Published in final edited form as:

Ann Biomed Eng. 2016 June ; 44(6): 2049–2061. doi:10.1007/s10439-016-1583-9.

Nanoparticle-Hydrogel: A Hybrid Biomaterial System for Localized Drug Delivery

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Abstract

Nanoparticles have offered a unique set of properties for drug delivery including high drug loading capacity, combinatorial delivery, controlled and sustained drug release, prolonged stability and lifetime, and targeted delivery. To further enhance therapeutic index, especially for localized application, nanoparticles have been increasingly combined with hydrogels to form a hybrid biomaterial system for controlled drug delivery. Herein, we review recent progresses in engineering such nanoparticle-hydrogel hybrid system (namely ‘NP-gel’) with a particular focus on its application for localized drug delivery. Specifically, we highlight four research areas where NP-gel has shown great promises, including (1) passively controlled drug release, (2) stimuli-responsive drug delivery, (3) site-specific drug delivery, and (4) detoxification. Overall, integrating therapeutic nanoparticles with hydrogel technologies creates a unique and robust hybrid biomaterial system that enables effective localized drug delivery.

Keywords

Nanomedicine; nanoparticle; hydrogel; hybrid biomaterial; drug delivery

1. Introduction

Nanoparticle technology offers a series of advantages for drug delivery, including high loading yield, combination therapy, controlled release, prolonged circulation, and targeted delivery.^{6, 14, 70, 96} As a result, a myriad of nanoparticle-based drug delivery systems have been developed to improve therapeutic index of drugs by altering their pharmacokinetics and biodistribution profiles, resulting in nanomedicines for clinical treatment of various diseases.^{59, 89, 90} Advances in biotechnology and biomedicine continue to accelerate the development of novel therapeutic nanoparticles aimed at further enhancing therapeutic efficacy.^{22, 95} For example, recent progress in genomics and proteomics has led to new nanoparticle formulations accommodating rational drug combinations for personalized treatment.^{2, 50, 60} Biological discovery on the network of interconnected pathways within a cell has also resulted in nanoparticle formulations capable of precisely modulating the tempo-spatial distribution of drug molecules to target the internal state of malignant cells for bioactivity.^{19, 64} Further understandings on disease pathogenesis, particularly that of cancer

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and infections, have triggered the development of highly responsive nanoparticles that conduct physicochemical changes, when exposed to external stimuli, to enable preferential drug release at the target site.^{26, 27} Moreover, biomimetic nanoparticles made of natural biomaterials have demonstrated superior biointerfacing capabilities, leading to innovative therapeutics especially for drug delivery, detoxification, and vaccination.^{40–43}

Meanwhile, on the front of nanotechnology development, therapeutic nanoparticles have been increasingly combined with other biomaterials to form hybrid systems for novel applications.^{17, 44, 71} In this perspective, loading nanoparticles into hydrogels has received much attention.^{61, 78, 83} Hydrogels are hydrophilic 3D polymer networks with extensive uses in tissue engineering and drug delivery.⁶⁹ Nanoparticles can be embedded into hydrogel network by mixing with monomer solution, followed by gelation (i.e., nanocomposite hydrogel, Figure 1A).²⁸ Alternatively, they can be incorporated into gel matrix after gel formation by allowing the gel network to swell and ‘breath in’ nanoparticles for entrapment, a method especially useful when nanoparticles interfere with the gelation process.⁹⁴ Furthermore, inorganic nanoparticles are often grown in situ within gel matrix by loading nanoparticle precursors into a gel first, followed by reduction reactions for nanoparticle formation.⁶³ With appropriate compositions, hydrogels not only preserve the structural integrity and the functionalities of the contained nanoparticles, but also offer additional engineering flexibility to improve the overall therapeutic efficacy. Besides hydrogel entrapment, directly using nanoparticles as cross-linkers to construct 3D hydrogel network offers another approach for nanoparticle assembly to acquire hydrogel-like properties (i.e., nanoparticle colloidal hydrogel, Figure 1B).^{33, 54, 110} In this approach, nanoparticles can be linked together through strong hydrophobic interactions or by mixing nanoparticles carry opposite surface charges.⁹⁹ Alternatively, nanoparticles can be covalently linked, acting as nodes to form a hydrogel network.²⁴

Overall, nanoparticle–hydrogel hybrid systems (denoted as ‘NP-gels’) judiciously integrate two distinct materials into one formulation with unique physicochemical and biological properties that neither one of the two building blocks can achieve independently.⁶¹ NP-gels have demonstrated superior biointerfacing properties and attracted increasing attention to address various biological and medical challenges. In this article, we provide a review on recent advances in engineering NP-gels, with a particular emphasis on their novel applications in drug delivery. Specifically, we highlight four areas where their development and use have received the most attention, including (1) passively controlled drug release, (2) stimuli-responsive drug delivery, (3) site-specific drug delivery, and (4) detoxification. Although this review focuses on nanoparticles in combination with hydrogels, the development principles in above areas can be applied to hydrogels combined with other delivery platforms featuring different sizes, geometries, or dimensions such as microparticles¹⁰⁸ and nanofibers.²¹ Overall, NP-gels have emerged as a versatile class of biomaterials, unleashing unique synergistic properties with strong application potential to improve drug delivery.

2. Passively controlled drug release

Both nanoparticles and hydrogels are widely used for controlled drug release. Drug molecules encapsulated within the hydrogel network are released through diffusion, swelling, and chemically controlled mechanisms.⁵⁶ Meanwhile, nanoparticles control release kinetics through their tailored polymer structure, particle size, and fabrication conditions.⁸⁸ By integrating the two platforms, NP-gels create hierarchical matrices with remarkable versatility in modulating drug release kinetics for various delivery purposes, which are difficult for each platform to achieve alone.

Hydrogels can offer tissue-like properties but may suffer from burst release and rapid diffusion of drug molecules out of the polymer matrix.¹³ In contrast, NP-gels that use nanoparticles as drug depot can overcome this drawback and significantly prolong drug release duration, which in turn can enhance drug bioavailability and patient compliance. For example, anti-inflammatory drug methylprednisolone(MP), effective in treating spinal cord injury was loaded into poly(lactic-co-glycolic acid) (PLGA) nanoparticles and then embedded within agarose hydrogels at a concentration of 2 mg/mL (based on PLGA mass); the continuous release of the fluorescence labeled MP was observed for 6 consecutive days.^{4, 10} These formulations extended effective drug release from a few hours up to a few days. Prolonged drug release by NP-gel formulation is also popular in ocular drug delivery. For example, drug-loading liposomes,³⁵ micelles,⁴⁷ and polymeric nanoparticles⁴⁶ have all been incorporated into various hydrogels for the slow release of glaucoma drugs. Another area of interest is localized antibiotic release. In this perspective, metallic nanoparticles made of silver, gold, or copper, which slowly release ions to cause strong bactericidal effects, have been widely used to formulate NP-gels and shown enhanced efficacy in treating bacterial infections including those caused by *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* bacteria.^{11, 76}

NP-gel formulation has also been used to directly modulate nanoparticle release with varying matrix porosity (i.e. the fraction of void space in the polymer network).^{7, 91} One example is the controlled release of nanoparticle-stabilized liposomes, an emerging class of antimicrobial delivery platform, for topical administration to treat bacterial infections (Figure 2).²⁸ In this formulation, carboxyl-modified gold nanoparticles were used as stabilizers for cationic liposomes consisting of L- α -phosphatidylcholine (EggPC, a zwitterionic phospholipid) and 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP, a cationic phospholipid) and the stabilized liposomes were loaded into a chemically cross-linked polyacrylamide hydrogel. The hydrogel viscoelasticity could be precisely tailored by varying the cross-linker poly(ethylene glycol) dimethacrylates (PEGDMA) concentration, which subsequently resulted in tunable release kinetics of the incorporated liposomes. Liposome release percentage correlated linearly with the square root of release time, consistent with a diffusion dominant Higuchi model characterized by weak interactions between liposomes and the gel matrix.^{37, 92} The hydrogel formulation preserved the structural integrity of the nanoparticle-stabilized liposomes and the released liposomes could fuse with bacterial membranes in response to acidic environment (i.e., pH = 4.5) relevant to various skin infections.^{82, 85} As another example, cisplatin self-assembled nanoparticles were loaded into hydrogel composed of poly(ethylene glycol)-*b*-poly(acrylic acid) (PEG-*b*-

PAA).¹¹⁷ Drug release from this NP-gel system was determined by two steps: first, nanoparticles were released from the hydrogel, which was controlled by network dissolution; second, cisplatin was released from the nanoparticles, which was controlled by ligand substitution with chloride ions in the surroundings. The two distinct release kinetics determined the overall cisplatin release profile and thus the drug's therapeutic efficacy.

Besides single drug delivery, NP-gels also combine fast diffusion-controlled release of drug molecules directly dispersed in hydrogel network with slow drug release from nanoparticle reservoirs, a unique feature useful for concurrent delivery of multiple drugs while achieving independent control of their release kinetics. This controlled release strategy is particularly suitable for the combinatorial delivery of neuroprotective and neuroregenerative agents for spinal cord injury repair. The former aims to enhance cell survival during the trauma of secondary injury and thus requires a delivery on the hours to days following the primary injury, while the latter aims to enhance axonal outgrowth and thus needs to be delivered for an extended period ranging from 7 to 28 days.^{74, 77} For example, an NP-gel was formulated with hyaluronan and methyl cellulose blend loaded with PLGA nanoparticles, which achieved independent delivery of neuroprotective agents such as 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F) quinoxaline (NBQX) and fibroblast growth factor-2 in a time span ranging from 1 to 4 days and neuroregenerative agents such as neurotrophin-3 and anti-NogoA up to 28 days.³ In addition to loading one drug into the hydrogel matrix and one drug into embedded nanoparticles, two or more different types of drugs can be loaded separately to different types of nanoparticles, which are then mixed as a cocktail to prepare an NP-gel. In this case, sequential drug release can be achieved by controlling the size and surface properties of the different nanoparticles. For example, cholesterol-bearing pullulan nanogel nanoparticles with a diameter of approximately 30 nm were mixed with 136 ± 4 nm liposomes (dimyristoylphosphatidylcholine:cholesterol = 3:1 mol:mol) and then loaded in a PEG hydrogel.⁸⁷ The study showed that 6% of the liposome-encapsulated dye had leaked from the nanogel-coated liposome complexes by day 40, whereas 100% of the dye had leaked by day 25 from the uncoated liposomes, implying that coating the nanogel stabilizes the lipid bilayer and strengthens the permeability barrier as an artificial cytoskeleton.

3. Stimuli-responsive drug delivery

Smart hydrogels that drastically change their volume in response to environmental stimuli such as temperature, pH, and chemical signals are attractive biomaterials for drug delivery.^{36, 72, 84} Such responsiveness can be coupled with additional cues such as light and magnetic field via nanoparticles embedded within the matrix, creating unique NP-gels capable of remotely controlling drug release.¹¹⁴ For example, nanoparticles made from melanin with an average diameter of approximately 250 nm showed UV-induced photothermal heating.⁶⁶ These nanoparticles were dispersed into heat degradable hydrogel networks physically cross-linked by amphiphilic PLGA-PEG-PLGA copolymer. Under UV irradiation, the hydrogel was able to disintegrate. Compared to UV light, near-infrared (NIR) light is relatively safer and able to penetrate deeper into the soft tissues.²⁹ For example, gold nanorods doped into a thermally responsive hydrogel made with methoxypoly(ethylene glycol)-poly(ϵ -caprolactone)-acryloyl chloride, glycidylmethacrylated chitooligosaccharide, *N*-isopropylacrylamide, and acrylamide, were able to induce the contraction of the thermo-

responsive hydrogels and trigger the release of loaded doxorubicin to inhibit breast cancer under NIR irradiation (Figure 3).⁷³ Other NIR-absorbing nanoparticles such as carbon nanotubes¹¹³ and graphene oxide nanoparticles¹¹⁶ were also incorporated into thermo-responsive polymers to harness NIR for remotely controlled drug delivery. Recently, upconversion core-shell nanoparticles made from NaYF₄:TmYb (core = NaYF₄:0.5 mol % Tm³⁺:30 mol % Yb³⁺; shell = NaYF₄, in a uniform hexagonal prism shape with an average length of 36.0 ± 1.1 nm and width of 32.0 ± 1.5 nm) capable of converting NIR light into UV light were also integrated with a photo-responsive hydrogel consisting of acrylamide monomer and the photocleavable PEG cross-linker.¹⁰⁷ The platform could “hide” large biomacromolecules (such as proteins) inside a polymer hydrogel, effectively “shutting down” their bioactivity, and then release them “on demand” using NIR light to enable their bioactivity.

Additionally, superparamagnetic particles that dissipate local heat upon the application of alternating magnetic field (AMF) have also been used as a trigger for remotely controlled “on-demand” drug release.^{49, 57} For example, superparamagnetic iron oxide (Fe₃O₄) nanoparticles (20–30 nm diameter) were incorporated into *N*-isopropylacrylamide (NIPAAm)-based matrix. Drug release was modulated by applying external AMF: continuous AMF accelerated drug release from the NP-gel, while pulse application of AMF caused pulsatile release in addition to continuous Fickian release profile.⁸⁰ Using hydrogel with a concentric-layered structure instead of amorphous structure further improved the responsiveness and drug release efficiency.¹⁰³ The synergy between nanoparticles and the hydrogel network has also led to NP-gels highly responsive to external pH changes. For example, silver nanoparticles were synthesized within a hydrogel containing 2-hydroxyethyl methacrylate), poly(ethylene glycol) methyl ether methacrylate, and methacrylic acid in situ.¹⁰⁶ Although the hydrogel itself had pH-responsive deswelling property due to the free carboxylic groups, the incorporation of silver nanoparticles significantly increased the deswelling rate. Such synergy was attributed to the presence of a large inter-phase region between the silver nanoparticles and the polymer matrix, which likely reduced the characteristic diffusion length of water molecules and accelerated the deswelling process.

To further enhance the responsiveness, a new type of hydrogel has been made by covalently linking nanoparticles onto hydrogel matrix.^{45, 105} Compared to physically embedding, covalent link allows for using various hydrogel responsiveness to modulate inter-particle distances, hence offering precise control of nanoscale interactions through bulk templates.¹¹⁵ Meanwhile, when nanoparticles are covalently linked, they form the nodes of the polymer network and reduce the relaxation length of hydrogel scaffolds, leading to significantly enhanced bulk response to environment stimuli.⁹ Permanent linkage to the network also prevents nanoparticles from diffusing out of the gel, thereby limiting the loss of responsive materials and the potential toxic effects in biomedical applications.⁶² These covalent NP-gels provide a system with better-defined coupling between nanoparticles and polymer matrix and thus open a way for better understanding of material structure-property relationship and subsequent modification for improved drug delivery properties.

Using nanoparticles as sole building blocks to form cohesive gel-like network represents an emerging class of NP-gel.⁵ Combining oppositely charged nanoparticles, especially those

that have already been established as drug nanocarriers such as PLGA,^{99, 101} gelatin,⁹⁸ and chitosan nanoparticles,¹⁰⁰ is a common approach to preparing this type of NP-gel. For example, positively charged chitosan-coated dextran nanoparticles (diameter: 340 nm, surface zeta potential: 10.6 ± 1.9 mV) and negatively alginate-coated dextran nanoparticles (diameter: 293 nm, surface zeta potential: -11.5 ± 1.7 mV) were mixed at 20% (w/v) to form colloidal hydrogel for glucose-responsive and self-regulated insulin delivery (Figure 4).³⁴ At a macroscopic level, the construct was made with nanoparticles of small sizes and uniform distributions, which ensured sufficient cohesive strength for gelation. Such cohesive force decreased at high shear rate, resulting in low viscosities suitable for injection. At a microscopic level, the nanoparticles allowed for simultaneous loading of insulin and two glucose responsive enzymes (glucose oxidase and catalase). In a hyperglycemic state glucose was catalytically converted to gluconic acid, which caused dissociation of the gel-like network and subsequent release of insulin. This NP-gel system allowed for fast and pulsatile release of insulin in response to glucose concentrations and thus provided better glucose control in a type 1 diabetic mouse model. An alternative approach to forming colloidal gel is to use nanoparticles with responsive hydrophobic interactions. In this approach, nanoparticles are typically consisted of a core made of a hydrophobic polymer and a shell made of a thermo-responsive polymer that undergoes hydrophilic-to-hydrophobic transition in response to temperature change.^{1, 23} When temperature is below a critical temperature, the polymeric shell is water-soluble and stabilizes the nanoparticle; however, when temperature is above a critical temperature, the polymeric shell becomes hydrophobic, which flocculates the dispersed nanoparticles into a hydrogel network.

4. Site-specific drug delivery

NP-gels detain nanoparticles within 3D polymer matrices that allows for better local drug delivery. Various NP-gel formulations have been developed for targeting drugs to disease sites at the spinal cord,^{4, 10, 74, 77} the eye,^{35, 46, 47} and the skin.^{28, 76} In these formulations, drug localization primarily relies on the properties of the hydrogel network, which allows nanoparticle design to be solely focused on modulating drug release. Such hybrid strategy offers an opportunity to decouple the spatial and temporal aspects in designing materials for drug delivery, resulting in a modular approach for highly functional drug targeting applications.

One such application is to use an anti-inflammatory tripeptide Lys-Pro-Val (KPV) loaded NP-gel for drug targeting to treat inflammatory bowel disease in the gastrointestinal (GI) tract.⁵³ In the study, a “double gavage” method was employed based on ion-induced polysaccharide gelation. Specifically, the first gavage was aimed to deliver 100 μ L of the polysaccharides solution (alginate, 7 g/L; chitosan, 3 g/L) with homogenous suspended NPs (2 mg/mL). The polysaccharides biomaterials were in liquid phase at the time of gavage, which allows for easy administration. Then a second gavage was performed with a 50 μ L solution containing 70 mmol/L calcium chloride and 30 mmol/L sodium sulfate. Once the ions and the polysaccharides solution were mixed, a hydrogel was formed. Since the cross-linking was through electrostatic interactions and sensitive to pH levels, the gel degradation could be finely controlled at different sites within the GI tract by simply varying the gel composition. Using this approach, polymeric nanoparticles loaded with KPV peptides were

encapsulated within hydrogel, forming a NP-gel formulation that was stable in gastric solutions of pH 1, 2, and 3 for 24 hours. However, when exposed to the intestinal solution with a higher pH level of 5, the hydrogel structure rapidly decomposed and the nanoparticles were released to the colonic lumen. Herein, the NP-gel formulation protected drug molecules during transit through the gastric gland and the small intestine, thereby maximizing the effective drug dosage to the site of action.

Site-specific drug targeting can also be achieved by modifying hydrogels with targeting ligands capable of specific binding to disease sites. For example, a silver-releasing antibacterial NP-gel consisting of silver nanoparticles and tissue-adhesive hydrogel has been developed.²⁵ In this design, the hydrogel building material PEG was modified with reactive catechol moieties to mimic the function of mussel adhesive proteins, in which the amino acid 3,4-dihydroxyphenylalanine (DOPA) that contains catechol played a critical role in enabling the mussel to adhere to various surfaces in an aqueous environment.⁵⁵ In the study, silver nitrate (AgNO_3 , 212 mM) was used to oxidize catechol gel ($\text{Ag}:\text{catechol} = 2:1$ mol/mol), leading to covalent cross-linking and hydrogel formation with simultaneous reduction of Ag(I) . Silver release was sustained for a period of at least two weeks in biological buffer solutions. The NP-gel was found to inhibit bacterial growth without significant cytotoxicity. Recently, gelatin hydrogel modified with DOPA showed similar bioadhesive properties and was able to withstand the shear force no less than 12.5 Pa inside the blood vessels (Figure 5).⁴⁸ In a mouse model of atherosclerosis, inflamed plaques treated with dexamethasone-eluting adhesive gels had reduced macrophage content and developed protective fibrous caps covering the plaque core. Treatment also lowered plasma cytokine levels and biomarkers of inflammation in the plaque. Meanwhile, the gel was shown to encapsulate both drug-loaded microparticles with diameters of 2~25 μm and fluorescently labeled nanoparticles with a diameter of 200 nm, and was able to durably adhere to the inside of a carotid artery in a living mouse. These glued particles released drugs directly into the vessel wall. Currently, novel bioadhesive hydrogels with remarkable performance under various physiological conditions are rapidly emerging.^{51, 67, 68} Combining drug-loaded nanoparticles with these hydrogels are expected to generate novel NP-gels with enhanced drug delivery efficiency and efficacy.

5. Detoxification

At first sight, it may appear a bit contradictory to dedicate a section to reviewing NP-gels for removing toxic compounds from the body, rather than delivering drugs. Upon closer inspection, these two opposing fields share many commonalities, as many new approaches in the field of detoxification rely on established drug delivery systems including nanoparticle technologies.²⁰ In fact, toxin-binding nanoparticles have recently attracted significant attention for detoxification applications aimed at removing both endogenous and exogenous poisonous from the body.¹¹² Among various detoxification platforms, red blood cell (RBC) membrane-coated nanoparticle system, where intact RBC membrane was wrapped onto polymeric nanoparticles (denoted as “nanosponges”), has been demonstrated as a robust toxin decoys for broad detoxification applications.⁴⁰ The ability of the nanosponges to neutralize pore-forming toxins indicated their application potential for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection.^{41, 42} Notably, MRSA

infection commonly localizes to skin and soft tissues.³⁰ In the infection, a critical element of virulence results from a diverse arsenal of pore-forming toxins secreted by the bacteria, which attack the host cells.^{31, 93} These distinctive features of MRSA infection recently motivated the development of a nanosponge–hydrogel hybrid formulation capable of localizing nanosponges at the infection site for localized anti-virulence treatment of MRSA infection (Figure 6).⁹⁷

In this NP-gel system, a 0.6% (w/w) PEGDMA crosslinker concentration was determined as it effectively retained nanosponges (with a diameter of 88.4 ± 0.3 nm, a surface zeta potential of -13.9 ± 0.9 mV, and a concentration of 2 mg/mL) within its matrix without compromising toxin transport for neutralization. Following subcutaneous injection to mice, nanosponges were effectively retained at the injection sites. In an MRSA subcutaneous mouse model, mice treated with the nanosponge–hydrogel hybrid showed markedly reduced MRSA skin lesion development. These results collectively indicate that the nanosponge–hydrogel hybrid formulation represents a new and effective detoxification strategy for the treatment of localized bacterial infection. Given the critical roles played by pore-forming toxins in pathogenesis of a wide range of bacteria, the nanosponge–hydrogel formulation holds significant potential to treat infectious diseases caused by various types of bacteria. More importantly, no antibiotics are involved in this new treatment, which is therefore unlikely to be affected by the existing bacterial antibiotic resistance mechanisms and will not exert selective pressure to bacteria for developing new resistance.

NP-gels offer additional advantages for detoxification applications. For example, confining detoxification nanoparticles within hydrogel network can potentially improve treatment safety. Particularly, for systemic detoxification, the conventional intravenous administration of nanoparticles for detoxification often leads to nanoparticle accumulation in the liver, posing a risk of secondary poisoning especially in liver-failure patients.^{39, 65} NP-gel formulation becomes attractive as the particle entrapment prevents their accumulation in liver. In addition, NP-gels can be easily removed from the body, a feature useful to limit the interaction of toxin-bound nanoparticles with the body to further enhance detoxification efficiency and safety. Furthermore, NP-gels can be molded to various shapes to recapitulate organ-specific detoxification mechanisms. For example, by using an advanced 3D printing technology, PEG hydrogels loaded with detoxification nanoparticles were molded to liver-mimetic structures with modified liver lobule configuration aimed to recapitulating the fast substances' exchange between blood stream and hepatic cells.³² The resulting NP-gel system had higher surface area than the original liver lobule and allowed toxins to enter the PEG matrix more effectively for neutralization.

For enzyme-based detoxification, hydrogel can encapsulate enzyme nanocomplexes and provide a confined environment similar to that of subcellular compartments for effective chemical transformation, molecule transport, and elimination of toxic metabolic wastes.^{12, 86} For example, invertase, glucose oxidase, and horseradish peroxidase with complementary functions were assembled and encapsulated within a thin layer of acrylamide gel to form enzyme nanocomplexes with a diameter approximately 30 ± 7 nm.⁵⁸ These nanocomplexes exhibited improved catalytic efficiency and enhanced stability when compared with free enzymes. Furthermore, the co-localized enzymes displayed complementary functions,

whereby toxic intermediates generated by one enzyme could be promptly eliminated by another enzyme. In the study, nanocomplexes containing alcohol oxidase and catalase could reduce blood alcohol levels in intoxicated mice, offering an alternative antidote and prophylactic for alcohol intoxication.⁵⁸

6. Summary

The innovative combination of nanoparticles and hydrogels, two entirely different types of biomaterials, has generated novel NP-gels with increased structural diversity and enhanced drug delivery properties. These hybrid biomaterials have shown superior capabilities in modulating drug release kinetics, releasing drugs in a remotely controlled and “on-demand” fashion, assisting site-specific drug targeting, and facilitating nanoparticle-based detoxification. These applications, collectively, have demonstrated NP-gels as a new and robust class of biomaterials with significant potential to improve drug delivery efficiency. Together with the development of NP-gels, nanoparticles have also been combined with other biomaterial platforms and devices, such as nanofibers,^{8, 79, 102} microneedle patches,^{15, 16} and nanomotors,^{81, 104} leading to more sophisticated drug delivery systems.

While significant progress has been made in developing and optimizing NP-gel formulations, challenges remain to improve their clinical applicability for drug delivery.³⁸ Especially for in vivo applications, one challenge is the foreign-body reactions, which frequently cause collagenous capsule formation and can potentially limit the performance of implantable NP-gels.^{52, 75} To address this challenge, novel material designs are emerging with superior capability of preventing capsule formation. Especially, the ultra-low-fouling zwitterionic hydrogels have been recently developed to resist the formation of a capsule for at least 3 months after subcutaneous implantation in mice.¹¹¹ These hydrogels also promote angiogenesis in surrounding tissue, with anti-inflammatory and pro-healing functions. Another set of major challenges lies in improving the ease of clinical usage of NP-gel formulation. In this respect, mechanisms that promote gelation at lower polymer concentrations and narrower gelation temperatures would reduce the risk of premature gelation inside the needle upon injection.¹⁰⁹ Similarly, for covalently cross-linked hydrogels, triggered gelation in situ may reduce the risk of syringe clogging. Novel cross-linkers or initiators can reduce potential *in vivo* toxicity and enable the use of single syringe as opposed to double-barreled syringes.¹⁸ With continual efforts, we expect NP-gel hybrid approaches to generate new designs of biomaterials and to facilitate the development of novel therapeutic and diagnostic tools in medicine.

Acknowledgments

This work is supported by the National Science Foundation Grant DMR-1505699 and the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number R01DK095168.

References

1. Al Ghanami RC, Saunders BR, Bosquillon C, Shakesheff KM, Alexander C. Responsive particulate dispersions for reversible building and deconstruction of 3D cell environments. *Soft Matter*. 2010; 6:5037–5044.

2. Aryal S, Hu CMJ, Zhang L. Polymeric nanoparticles with precise ratiometric control over drug loading for combination therapy. *Mol Pharm*. 2011; 8:1401–1407. [PubMed: 21696189]
3. Baumann MD, Kang CE, Stanwick JC, Wang Y, Kim H, Lapitsky Y, Shoichet MS. An injectable drug delivery platform for sustained combination therapy. *J Control Release*. 2009; 138:205–213. [PubMed: 19442692]
4. Baumann MD, Kang CE, Tator CH, Shoichet MS. Intrathecal delivery of a polymeric nanocomposite hydrogel after spinal cord injury. *Biomaterials*. 2010; 31:7631–7639. [PubMed: 20656347]
5. Bishop KJM, Wilmer CE, Soh S, Grzybowski BA. Nanoscale forces and their uses in self-assembly. *Small*. 2009; 5:1600–1630. [PubMed: 19517482]
6. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol*. 2015; 33:941–951. [PubMed: 26348965]
7. Caccavo D, Cascone S, Lamberti G, Barba AA. Modeling the drug release from hydrogel-based matrices. *Mol Pharm*. 2015; 12:474–483. [PubMed: 25495793]
8. Chen M, Gao S, Dong M, Song J, Yang C, Howard KA, Kjems J, Besenbacher F. Chitosan/siRNA nanoparticles encapsulated in PLGA nanofibers for siRNA delivery. *ACS Nano*. 2012; 6:4835–4844. [PubMed: 22621383]
9. Cho EC, Kim JW, Fernandez-Nieves A, Weitz DA. Highly responsive hydrogel scaffolds formed by three-dimensional organization of microgel nanoparticles. *Nano Lett*. 2008; 8:168–172. [PubMed: 18085810]
10. Chvatal SA, Kim YT, Bratt-Leal AM, Lee H, Bellamkonda RV. Spatial distribution and acute anti-inflammatory effects of methylprednisolone after sustained local delivery to the contused spinal cord. *Biomaterials*. 2008; 29:1967–1975. [PubMed: 18255138]
11. Cometa S, Iatta R, Ricci MA, Ferretti C, De Giglio E. Analytical characterization and antimicrobial properties of novel copper nanoparticle-loaded electrosynthesized hydrogel coatings. *J Bioact Compatible Polym*. 2013; 28:508–522.
12. Conrado RJ, Varner JD, DeLisa MP. Engineering the spatial organization of metabolic enzymes: Mimicking nature's synergy. *Curr Opin Biotechnol*. 2008; 19:492–499. [PubMed: 18725290]
13. Dang TT, Thai AV, Cohen J, Slosberg JE, Siniakowicz K, Doloff JC, Ma M, Hollister-Lock J, Tang KM, Gu Z, Cheng H, Weir GC, Langer R, Anderson DG. Enhanced function of immuno-isolated islets in diabetes therapy by co-encapsulation with an anti-inflammatory drug. *Biomaterials*. 2013; 34:5792–5801. [PubMed: 23660251]
14. Davis ME, Chen Z, Shin DM. Nanoparticle therapeutics: An emerging treatment modality for cancer. *Nat Rev Drug Discov*. 2008; 7:771–782. [PubMed: 18758474]
15. DeMuth PC, Su X, Samuel RE, Hammond PT, Irvine DJ. Nano-layered microneedles for transcutaneous delivery of polymer nanoparticles and plasmid DNA. *Adv Mater*. 2010; 22:4851–4856. [PubMed: 20859938]
16. DeMuth PC, Moon JJ, Suh H, Hammond PT, Irvine DJ. Releasable layer-by-layer assembly of stabilized lipid nanocapsules on microneedles for enhanced transcutaneous vaccine delivery. *ACS Nano*. 2012; 6:8041–8051. [PubMed: 22920601]
17. Dvir T, Timko BP, Kohane DS, Langer R. Nanotechnological strategies for engineering complex tissues. *Nat Nanotech*. 2011; 6:13–22.
18. Fairbanks BD, Schwartz MP, Bowman CN, Anseth KS. Photoinitiated polymerization of PEG-diacrylate with lithium phenyl-2,4,6-trimethylbenzoylphosphine: Polymerization rate and cytocompatibility. *Biomaterials*. 2009; 30:6702–6707. [PubMed: 19783300]
19. Fang RH, Zhang L. Combinatorial nanotherapeutics: Rewiring, then killing, cancer cells. *Sci Signal*. 2014; 7:pe13. [PubMed: 24825918]
20. Fang RH, Luk BT, Hu CMJ, Zhang L. Engineered nanoparticles mimicking cell membranes for toxin neutralization. *Adv Drug Del Rev*. 2015; 90:69–80.
21. Fang Y, Wang C-F, Zhang Z-H, Shao H, Chen S. Robust self-healing hydrogels assisted by cross-linked nanofiber networks. *Sci Rep*. 2013; 3:article number 2811.
22. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS Nano*. 2009; 3:16–20. [PubMed: 19206243]

23. Fraylich MR, Liu R, Richardson SM, Baird P, Hoyland J, Freemont AJ, Alexander C, Shakesheff K, Cellesi F, Saunders BR. Thermally-triggered gelation of PLGA dispersions: Towards an injectable colloidal cell delivery system. *J Colloid Interface Sci.* 2010; 344:61–69. [PubMed: 20070971]
24. Fuhrer R, Athanassiou EK, Luechinger NA, Stark WJ. Crosslinking metal nanoparticles into the polymer backbone of hydrogels enables preparation of soft, magnetic field-driven actuators with muscle-like flexibility. *Small.* 2009; 5:383–388. [PubMed: 19180549]
25. Fullenkamp DE, Rivera JG, Gong Y-k, Lau KHA, He L, Varshney R, Messersmith PB. Mussel-inspired silver-releasing antibacterial hydrogels. *Biomaterials.* 2012; 33:3783–3791. [PubMed: 22374454]
26. Gao W, Chan JM, Farokhzad OC. pH-responsive nanoparticles for drug delivery. *Mol Pharm.* 2010; 7:1913–1920. [PubMed: 20836539]
27. Gao W, Thamphiwatana S, Angsantikul P, Zhang L. Nanoparticle approaches against bacterial infections. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2014; 6:532–547. [PubMed: 25044325]
28. Gao W, Vecchio D, Li J, Zhu J, Zhang Q, Fu V, Li J, Thamphiwatana S, Lu D, Zhang L. Hydrogel containing nanoparticle-stabilized liposomes for topical antimicrobial delivery. *ACS Nano.* 2014; 8:2900–2907. [PubMed: 24483239]
29. Gobin AM, Lee MH, Halas NJ, James WD, Drezek RA, West JL. Near-infrared resonant nanoshells for combined optical imaging and photothermal cancer therapy. *Nano Lett.* 2007; 7:1929–1934. [PubMed: 17550297]
30. Gordon RJ, Lowy FD. Pathogenesis of methicillin-resistant staphylococcus aureus infection. *Clin Infect Dis.* 2008; 46:S350–S359. [PubMed: 18462090]
31. Gorwitz RJ. Understanding the success of methicillin-resistant staphylococcus aureus strains causing epidemic disease in the community. *J Infect Dis.* 2008; 197:179–182. [PubMed: 18173362]
32. Gou M, Qu X, Zhu W, Xiang M, Yang J, Zhang K, Wei Y, Chen S. Bio-inspired detoxification using 3d-printed hydrogel nanocomposites. *Nat Commun.* 2014; 5:article number 3774.
33. Grzelczak M, Vermant J, Furst EM, Liz-Marzan LM. Directed self-assembly of nanoparticles. *ACS Nano.* 2010; 4:3591–3605. [PubMed: 20568710]
34. Gu Z, Aimetti AA, Wang Q, Dang TT, Zhang Y, Veisoh O, Cheng H, Langer RS, Anderson DG. Injectable nano-network for glucose-mediated insulin delivery. *ACS Nano.* 2013; 7:4194–4201. [PubMed: 23638642]
35. Gulsen D, Li CC, Chauhan A. Dispersion of dmpc liposomes in contact lenses for ophthalmic drug delivery. *Curr Eye Res.* 2005; 30:1071–1080. [PubMed: 16354620]
36. Gupta P, Vermani K, Garg S. Hydrogels: From controlled release to ph-responsive drug delivery. *Drug Discov Today.* 2002; 7:569–579. [PubMed: 12047857]
37. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. *J Pharm Sci.* 1961; 50:874–875. [PubMed: 13907269]
38. Hoare TR, Kohane DS. Hydrogels in drug delivery: Progress and challenges. *Polymer.* 2008; 49:1993–2007.
39. Hoshino Y, Koide H, Furuya K, Haberaecker WW III, Lee S-H, Kodama T, Kanazawa H, Oku N, Shea KJ. The rational design of a synthetic polymer nanoparticle that neutralizes a toxic peptide in vivo. *Proc Natl Acad Sci U S A.* 2012; 109:33–38. [PubMed: 22198772]
40. Hu CMJ, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. *Proc Natl Acad Sci U S A.* 2011; 108:10980–10985. [PubMed: 21690347]
41. Hu CMJ, Fang RH, Copp J, Luk BT, Zhang L. A biomimetic nanosponge that absorbs pore-forming toxins. *Nat Nanotech.* 2013; 8:336–340.
42. Hu CMJ, Fang RH, Luk BT, Zhang L. Nanoparticle-detained toxins for safe and effective vaccination. *Nat Nanotech.* 2013; 8:933–938.
43. Hu CMJ, Fang RH, Wang KC, Luk BT, Thamphiwatana S, Dehaini D, Phu N, Angsantikul P, Wen CH, Kroll AV, Carpenter C, Ramesh M, Qu V, Patel SH, Zhu J, Shi W, Hofman FM, Chen TC,

- Gao W, Zhang K, Chien S, Zhang L. Nanoparticle biointerfacing by platelet membrane cloaking. *Nature*. 2015; 526:118–121. [PubMed: 26374997]
44. Huebsch N, Mooney DJ. Inspiration and application in the evolution of biomaterials. *Nature*. 2009; 462:426–432. [PubMed: 19940912]
 45. Ilg P. Stimuli-responsive hydrogels cross-linked by magnetic nanoparticles. *Soft Matter*. 2013; 9:3465–3468.
 46. Jung HJ, Abou-Jaoude M, Carbia BE, Plummer C, Chauhan A. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. *J Control Release*. 2013; 165:82–89. [PubMed: 23123188]
 47. Kapoor Y, Chauhan A. Drug and surfactant transport in cyclosporine a and brij 98 laden p-hema hydrogels. *J Colloid Interface Sci*. 2008; 322:624–633. [PubMed: 18359493]
 48. Kastrup CJ, Nahrendorf M, Figueiredo JL, Lee H, Kambhampati S, Lee T, Cho SW, Gorbatov R, Iwamoto Y, Dang TT, Dutta P, Yeon JH, Cheng H, Pritchard CD, Vegas AJ, Siegel CD, MacDougall S, Okonkwo M, Anh T, Stone JR, Coury AJ, Weissleder R, Langer R, Anderson DG. Painting blood vessels and atherosclerotic plaques with an adhesive drug depot. *Proc Natl Acad Sci U S A*. 2012; 109:21444–21449. [PubMed: 23236189]
 49. Ke H, Jianfei S, Zhaobin G, Peng W, Qiang C, Ming M, Ning G. A novel magnetic hydrogel with aligned magnetic colloidal assemblies showing controllable enhancement of magnetothermal effect in the presence of alternating magnetic field. *Adv Mater*. 2015; 27:2507–2514. [PubMed: 25753892]
 50. Kolishetti N, Dhar S, Valencia PM, Lin LQ, Karnik R, Lippard SJ, Langer R, Farokhzad OC. Engineering of self-assembled nanoparticle platform for precisely controlled combination drug therapy. *Proc Natl Acad Sci U S A*. 2010; 107:17939–17944. [PubMed: 20921363]
 51. Lang N, Pereira MJ, Lee Y, Friehs I, Vasilyev NV, Feins EN, Ablasser K, O’Cearbhaill ED, Xu C, Fabozzo A, Padera R, Wasserman S, Freudenthal F, Ferreira LS, Langer R, Karp JM, del Nido PJ. A blood-resistant surgical glue for minimally invasive repair of vessels and heart defects. *Sci Transl Med*. 2014; 6:218ra216.
 52. Langer R. Perspectives and challenges in tissue engineering and regenerative medicine. *Adv Mater*. 2009; 21:3235–3236. [PubMed: 20882493]
 53. Laroui H, Dalmasso G, Nguyen HTT, Yan Y, Sitaraman SV, Merlin D. Drug-loaded nanoparticles targeted to the colon with polysaccharide hydrogel reduce colitis in a mouse model. *Gastroenterology*. 2010; 138:843–853. [PubMed: 19909746]
 54. Li F, Josephson DP, Stein A. Colloidal assembly: The road from particles to colloidal molecules and crystals. *Angew Chem Int Ed*. 2011; 50:360–388.
 55. Li L, Smitthipong W, Zeng H. Mussel-inspired hydrogels for biomedical and environmental applications. *Polym Chem*. 2015; 6:353–358.
 56. Lin CC, Metters AT. Hydrogels in controlled release formulations: Network design and mathematical modeling. *Adv Drug Del Rev*. 2006; 58:1379–1408.
 57. Liu TY, Hu SH, Liu KH, Liu DM, Chen SY. Study on controlled drug permeation of magnetic-sensitive ferrogels: Effect of Fe₃O₄ and PVA. *J Control Release*. 2008; 126:228–236. [PubMed: 18237812]
 58. Liu Y, Du J, Yan M, Lau MY, Hu J, Han H, Yang OO, Liang S, Wei W, Wang H, Li J, Zhu X, Shi L, Chen W, Ji C, Lu Y. Biomimetic enzyme nanocomplexes and their use as antidotes and preventive measures for alcohol intoxication. *Nat Nanotech*. 2013; 8:187–192.
 59. Lobatto ME, Fuster V, Fayad ZA, Mulder WJM. Perspectives and opportunities for nanomedicine in the management of atherosclerosis. *Nat Rev Drug Discov*. 2011; 10:835–852. [PubMed: 22015921]
 60. Ma L, Kohli M, Smith A. Nanoparticles for combination drug therapy. *ACS Nano*. 2013; 7:9518–9525. [PubMed: 24274814]
 61. Merino S, Martin C, Kostarelos K, Prato M, Vazquez E. Nanocomposite hydrogels: 3d polymer-nanoparticle synergies for on-demand drug delivery. *ACS Nano*. 2015; 9:4686–4697. [PubMed: 25938172]

62. Messing R, Frickel N, Belkoura L, Strey R, Rahn H, Odenbach S, Schmidt AM. Cobalt ferrite nanoparticles as multifunctional cross-linkers in paam ferrohydrogels. *Macromolecules*. 2011; 44:2990–2999.
63. Mohan YM, Lee K, Premkumar T, Geckeler KE. Hydrogel networks as nanoreactors: A novel approach to silver nanoparticles for antibacterial applications. *Polymer*. 2007; 48:158–164.
64. Morton SW, Lee MJ, Deng ZJ, Dreaden EC, Sioue E, Shopsowitz KE, Shah NJ, Yaffe MB, Hammond PT. A nanoparticle-based combination chemotherapy delivery system for enhanced tumor killing by dynamic rewiring of signaling pathways. *Sci Signal*. 2014; 7:ra44. [PubMed: 24825919]
65. Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. *Science*. 2006; 311:622–627. [PubMed: 16456071]
66. Ninh C, Cramer M, Bettinger CJ. Photoresponsive hydrogel networks using melanin nanoparticle photothermal sensitizers. *Biomater Sci*. 2014; 2:766–774. [PubMed: 26828866]
67. Park CG, Shasteen C, Amoozgar Z, Park J, Kim SN, Lee JE, Lee MJ, Suh Y, Seok HK, Yeo Y, Choy YB. Photo-crosslinkable chitosan hydrogel as a bioadhesive for esophageal stents. *Macromol Res*. 2015; 23:882–884.
68. Patel RG, Purwada A, Cerchietti L, Inghirami G, Melnick A, Gaharwar AK, Singh A. Microscale bioadhesive hydrogel arrays for cell engineering applications. *Cell Mol Bioeng*. 2014; 7:394–408. [PubMed: 25328548]
69. Peppas NA, Hilt JZ, Khademhosseini A, Langer R. Hydrogels in biology and medicine: From molecular principles to bionanotechnology. *Adv Mater*. 2006; 18:1345–1360.
70. Petros RA, DeSimone JM. Strategies in the design of nanoparticles for therapeutic applications. *Nat Rev Drug Discov*. 2010; 9:615–627. [PubMed: 20616808]
71. Place ES, Evans ND, Stevens MM. Complexity in biomaterials for tissue engineering. *Nat Mater*. 2009; 8:457–470. [PubMed: 19458646]
72. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. *Adv Drug Del Rev*. 2001; 53:321–339.
73. Qu Y, Chu BY, Peng JR, Liao JF, Qi TT, Shi K, Zhang XN, Wei YQ, Qian ZY. A biodegradable thermo-responsive hybrid hydrogel: Therapeutic applications in preventing the post-operative recurrence of breast cancer. *NPG Asia Materials*. 2015; 7:e207.
74. Ramer LM, Ramer MS, Steeves JD. Setting the stage for functional repair of spinal cord injuries: A cast of thousands. *Spinal Cord*. 2005; 43:134–161. [PubMed: 15672094]
75. Ratner BD. Reducing capsular thickness and enhancing angiogenesis around implant drug release systems. *J Control Release*. 2002; 78:211–218. [PubMed: 11772462]
76. Rattanaeuangsrikul V, Pimpha N, Supaphol P. In vitro efficacy and toxicology evaluation of silver nanoparticle-loaded gelatin hydrogel pads as antibacterial wound dressings. *J Appl Polym Sci*. 2012; 124:1668–1682.
77. Romero MI, Rangappa N, Garry MG, Smith GM. Functional regeneration of chronically injured sensory afferents into adult spinal cord after neurotrophin gene therapy. *J Neurosci*. 2001; 21:8408–8416. [PubMed: 11606629]
78. Roux R, Ladaviere C, Montebault A, Delair T. Particle assemblies: Toward new tools for regenerative medicine. *Mater Sci Eng C Mater Biol Appl*. 2013; 33:997–1007. [PubMed: 23827536]
79. Saquing CD, Manasco JL, Khan SA. Electrospun nanoparticle-nanofiber composites via a one-step synthesis. *Small*. 2009; 5:944–951. [PubMed: 19283795]
80. Satarkar NS, Hilt JZ. Magnetic hydrogel nanocomposites for remote controlled pulsatile drug release. *J Control Release*. 2008; 130:246–251. [PubMed: 18606201]
81. Sattayasamitsathit S, Kou H, Gao W, Thavarajah W, Kaufmann K, Zhang L, Wang J. Fully loaded micromotors for combinatorial delivery and autonomous release of cargoes. *Small*. 2014; 10:2830–2833. [PubMed: 24706367]
82. Schaefer-Korting M, Mehnert W, Korting HC. Lipid nanoparticles for improved topical application of drugs for skin diseases. *Adv Drug Del Rev*. 2007; 59:427–443.
83. Schexnailder P, Schmidt G. Nanocomposite polymer hydrogels. *Colloid Polym Sci*. 2009; 287:1–11.

84. Schmaljohann D. Thermo- and pH-responsive polymers in drug delivery. *Adv Drug Del Rev.* 2006; 58:1655–1670.
85. Schmid-Wendtner MH, Korting HC. The pH of the skin surface and its impact on the barrier function. *Skin Pharmacol Physiol.* 2006; 19:296–302. [PubMed: 16864974]
86. Schoffelen S, van Hest JCM. Multi-enzyme systems: Bringing enzymes together in vitro. *Soft Matter.* 2012; 8:1736–1746.
87. Sekine Y, Moritani Y, Ikeda-Fukazawa T, Sasaki Y, Akiyoshi K. A hybrid hydrogel biomaterial by nanogel engineering: Bottom-up design with nanogel and liposome building blocks to develop a multidrug delivery system. *Adv Healthc Mater.* 2012; 1:722–728. [PubMed: 23184823]
88. Sethi M, Sukumar R, Karve S, Werner ME, Wang EC, Moore DT, Kowalczyk SR, Zhang L, Wang AZ. Effect of drug release kinetics on nanoparticle therapeutic efficacy and toxicity. *Nanoscale.* 2014; 6:2321–2327. [PubMed: 24418914]
89. Shi J, Votruba AR, Farokhzad OC, Langer R. Nanotechnology in drug delivery and tissue engineering: From discovery to applications. *Nano Lett.* 2010; 10:3223–3230. [PubMed: 20726522]
90. Shi J, Xiao Z, Kamaly N, Farokhzad OC. Self-assembled targeted nanoparticles: Evolution of technologies and bench to bedside translation. *Acc Chem Res.* 2011; 44:1123–1134. [PubMed: 21692448]
91. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (hpmc). *Adv Drug Del Rev.* 2001; 48:139–157.
92. Siepmann J, Peppas NA. Higuchi equation: Derivation, applications, use and misuse. *Int J Pharm.* 2011; 418:6–12. [PubMed: 21458553]
93. Singer AJ, Talan DA. Management of skin abscesses in the era of methicillin-resistant staphylococcus aureus. *New Engl J Med.* 2014; 370:1039–1047. [PubMed: 24620867]
94. Thomas V, Yallapu MM, Sreedhar B, Bajpai SK. Breathing-in/breathing-out approach to preparing nanosilver-loaded hydrogels: Highly efficient antibacterial nanocomposites. *J Appl Polym Sci.* 2009; 111:934–944.
95. Timko BP, Whitehead K, Gao W, Kohane DS, Farokhzad O, Anderson D, Langer R. Advances in drug delivery. *Annu Rev Mater Res.* 2011; 41:1–20.
96. Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. *Annu Rev Med.* 2012; 63:185–198. [PubMed: 21888516]
97. Wang F, Gao W, Thamphiwatana S, Luk BT, Angsantikul P, Zhang Q, Hu CMJ, Fang RH, Copp JA, Pornpattananankul D, Lu W, Zhang L. Hydrogel retaining toxin-absorbing nanosponges for local treatment of methicillin-resistant staphylococcus aureus infection. *Adv Mater.* 2015; 27:3437–3443. [PubMed: 25931231]
98. Wang H, Hansen MB, Loewik DWPM, van Hest JCM, Li Y, Jansen JA, Leeuwenburgh SCG. Oppositely charged gelatin nanospheres as building blocks for injectable and biodegradable gels. *Adv Mater.* 2011; 23:H119–H124. [PubMed: 21394793]
99. Wang Q, Wang L, Detamore MS, Berkland C. Biodegradable colloidal gels as moldable tissue engineering scaffolds. *Adv Mater.* 2008; 20:236–239.
100. Wang Q, Jamal S, Detamore MS, Berkland C. PLGA-chitosan/PLGA-alginate nanoparticle blends as biodegradable colloidal gels for seeding human umbilical cord mesenchymal stem cells. *J Biomed Mater Res A.* 2011; 96A:520–527. [PubMed: 21254383]
101. Wang Q, Gu Z, Jamal S, Detamore MS, Berkland C. Hybrid hydroxyapatite nanoparticle colloidal gels are injectable fillers for bone tissue engineering. *Tissue Eng Part A.* 2013; 19:2586–2593. [PubMed: 23815275]
102. Wang S, Zhao Y, Shen M, Shi X. Electrospun hybrid nanofibers doped with nanoparticles or nanotubes for biomedical applications. *Ther Deliv.* 2012; 3:1155–1169. [PubMed: 23116009]
103. Wang Y, Li B, Zhou Y, Han Z, Feng Y, Wei D. A facile concentric-layered magnetic chitosan hydrogel with magnetic field remote stimulated drug release. *J Control Release.* 2013; 172:E90.
104. Wu Z, de Avila BEF, Martin A, Christianson C, Gao W, Thamphiwatana SK, Escarpa A, He Q, Zhang L, Wang J. RBC micromotors carrying multiple cargos towards potential theranostic applications. *Nanoscale.* 2015; 7:13680–13686. [PubMed: 26214151]

105. Xia L-W, Xie R, Ju X-J, Wang W, Chen Q, Chu L-Y. Nano-structured smart hydrogels with rapid response and high elasticity. *Nat Commun.* 2013; 4:article number 2226.
106. Xiang Y, Chen D. Preparation of a novel pH-responsive silver nanoparticle/poly (HEMA-PEGMA-MAA) composite hydrogel. *Eur Polym J.* 2007; 43:4178–4187.
107. Yan B, Boyer JC, Habault D, Branda NR, Zhao Y. Near infrared light triggered release of biomacromolecules from hydrogels loaded with upconversion nanoparticles. *J Am Chem Soc.* 2012; 134:16558–16561. [PubMed: 23013429]
108. Yoon YM, Lewis JS, Carstens MR, Campbell-Thompson M, Wasserfall CH, Atkinson MA, Keselowsky BG. A combination hydrogel microparticle-based vaccine prevents type 1 diabetes in non-obese diabetic mice. *Sci Rep.* 2015; 5
109. Yu L, Ding J. Injectable hydrogels as unique biomedical materials. *Chem Soc Rev.* 2008; 37:1473–1481. [PubMed: 18648673]
110. Zhang J, Li Y, Zhang X, Yang B. Colloidal self-assembly meets nanofabrication: From two-dimensional colloidal crystals to nanostructure arrays. *Adv Mater.* 2010; 22:4249–4269. [PubMed: 20803529]
111. Zhang L, Cao Z, Bai T, Carr L, Ella-Menye JR, Irvin C, Ratner BD, Jiang S. Zwitterionic hydrogels implanted in mice resist the foreign-body reaction. *Nat Biotechnol.* 2013; 31:553–556. [PubMed: 23666011]
112. Zhang L, Leroux JC. Current and forthcoming approaches for systemic detoxification preface. *Adv Drug Del Rev.* 2015; 90:1–2.
113. Zhang X, Pint CL, Lee MH, Schubert BE, Jamshidi A, Takei K, Ko H, Gillies A, Bardhan R, Urban JJ, Wu M, Fearing R, Javey A. Optically- and thermally-responsive programmable materials based on carbon nanotube-hydrogel polymer composites. *Nano Lett.* 2011; 11:3239–3244. [PubMed: 21736337]
114. Zhao X, Kim J, Cezar CA, Huebsch N, Lee K, Bouhadir K, Mooney DJ. Active scaffolds for on-demand drug and cell delivery. *Proc Natl Acad Sci U S A.* 2011; 108:67–72. [PubMed: 21149682]
115. Zhao XL, Ding XB, Deng ZH, Zheng ZH, Peng YX, Tian CR, Long XP. A kind of smart gold nanoparticle-hydrogel composite with tunable thermo-switchable electrical properties. *New J Chem.* 2006; 30:915–920.
116. Zhu CH, Lu Y, Peng J, Chen JF, Yu SH. Photothermally sensitive poly(n-isopropylacrylamide)/graphene oxide nanocomposite hydrogels as remote light-controlled liquid microvalves. *Adv Funct Mater.* 2012; 22:4017–4022.
117. Zhu W, Li Y, Liu L, Chen Y, Wang C, Xi F. Supramolecular hydrogels from cisplatin-loaded block copolymer nanoparticles and alpha-cyclodextrins with a stepwise delivery property. *Biomacromolecules.* 2010; 11:3086–3092. [PubMed: 20958000]

Figure 1. Schematic illustrations of two types of nanoparticle-hydrogel (NP-gel) systems: (A) nanocomposite hydrogel, where nanoparticles are embedded into hydrogel network, and (B) nanoparticle colloidal hydrogel, where nanoparticles are directly used as cross-linkers to construct 3D hydrogel network.

Figure 2.

(A) Schematic illustration of hydrogel containing nanoparticle-stabilized liposomes for topical antimicrobial delivery. Carboxyl-modified gold nanoparticles (AuC) were adsorbed onto the outer surfaces of cationic liposomes to stabilize them against fusion. The AuC-liposomes were subsequently embedded into an acrylamide-based hydrogel. At neutral pH, AuC-liposomes were released from the hydrogel in their entirety. When the pH drops below the pKa value of the carboxylic group ($pK_a \sim 5$), the AuC stabilizers detached from the liposomes, resulting in the formation of bare liposomes with resumed fusion activity. (B) Accumulative liposome release profile from the hydrogel made with three different cross-linker concentrations of 0.6, 0.7, and 0.8 vol %, respectively. (C–E) Fluorescence study of the fusion interaction between hydrogel-released liposomes and *S. aureus* bacteria. Liposomes were labeled with fluorescent dye RhB (red) and the bacteria were stained with DAPI (blue). (C) Control bacteria without any treatment, (D) bacteria incubated with AuC-liposome-loaded hydrogel at pH = 7.4, (E) bacteria incubated with AuC-liposome-loaded hydrogel at pH = 4.5. Scale bar, 1 μ m. Reproduced with permission from Ref. 28.

Figure 3.

(A) Schematic illustration of a hybrid hydrogel system in which gold nanorods (GNRs) were doped into a thermally responsive hydrogel. A near-infrared (NIR) laser was used to trigger the release of loaded Doxorubicin (DOX) by utilizing the photothermal effect of GNRs to induce the contraction of the thermo-responsive hydrogels. SEM images of hydrogels at (B) 25°C and (C) 45°C (C). (D) DOX-release profiles in the presence and absence of NIR laser at pH 5.0 and 7.4. (E) In vivo survival rate of mice bearing breast cancer treated by different samples. Reproduced with permission from Ref. 73.

Figure 4.

(A) Nanoparticles encapsulating insulin and glucosespecific enzymes (GOx, glucose oxidase; CAT, catalase) are made of acidic sensitive acetal-modified dextran (B) and coated with chitosan and alginate, respectively. (C) NP-gel is formed by mixing oppositely charged nanoparticles together and efficiently degrades to release insulin upon the catalytic generation of gluconic acid under hyperglycemic conditions. (D) Schematic of glucose-mediated insulin delivery for type 1 diabetes treatment using the STZ-induced diabetic mice model. (E) SEM images of nanoparticles coated with chitosan and alginate and formation of a NP-gel. (F) In vitro accumulated insulin release of the NP-gel in different glucose concentrations at 37°C. (G) Self-regulated profile of the NP-gel presents the rate of insulin release as a function of glucose concentration. Reproduced with permission from Ref. 34.

Figure 5.

(A) Chemical structure of alginate-catechol, synthesized from alginate. (B) Schematic of a microfluidic system used to compare the adhesion of alginate and alginate-catechol gels. (C) Schematic of the gel (green) being deposited on endothelial cells (blue) grown inside the device. (D) Fluorescence images of the gels containing fluorescent particles (green and purple) coated on endothelial cells in microfluidic channels (dashed lines). The unmodified alginate does not remain adhered at physiological shear stress, whereas the alginate-catechol remains adhered above physiological shear stress. (E) Quantifying the percent of gel that remained covered on the microfluidic channels at various shear stresses. (F) Quantifying the shear strength of the gels using a lap-shear tensile strain test. (G) Intravital fluorescence microscopy image of a carotid artery in a living mouse coated with the adhesive gel containing 200-nm particles (green). A fluorescent dye (red) is seen in the artery after it was injected intravenously, indicating that blood flowed through it. (H) Histological section of one wall of a carotid artery (red, elastin) coated for 28 d with the adhesive gel (green fluorescent particles). (I) Intravital microscopy images of the gel adhered to a carotid artery in a living mouse on days 1 and 5 after deposition. Reproduced with permission from Ref. 48.

Figure 6.

(A) Schematic illustration of a hydrogel retaining toxin-absorbing nanosponges (NS-gel) for local treatment of MRSA infection. The nanosponge was constructed with a polymeric core wrapped in natural RBC bilayer membrane and was subsequently embedded into an acrylamide-based hydrogel. (B) A scanning electron microscopy (SEM) image of the NS-gel. Scale bar, 1 μm. (C) A transmission electron microscopy (TEM) image showing the spherical core-shell structure of the nanosponges under negative staining with uranyl acetate. Scale bar, 50 nm. (D) In vivo nanosponge retention by hydrogel. Nanosponges labeled with DiD fluorescent dye was used to formulate NS-gel, which was then injected subcutaneously under the loose skin over the left flank of the mice. Free nanosponges (without hydrogel) were injected as a control group at the right flank of the same mice. Fluorescence images taken at different time points show the retention of the nanosponges under mouse skin. (E) In vivo treatment of MRSA infection. 1×10^9 CFU of MRSA 252 was mixed with 0.2 mL of 2 mg/mL NS-gel or empty gels, followed by subcutaneous injection to the backs of the mice ($n = 9$). Skin lesions were monitored and photographed on day 1–4 after the injections and the lesion sizes were measured. Bars represent median values. * $P < 0.05$, n.s.: not significant. Reproduced with permission from Ref. 97.