microfish. 3D-printed hydrogels have also been incorporated with RBC-NPs for similar

detoxification applications [141]. In the system, RBC-NPs were mixed into a PEGDA mixture, which was then photopolymerized. The resulting platform contained multiple channels for toxins to be neutralized by the RBC-NPs and allowed for localized, controlled release of therapeutic compounds for detoxification. In another example, a 3D-printed PEGDA hydrogel was again functionalized with PDA nanoparticles in order to attract, capture, and sense melittin, a commonly used and widely studied pore-forming toxin [92]. The 3D hydrogel matrix was shaped with inspiration from the structure of the liver, which has a hexagonal lobule structure centered around the hepatic vein that allows for efficient removal of waste and foreign bodies. The resulting 3D-printed superstructure platform exhibited higher specific surface area to allow for easy entry of toxins into the detoxification device and was able to abrogate the virulence of melittin.

3.3 Immune Modulation

Therapies focusing on modulation of the immune system hold significant promise for treating a number of diseases, and these treatments aim to either reduce or augment endogenous immunity depending on the condition being targeted [142]. However, there remain significant challenges associated with developing such therapies, including the fact that many immunomodulatory compounds act nonspecifically and can cause severe adverse effects in patients. This creates issues with achieving proper therapeutic dosing, as exposure to the drug must be limited to reduce systemic toxicity and minimize complications from treatment [143]. A compelling approach for improving immunotherapies is to confine them at a specific site of interest, and this is an area in which nanoparticle–hydrogel hybrids can excel. By leveraging the controlled and sustained release properties of nanoparticle–hydrogel hybrids, it is possible to prevent unwanted systemic exposure to immunomodulatory payloads, thereby improving their safety and maximizing their therapeutic potential.

The localized delivery of immunotherapeutics can be used to effectively modulate macrophages, which play a large role in the progression and regression of various conditions, including cancer, wound healing, and many others. In cancer, tumor-associated macrophages display an M2 phenotype, whereas M1 macrophages are desired to help reduce tumor burden through their proinflammatory characteristics [144]. Additionally, tumor cells oftentimes upregulate CD47, a “don’t eat me” signal, in order to prevent destruction by macrophages [145]. In one notable example, an *in situ* forming immunotherapeutic fibrin gel was developed to prevent tumor reoccurrence by blocking the CD47-SIRPα pathway and scavenging hydrogen ions [62]. Anti-CD47-loaded $CaCO_3$ nanoparticles, which could be mixed into either the fibrinogen or thrombin percursor solutions prior to spraying, reacted with the readily available ions in the tumor microenvironment (TME). This led to the release of the encapsulated anti-CD47 and reduced the evasiveness of the nearby tumor cells. The concomitant reduction in hydrogen ions also allowed for improved macrophage function to assist in the clearance of the remaining tumor cells. In contrast to antitumor applications, the induction of M2 macrophages can assist in wound healing to allow for the rebuilding and regeneration of tissue, whereas the presence of M1 macrophages inhibits the healing process [146]. In order to induce the polarization of M2-like macrophages for enhanced wound healing, a gelatin methacryloyl hydrogel was used to recruit immune cells and expose them

to hyaluronan nanoparticles loaded with miR-223 5p mimic microRNA [147]. Whereas free microRNA would be rapidly degraded by enzymes in the local environment, encapsulation of the payload within nanoparticles provided protective shielding. At the same time, the hydrogel component allowed for sustained exposure of the M2-promoting microRNA signal at the wound site. Overall, this combined platform facilitated the delivery of high concentrations of intact therapeutics while minimizing off-target effects, an outcome that would be difficult to accomplish by other methods.

Achieving the sustained release immunotherapeutic payloads helps to enhance their efficacy by lengthening the therapeutic window. Controlling the release profile of immunomodulatory compounds also helps to prevent large spikes in serum concentration, which can induce harmful conditions such as cytokine storms [148]. Alginate hydrogels are biocompatible, noninflammatory, and highly tunable, allowing for changes in stiffness, degradation, and cell adhesion, which makes them excellent candidates for usage in therapeutic applications [149]. It was recently demonstrated that pores could be generated within these gels by the hydrolysis of specially synthesized alginate monomer beads, thus enabling the more efficient recruitment of immune cells (Fig. 8) [150]. This macroporous alginate hydrogel platform was adapted to deliver a diabetes-relevant peptide antigen loaded within PLGA particles to dendritic cells in order to generate antigen-specific regulatory T cells for treating autoimmune disorders. In another example, gold nanoparticles conjugated with granulocyte-macrophage colony-stimulating factor (GM-CSF) were loaded in a porous alginate hydrogel superstructure platform and used to mediate the local enrichment of dendritic cells within the gel [151]. GM-CSF is a glycoprotein that is responsible for inducing the differentiation, proliferation, and migration of dendritic cells [152]. Sustained release of GM-CSF *in vivo* led to the accumulation of millions of dendritic cells with an immature phenotype.

The release of immunomodulatory compounds from nanoparticle–hydrogel superstructures can also be triggered using various stimuli. Laser irradiation of hydrogels, which leads to a transient local elevation of temperature, is commonly used to facilitate the release of therapeutics. One approach leveraged this phenomenon for the local delivery of a nucleic acid-based adjuvant for cancer immunotherapy [61]. Here, a responsive hydrogel was fabricated by mixing oligodeoxynucleotide-modified gold nanoparticles and hexapod-like structured DNA. In response to laser irradiation, the gold nanoparticles introduced heat that disrupted the hydrogel to achieve precise release of the DNA, which contained immune-activating CpG motifs that have a strong adjuvating effect on the immune system. Elevated levels of IgG antibodies against tumor-associated antigens and antigen-specific cytokine production from splenocytes were observed, promoting control of tumor growth in a murine model. In another example, a thermoresponsive hydrogel loaded with quantum dots was leveraged for personalized anticancer vaccination [153]. Here, the quantum dots were coated with the membrane derived from surgically removed tumor cells and then loaded into a hydrogel alongside GM-CSF and lipopolysaccharide. Release of these proinflammatory compounds along with the tumor membrane antigens in response to NIR irradiation allowed for the efficient recruitment and activation of dendritic cells. The moderate increase in heat also increased blood flow and vascular permeability, thus facilitating T cell entry into the tumor and improving the overall outcome. In addition to using light as a stimulus, acidic pH

and reactive oxygen species have been employed as triggers for the release of payloads from nanoparticle–hydrogels. In one such case, a bioresponsive hydrogel was designed to deliver checkpoint blockade antibodies and zebularine, a hypomethylation agent, into the TME [154]. The antibodies were first loaded into $CaCO_3$ nanoparticles, which were then incorporated with zebularine into a hydrogel designed to hydrolyze in the presence of reactive oxygen species. In a pH-responsive manner, the antibody payload was released from the $CaCO_3$ nanoparticles after reacting with the hydrogen ions abundant in the TME.

3.4 Tissue Engineering

Tissue engineering is a multidisciplinary field that aims to develop biological substitutes to grow, maintain, restore, or enhance tissue functions using a combination of cells and scaffolds [155]. Hydrogel-based scaffolds can be used to recapitulate many of the characteristics that are suitable for the regeneration of tissues [156]. Their advantages include biocompatibility and high porosity, which makes them able to facilitate cell growth, differentiation, and neovascularization. In addition, hydrogels offer the structural integrity to guide cellular organization, encapsulate and deliver cells, and serve as depots for therapeutic agents [156]. Importantly, the high permeability and tunable biodegradability of hydrogels allows them to eventually be replaced by a newly grown tissue, making them an ideal candidate for mimicking the extracellular matrix (ECM) [124, 157]. Recently, there have been various approaches utilizing nanoparticle–hydrogel superstructure systems to provide tailored biological performance, controllable mechanical properties, and electrical conductivity [158, 159].

Nanoparticles enable the controlled release of bioactive agents and can be used to overcome limitations such as poor solubility and short blood residence time. They can also be engineered with controlled release, specific targeting, and stimuli-responsive characteristics [160]. As such, nanoparticles have been incorporated into hydrogel-based platforms as a means to enhance therapeutic outcomes in tissue engineering applications by reducing toxicity and increasing drug bioavailability [161]. Hydrogels incorporated with drug-loaded nanoparticles can serve the dual purpose of providing a physical scaffold and delivering therapeutic payloads to accelerate tissue regeneration. For example, moldable colloidal gels have been fabricated by mixing oppositely charged PLGA nanoparticles [162]. The electrostatic interaction between the nanoparticles drove hydrogel formation, resulting in a formulation with shear-thinning properties. In a later work, colloidal gels were synthesized using drug-loaded PLGA nanoparticles, and their use as injectable bone fillers to facilitate osteoconductive bond formation was evaluated [163]. Drug release tests showed that the dexamethasone loaded into the PLGA was slowly released over the course of two months. *In vivo* studies revealed that the PLGA-based colloidal gels could facilitate osteoconductive bone formation in rat cranial bone defects.

The emergence of 3D printing technologies has enabled the ready fabrication of scaffolds that match defect sites, and functional materials can be directly incorporated during the printing process [164–167]. Digital light processing (DLP)-based 3D printing technology enables the rapid fabrication of hydrogels with integrated structure [92]. In an example of a nanoparticle–hydrogel hybrid system, a DLP-based 3D printer was used to generate

nanoparticle-embedded nerve conduits [168]. XMU-MP-1, a Hippo pathway inhibitor known to promote nerve regeneration and functional restoration, was loaded into the nanoparticles for sustained release. Designed to match nerve defects, the XMU-MP-1 nanoparticle-embedded hydrogels provided guidance for axonal elongation. Furthermore, the study showed that the nerve conduit could slowly release XMU-MP-1, and *in vivo* therapeutic efficacy was comparable to that of an autograft. Apart from relying on nanoparticle-encapsulated drug payloads, some nanomaterials exhibit inherent bioactivity and have been shown to promote osteogenic mesenchymal stem cell differentiation. In one study, gold nanoparticles were incorporated into gelatin scaffolds by photo-crosslinking for bone regeneration [169]. When placed into parietal bone defects in rabbits, the scaffolds were degraded by cell-secreted enzymes. This released the gold nanoparticles into the local region, resulting in the enhanced proliferation of osteoblasts.

Cardiac tissue is distinguished from other tissues such as bones and skin due to its limited regenerative capacity [170]. It has previously been demonstrated that cardiomyocytes and related progenitor cells proliferate and differentiate when subjected to electrical stimulation, and this has led to the development of conductive hydrogels for cardiac tissue engineering applications [159]. There are some challenges in mimicking cardiac tissue using traditional hydrogel scaffolds, which typically are electrically insulating, lack nanofibrous architectures, and mechanically weak [171]. To fabricate mechanically strong tissue scaffolds, carbon nanotubes (CNTs) were incorporated into GelMA hydrogels via hydrophobic interactions between the polypeptide chains of the gelatin and the sidewalls of the nanotubes. By adjusting the amount of CNTs incorporated, the mechanical properties of the GelMA could be adjusted without compromising its bioactivity, high porosity, and degradability. In addition, the hybrid system could by photopatterned by UV light to modulate its size and shape, thereby enabling facile fabrication of ECM-mimicking 3D scaffolds [172]. In a later work, CNT-incorporated GelMA hydrogels were employed as cardiac patches that demonstrated improved mechanical stability and were able to enhance electrophysiological functions (Fig. 9) [63]. The inclusion of CNTs into the hydrogel platform promoted cell adhesion and improved electrical coupling between cells. Rat myocardial cells grown on the hybrid superstructure showed 3-fold higher spontaneous synchronous beating rates and an 85% lower excitation threshold compared to those cultured on pristine GelMA hydrogels. In addition, hybrid hydrogels showed protective effects against a model cardiac inhibitor and a cytotoxic compound.

An injectable CNT-functionalized reverse thermal gel (RTG) system was reported to replicate the unique electrophysiological property of native cardiac tissue [173]. RTG systems are appealing in cardiac tissue engineering applications, as they undergo sol to gel transition through temperature stimuli. This can be carried out without the need for UV irradiation or the potentially irritating solvents required for other polymeric materials, resulting in a lower chance of toxicity. Additionally, these gels have minimal swelling issues since their formation is driven by hydrophobic interactions. Other than using CNT to confer electrical conductivity, gold nanoparticles have also been incorporated by various means into hydrogels for similar purposes [174, 175]. In a recent example based on an RTG system, gold nanoparticles were employed to provide topographical and electrophysiological cues for cardiac cell growth [176]. In the nanoparticle–hydrogel culture platform, neonatal rat

ventricular myocytes cocultured with cardiac fibroblasts could survive for up to 21 days. This resulted in a higher level of connexin 43, the predominant gap-junction protein in the heart, compared to conventional 2D culture systems and an unmodified RTG hydrogel without nanoparticles.

4. Opportunities and Challenges

We have discussed an emerging class of nanoparticle–hydrogel composites that has the potential to be used for a wide range of biomedical applications. The superstructure systems described in this review offer a means to overcome the limitations and drawbacks associated with the use of either nanoparticles or hydrogels alone. In these platforms, the nanoparticle component can serve multiple roles, including as a means of encapsulating therapeutic agents, bestowing stimuli-responsiveness, and altering mechanical properties. The hydrogel structure allows for localized delivery, enhanced biocompatibility, and nanoparticle protection, among others. The combined nanoparticle–hydrogel structures have shown the ability to excel at assisting localized drug delivery, modulating drug release kinetics, enhancing nanoparticle-based detoxification, delivering immunotherapeutic agents, and functioning as tissue scaffolds. A vast number of nanoparticle–hydrogel combinations can be created due to the wide availability of nanomaterials and gel matrices [177], indicating a wide array of possibilities for their application in biomedical engineering. In order to attain the desired performance, a better understanding of the interactions and the mechanisms involved in the formation of these composite systems are of significant importance, and a focus should be placed on the following areas: efficient and effective incorporation of the nanoparticle component to maximize therapeutic loading while maintaining the integrity of each component; tunable mechanical performance to match application-specific requirements, particularly for tissue engineering; biocompatibility, which is essential for all biomedical applications but may be compromised during gelation or degradation; and long-term stability to minimize treatment frequency and improve patient compliance.

Although significant progress has been made in the development of nanoparticle–hydrogel superstructures, the synthesis and *in vivo* application of these hybrid superstructures still faces many challenges. One of the most notable is clearance of the structure after the complete release of encapsulated therapeutic agents. Despite the high biocompatibility of the individual components, their prolonged retention poses a risk of adverse effects such as foreign-body responses. This issue may be addressed by utilizing sophisticated strategies for controlled degradation, potentially involving simultaneous control of polymer cleavage rates [178], variation of crosslinker substituents [179], and use of homogenous polymer networks [180]. Other challenges include achieving gelation at the optimal time, whether that be prior to implantation or *in situ*. Premature gelation increases the risk of low or uneven incorporation of nanoparticles within the structure, leading to suboptimal delivery of therapeutic payloads. Conversely, delayed gelation poses risk of delivery to undesired areas, rather than localization directly to the affected area. Utilizing smart polymer systems that quickly gelate in response to specific stimuli may represent a viable approach for addressing this issue [181]. With nanoparticle–hydrogel hybrid systems, it is also essential to consider the complexity of the biological environment. Applications such as immune modulation and tissue engineering rely on the ability of the platform to interact with individual cells and the

microenvironment both adjacent to and inside the structure itself. As such, platforms designed for these purposes must incorporate components that can correctly interface with the body. Overall, the assembly of different nanoparticle and hydrogel platforms together into novel superstructures presents an intriguing methodology by which many of the challenges facing traditional therapeutics can potentially be addressed. With continued development and improved understanding, we anticipate that superstructure platforms will become increasingly popular in the coming years.

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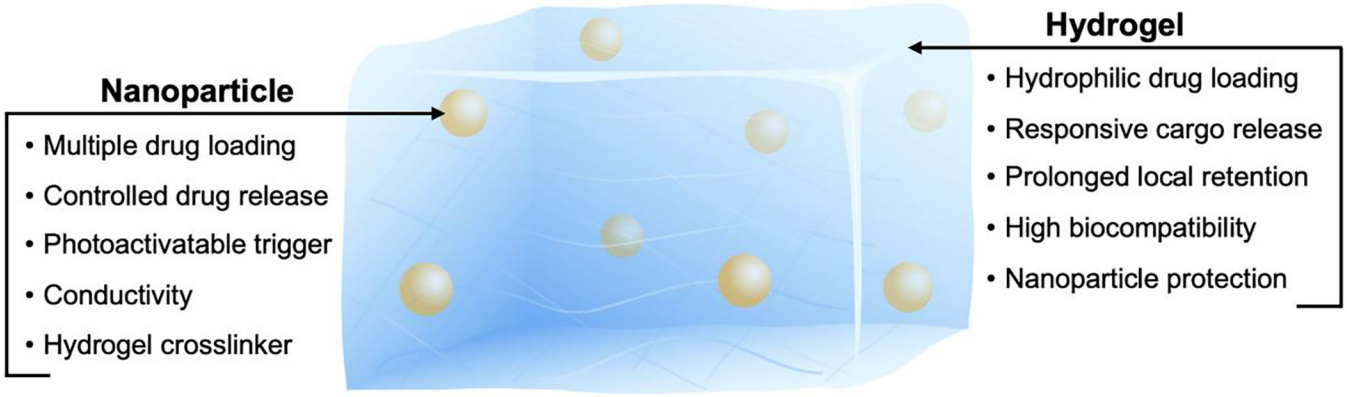

Fig. 1.

Nanoparticle–hydrogel superstructures for biomedical applications. Nanoparticle–hydrogel systems combine the unique advantages of their constituent components, which has enabled them to excel in applications such as drug delivery, immune modulation, detoxification, and tissue engineering.

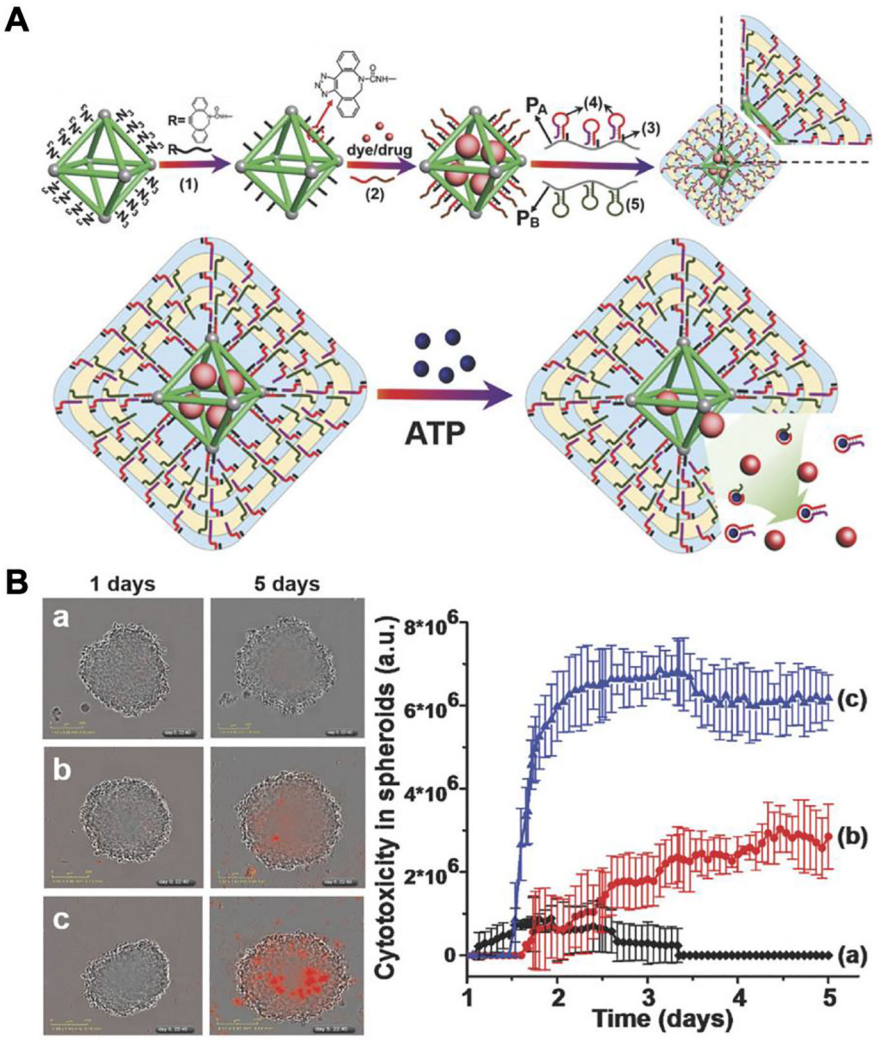

Fig. 2.

Stimuli-responsive polyacrylamide hydrogel-coated MOF nanoparticles. (A) MOF nanoparticles are modified with nucleic acids and loaded with drugs. The nanoparticles can then be coated with DNA-functionalized acrylamide polymers. Upon incubation with ATP, triggered release can be achieved. (B) Tumor spheroids treated with (a) unloaded hydrogel-coated MOF nanoparticles, (b) uncoated MOF nanoparticles, or (c) the hydrogel-coated MOF nanoparticles and the corresponding cytotoxicity in spheroids. Adapted with permission [34]. Copyright 2017, WILEY-VCH.

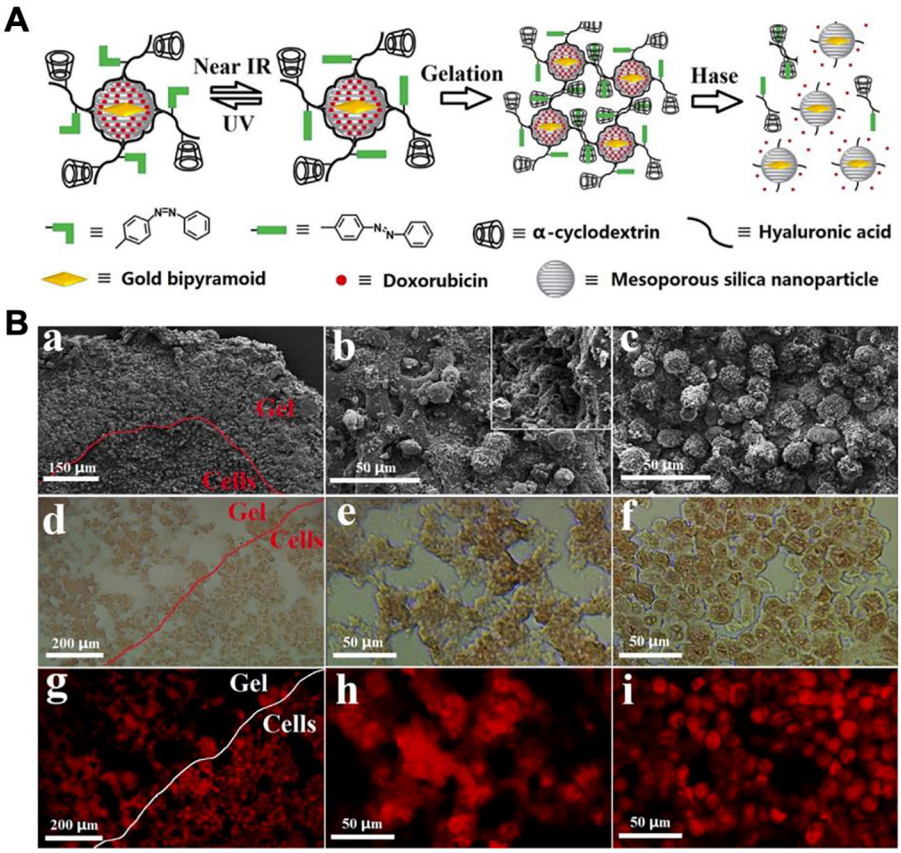

Fig. 3.

Light-inducible hydrogels based on mesoporous silica nanoparticles. (A) Mesoporous silica nanoparticles functionalized with an azobenzene group and α-cyclodextrin can form a hydrogel structure when exposed to NIR irradiation. When subjected to hyaluronidase (Hase) treatment, the hydrogel dissociates. (B) Scanning electron microscopy (a-c), optical microscopy (d-f), and fluorescence microscopy (g-i) demonstrate coating of tumor spheroids with the mesoporous silica nanoparticle-based hydrogel. The middle and right columns show higher magnification images of the hydrogel and cell sections, respectively. Adapted with permission [109]. Copyright 2016, American Chemical Society.

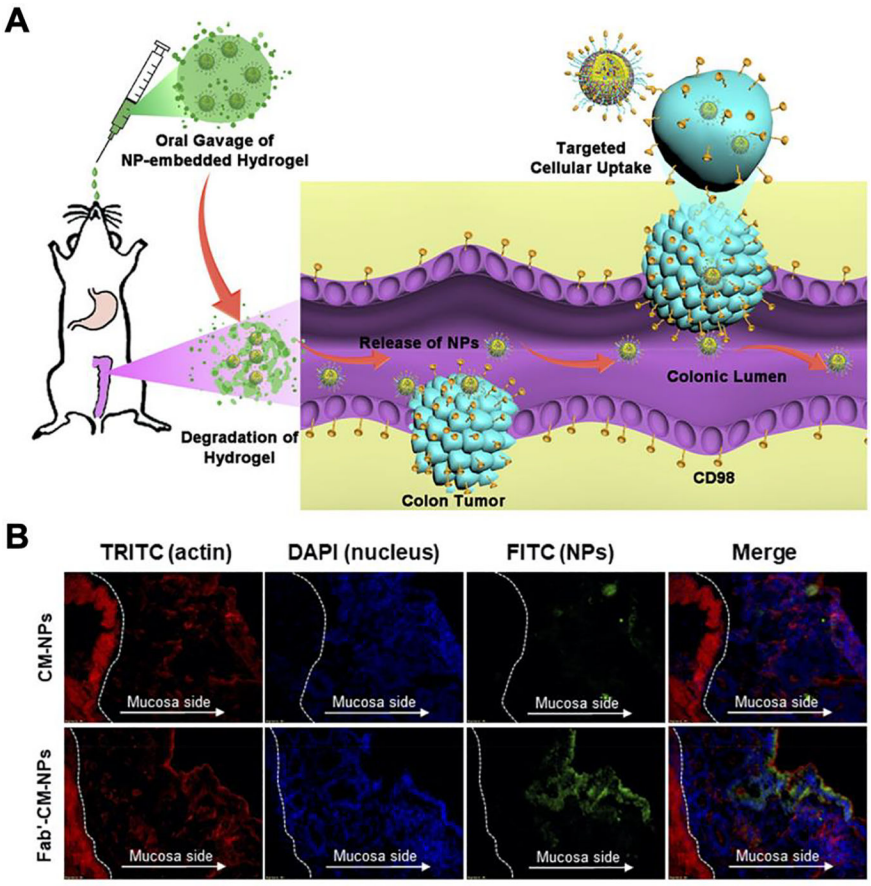

Fig. 4.

Oral delivery of Fab′ -functionalized nanoparticles coated with hydrogels. (A) When the nanoparticle (NP)-embedded hydrogels reach the colon, the nanoparticles are released and can be internalized by tumor cells. (B) Coumarin 6-loaded nanoparticles (CM-NPs) are taken up significantly more by tumor tissue when functionalized with Fab'. Adapted with permission [128]. Copyright 2018, American Chemical Society

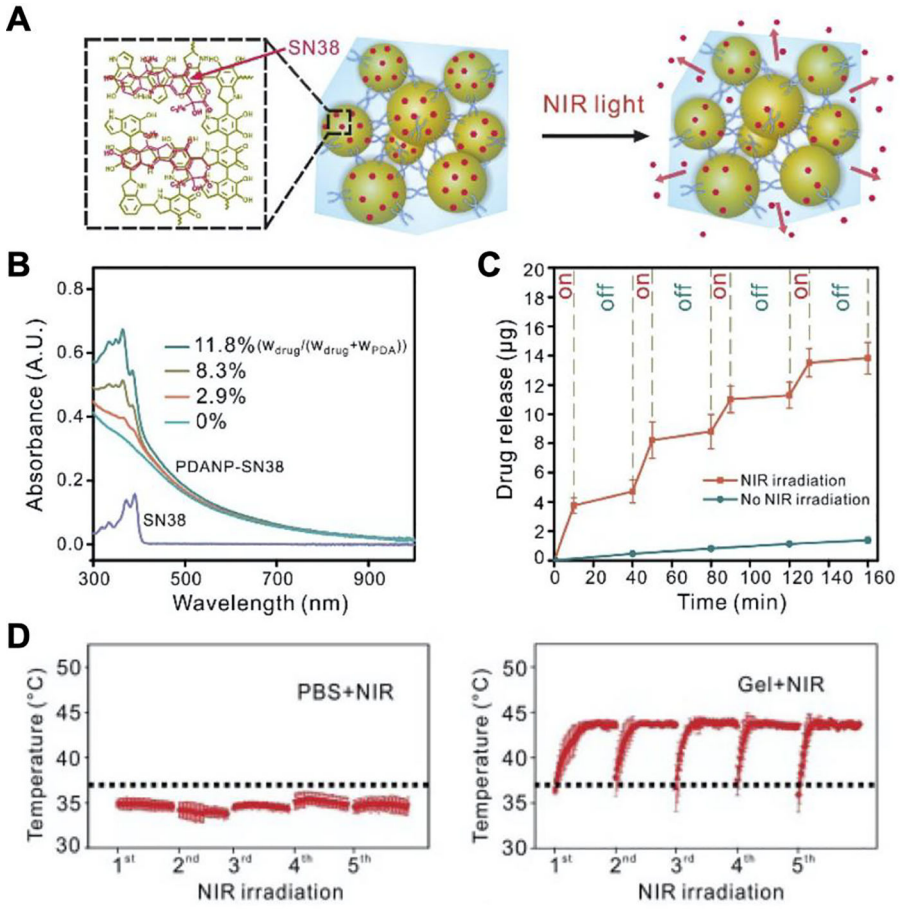

Fig. 5.

Thermoresponsive polydopamine nanoparticle-knotted PEG hydrogel. (A) The nanoparticle–hydrogel network can be incorporated with SN38, a chemotherapeutic, by π−π stacking. The drug can then be released upon NIR irradiation. (B) Absorbance profiles confirm successful loading of hydrogels with different amounts of SN38. (C) Drug release can be modulated in an on-demand manner upon NIR irradiation. (D) The nanoparticle–hydrogel formulation can significantly increase tumor-site temperature upon NIR irradiation. Adapted with permission [54]. Copyright 2017, American Chemical Society.

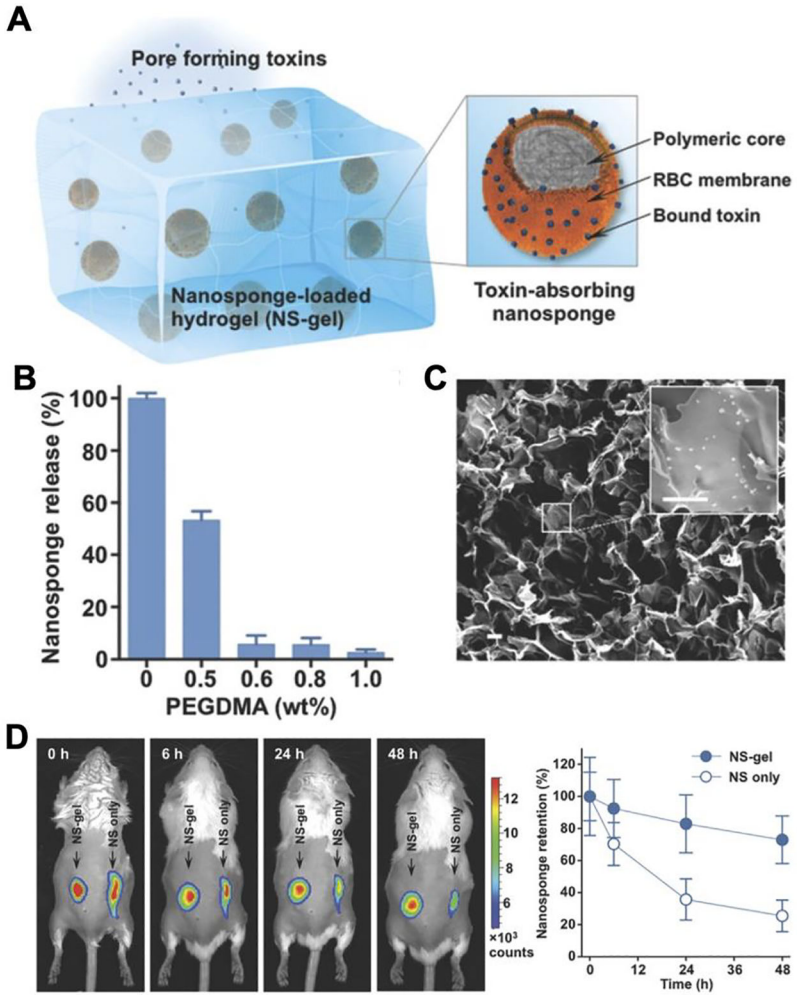

Fig. 6.

Hydrogels loaded with cell membrane-coated nanoparticles for toxin neutralization. (A) Hydrogels are formulated with red blood cell (RBC) membrane-coated nanosponges (NS) that are capable of binding and neutralizing pore-forming toxins. (B) NS are better retained within the hydrogel when a higher concentration of crosslinker is used. (C) Scanning electron microscopy is used to visualize the NS–hydrogel structure. (D) NS incorporated within the hydrogels retain at the injection site better than free NS. Adapted with permission [134]. Copyright 2015, WILEY- VCH.

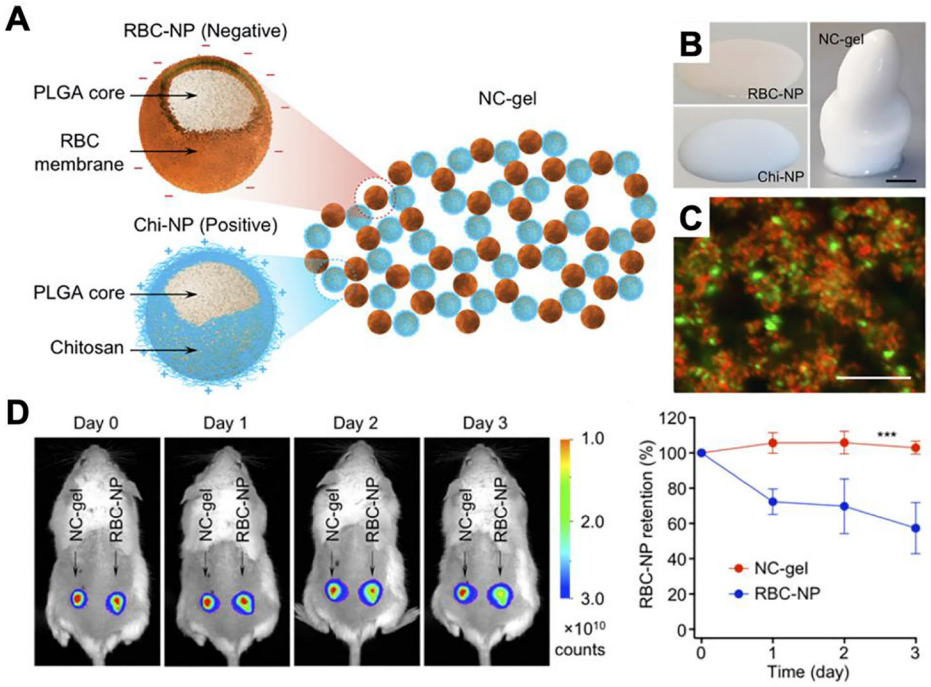

Fig. 7.

Colloidal hydrogel with cell membrane-coated nanoparticles for toxin neutralization. (A) The nanosponge colloidal (NC) gels are formed by the electrostatic interaction between negatively charged RBC-NPs and chitosan-coated nanoparticles (Chi-NPs). (B) Macroscopic images demonstrate the structure of the NC gel. (C) Fluorescent imaging shows that the NC gels are formed by a network of RBC-NPs (red) and Chi-NPs (green). (D) When incorporated into NC gels, RBC-NPs retain better at the site of injection. Adapted with permission [59]. Copyright 2017, American Chemical Society.

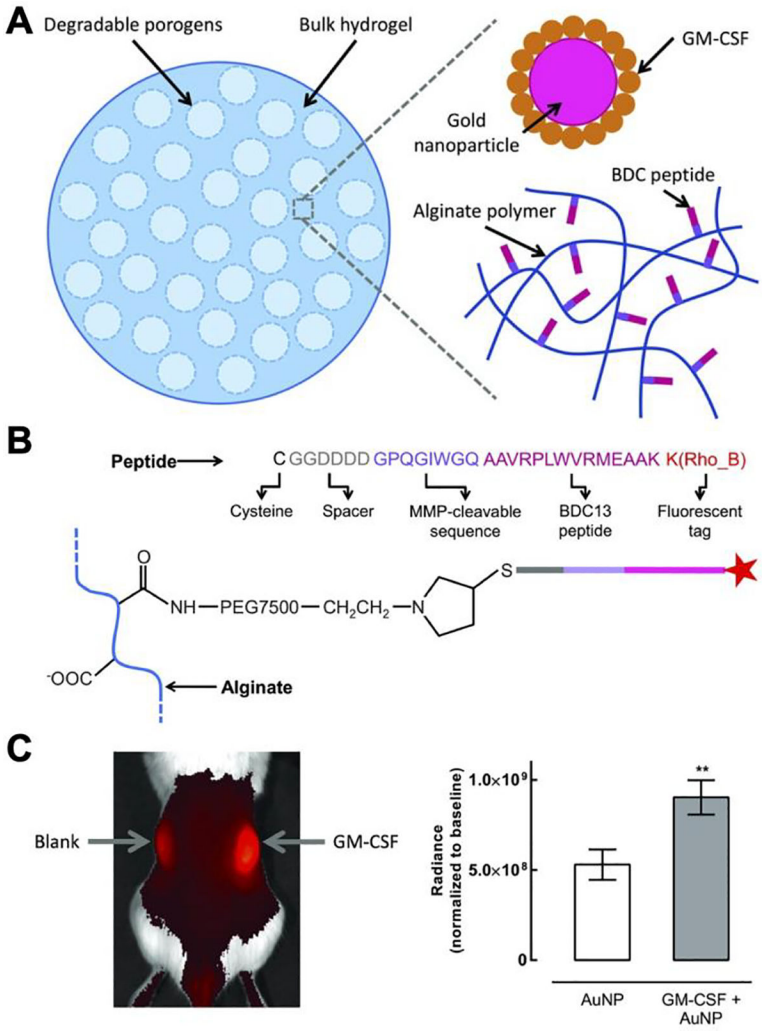

Fig. 8.

Porous hydrogels containing protein-conjugated gold nanoparticles for immune modulation. (A) A porous alginate gel functionalized with a diabetes-relevant BDC peptide is incorporated with GM-CSF-conjugated gold nanoparticles. (B) The peptide, which is fluorescently labeled and contains a matrix metallopeptidase-cleavable sequence, is linked to the alginate via a PEG tether. (C) When administered subcutaneously, the hydrogel containing GM-CSF-conjugated gold nanoparticles exhibits significantly higher metallopeptidase activity. Adapted with permission [150]. Copyright 2017, WILEY-VCH.

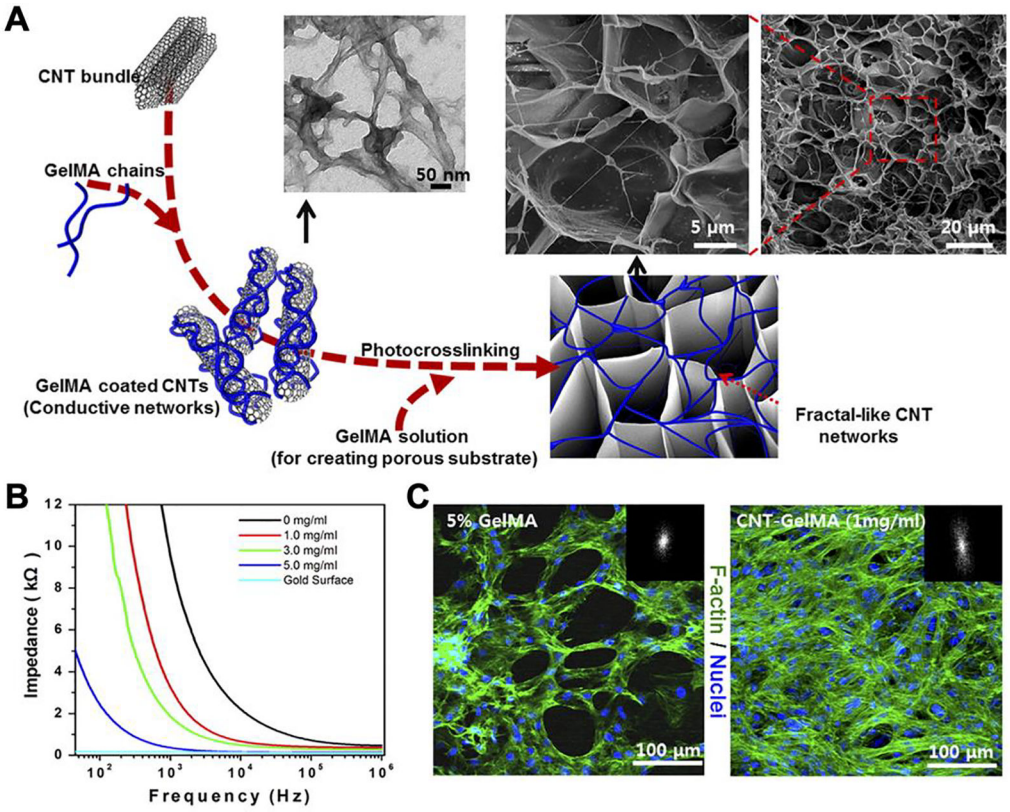

Fig. 9.

Carbon nanotube (CNT)-embedded hydrogel sheets for cardiac scaffolds. (A) CNT bundles are coated with GelMA and crosslinked to form fractal-like networks. (B) With increasing amounts of CNT, the hydrogels become increasingly conductive. (C) A more uniform distribution of cardiomyocytes is seen when the cells are cultured onto CNT-incorporated hydrogels. Adapted with permission [63]. Copyright 2013, American Chemical Society.

Table 1.

Advantages of nanoparticle–hydrogel superstructures for biomedical applications.

Application	Advantages of the nanoparticle–hydrogel superstructure
Drug delivery	• Enhanced stability and protection of the cargo • Prolonged retention and sustained release • Responsive cargo release by external and internal stimuli
Detoxification	• Confinement of detoxification agent to disease site • Prolonged retention and sustained release
Immune modulation	• Reduction of off-target effects • Controlled maintenance of therapeutic dosages • Responsive cargo release by external and internal stimuli
Tissue engineering	• Tunable mechanical properties • Controlled and localized drug delivery • Enhanced bioavailability of bioactive agents