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Supramolecular hydrogels: Synthesis, properties and their biomedical applications

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REVIEW

Supramolecular hydrogels: Synthesis, properties and their biomedical applications

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As a novel class of three-dimensional (3D) hydrophilic cross-linked polymers, supramolecular hydrogels not only display unique physicochemical properties (*e.g.*, water-retention ability, drug loading capacity, biodegradability and biocompatibility, biostability) as well as specific functionalities (*e.g.*, optoelectronic property, bioactivity, self-healing ability, shape memory ability), but also have the capability to undergo reversible gel-sol transition in response to various environmental stimuli inherent to the noncovalent cross-linkages, thereby showing great potential as promising biomaterial scaffolds for diagnosis and therapy. In this Review, we summarized the recent progress in the design and synthesis of supramolecular hydrogels through specific, directional noncovalent interactions, with a particular emphasis on the structure-property relationship, as well as their wide-ranging applications in disease diagnosis and therapy including bioimaging, biodetection, therapeutic delivery, and tissue engineering. We believe that these current achievements on supramolecular hydrogels will greatly stimulate new ideas and inspire persistent efforts in this hot topic area in future.

Introduction

Hydrogels are 3D hydrophilic cross-linked polymer networks with physical characteristics similar to soft biological tissues, which can hold a large amount of water via surface tension or capillary effect, making them increasingly important for widespread applications ranging from academic research to industrial fields.[1-9] In view of the types of the driving forces for cross-linking, hydrogels can be divided into two major categories: synthetic hydrogels and supramolecular hydrogels. Generally, synthetic hydrogels are formed by permanent chemical cross-links between the polymer chains via non-reversible covalent bonds. Since the first example of synthetic hydrogels was reported by Wichterle and Lim in 1960,[10] synthetic hydrogels based on both natural and synthetic polymers have been of great interest for a wide range of biomedical applications from drug delivery to tissue engineering owing to their hydrophilic character and potential to be biocompatible.[11,12] However, such hydrogels are often brittle, at times opaque and without the ability to self-heal when the cross-linked network is broken, thus greatly limiting their application in various biomedical fields. For example, the incorporation of drugs by sorption may be time-consuming and offer only limited loading content. Furthermore, the cross-linking reaction may also conjugate drugs to the hydrogel or even undermine the integrity of drugs, while the hydrogel itself may become non-biodegradable with an ill-defined composition.[13] Therefore, an advanced delivery formulation in which gelation and drug loading can be achieved simultaneously in aqueous media without covalent cross-linking is keenly anticipated.

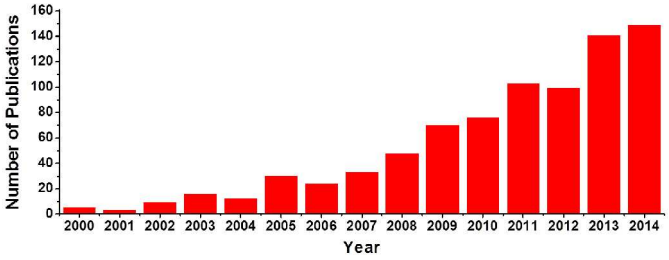

Fig. 1 Histogram of the number of publications by year on "supramolecular hydrogel" in the Web of Science.

Supramolecular hydrogels, which perfectly combine the advantages of synthetic hydrogels with those of supramolecular polymers,[14-18] are a novel class of noncovalently cross-linked polymer materials.[5-9] The supramolecular cross-linking by various noncovalent interactions such as hydrogen bonding, metal-ligand coordination, host-guest recognition, and electrostatic interaction remarkably reduces the structural flexibility and alters the macroscopic performance, resulting in the formation of 3D cross-linked networks. In sharp contrast, such noncovalent hydrogels show not only the moderate mechanical properties gained from polymeric building blocks, but also reversible gel-sol transition behavior in response to a wide variety of bio-related stimuli (*e.g.*, pH, redox agents, enzymes, bioactive molecules) and processability inherent to the supramolecular cross-linking units, which can serve as either intelligent carriers for delivering versatile therapeutic agents (*e.g.*, drugs, genes, proteins) or promising matrices for repairing and regenerating tissues and organs in the human

body. In recent years, a rapidly growing number of publications on supramolecular hydrogels have been reported (Fig. 1). Considering recent advances in this emerging area, a systematic summary of the synthesis, properties, and bioapplications of supramolecular hydrogels is urgently required.

In this review, we summarized recent developments in the design and synthesis of supramolecular hydrogels, as well as their applications in disease diagnosis and therapy such as bioimaging, biodetection, therapeutic delivery, and tissue engineering. We expect that, based on our review of current representative achievements in this area, the important position and bright prospect of supramolecular hydrogels as promising biomaterial scaffolds for clinical diagnosis and therapy are clearly presented.

Design and preparation

Noncovalent interactions

As a novel class of 3D cross-linked polymer materials, hydrogels can be acquired by using either a covalent cross-linking or a noncovalent cross-linking approach. Covalent cross-linking generally affords relatively brittle chemical hydrogels with poor transparency. Such hydrogels lack the ability to self-heal once the cross-linked network is broken. In contrast, the dynamic and reversible noncovalent interactions can be used either as the structural cross-linkages (*direct formation*) or for driving nanofiber formation with subsequent inter-nanofiber entanglement (*indirect formation*), leading to the formation of supramolecular hydrogels. The thermodynamic and molecular dynamic parameters of the supramolecular cross-linkages are crucial in determining the physiochemical properties and macroscopic behaviors of the resultant supramolecular hydrogel materials. In general, the equilibrium constant directly affects the cross-link density of the supramolecular hydrogels, whilst the kinetics directly affects the dynamic nature of the cross-linkages between polymer chains.[7]

Over the past two decades, supramolecular hydrogels have been developed using a wide variety of supramolecular motifs, such as hydrogen bonding, metal-ligand coordination, host-guest recognition and electrostatic interaction (Fig. 2a). On account of the specificity and directionality, hydrogen bonding can be used as the main driving force to construct biological and synthetic supramolecular hydrogels with smart response to environmental pH variation, which can be regarded as promising drug vehicles for cancer therapy.[5] However, one major disadvantage of the hydrogen bonding is the ease of disassociation against polar solvents such as water. Metal-ligand coordination is extremely promising for the design of tough and stiff supramolecular hydrogels along with exceptional photoelectric properties in aqueous media. Some metallo-supramolecular hydrogel systems do not show dynamic feature on experimental time-scales because some metal ions such as Ru(II) are essentially inert.[19] Host-guest recognition based on a wide variety of macrocycles including cyclodextrin (CD), crown ether, calixarene, cucurbit[n]uril (CB[n]), and pillar[n]arene is another fascinating and widely used noncovalent interaction. Particularly, CD and CB[n]-based host-guest couples are nontoxic and biocompatible, and are primarily useful in water, thereby providing a powerful platform to build smart supramolecular hydrogels for numerous biological applications.[7,8,13] In addition, strong, multivalent electrostatic interaction between two oppositely charged polyelectrolytes usually results in the formation of extremely strong, opaque materials.[20] However, the addition of a neutral hydrophilic block to the polyelectrolyte chain can effectively prevent macroscopic phase separation, thereby producing supramolecular hydrogels. In sharp contrast, the combined use of multiple orthogonal noncovalent interactions into one system will endow the resultant supramolecular hydrogels with enhanced mechanical properties and biostability, as well as multiple stimuli-responsiveness.

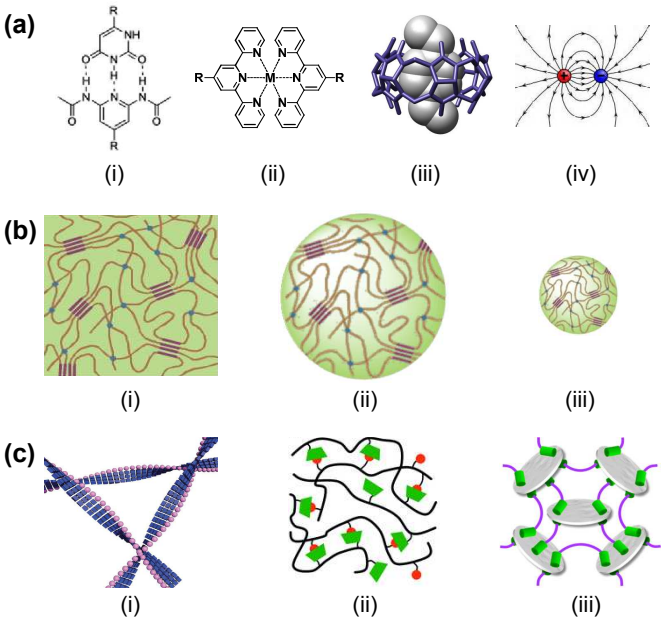

Fig. 2 (a) Types of noncovalent interactions for the preparation of supramolecular hydrogels (i) hydrogen bonding, (ii) metal-ligand coordination, (iii) host–guest recognition and (iv) electrostatic interaction. (b) Classes of supramolecular hydrogels in view of the size: (i) macrohydrogel, (ii) microhydrogel and (iii) nanohydrogel. (c) Classes of supramolecular hydrogels according to the types of the building blocks: (i) molecular hydrogel, (ii) supramolecular polymeric hydrogel and (iii) supramolecular hybrid hydrogel.

Size

On the basis of the size of cross-linked networks, supramolecular hydrogels can be divided into three major types: (i) macrohydrogel, (ii) microhydrogel and (iii) nanohydrogel (Fig. 2b). Herein, the macrohydrogels refer to macroscale supramolecular hydrogels, which generally possess infinite cross-linked networks. In most cases, multivalent noncovalent interactions often lead to uncontrollable growth of cross-linking networks, further yielding macrohydrogels. Owing to their 3D dynamic cross-linked networks and *in situ* gelation when arriving at the tissues, such hydrogels show extreme potential as injectable scaffolds for controlled delivery of drugs, genes, and proteins, as well as *in vivo* tissue regeneration and repair.

The internal structure of microhydrogels and nanohydrogels is similar to that of macrohydrogels, but varies in size and responsiveness. Nowadays, numerous strategies have been explored to engineer microscale and nanoscale hydrogels for a wide range of biomedical applications. The microhydrogels refer to microscale hydrogels, which have the size of between 1 and 100 μm comparable to that of the human cells. Particularly, nano-engineered hydrogels with less than 200 nm in size, namely, nanohydrogels, can be effectively endocytosized by the

cells, which offer an innovative platform for safe and efficient delivery of drugs, genes, and proteins towards the targeted cells, tissues and organs of the human body.[21,22] In recent years, our group developed several kinds of nanohydrogels based different noncovalent interactions, which show great potential in bioimaging and drug delivery.[23-25] To our knowledge, the size of nanohydrogels has an extremely important effect on their properties/functions, internalization pathways, cytotoxicity, and therapeutic efficacy,[26] thus, it becomes urgent to develop simple but efficient approaches for the control of the nanohydrogel size. In an example, the alteration of the molar ratio of chemical compounds leads to a dramatic change in size of nanohydrogels, which provides a robust platform for the preparation of size-controlled supramolecular carriers for cancer diagnosis and therapy.[24,27] However, nanohydrogels are still in preliminary development stages but hold tremendous promise to offer an intelligent vaccine strategy for the control of several chronic diseases ranging from cancers to infectious diseases.

Building blocks

In view of the types of building blocks, supramolecular hydrogels mainly involve molecular hydrogels, supramolecular polymeric hydrogels and supramolecular hybrid hydrogels (Fig. 2c). For molecular hydrogels,[28-37] low-molecular-weight building blocks (*e.g.*, peptide amphiphiles,[28-31] hydrophilic macrocyclic hosts,[32,33] synthetic molecules tagged with supramolecular motifs[34,35]) firstly form fiber-like structures driven by various noncovalent interactions, and then a subsequent noncovalent cross-linking/entanglement occurs between the resultant supramolecular nanofibers. The preparation of molecular hydrogels clearly involves two main stages, the self-assembly and cross-linking of supramolecular nanofibers. Such hydrogels consisting of a 3D network of well-defined nanofibers can be smoothly degraded in physiological conditions because of low-molecular-weight building blocks and smart responsiveness to various biological stimuli. In addition, direct multivalent supramolecular interactions of multitopic low-molecular-weight building blocks also lead to the formation of molecular hydrogels.[36,37]

Supramolecular polymeric hydrogels[38-44] can be formed by the multivalent noncovalent cross-linking between multitopic conventional polymer chains functionalized with multiple complementary supramolecular motifs. Among them, host-guest supramolecular polymeric hydrogels not only display high flexibility and excellent biostability, but also have the ability to reversibly modulate their microscopic structures and macroscopic properties in response to certain external stimuli due to their soft polymer backbone and strong host-guest binding. In particular, a variety of CD-based supramolecular polymeric hydrogels have been widely developed in the past decade, which can be used as smart drug carriers for controlled drug delivery as well as injectable engineered biomaterials for tissue engineering. In contrast to the above hydrogels, supramolecular hybrid hydrogels[45-56] contain a certain amount of inorganic components (*e.g.*, carbon nanotubes,[45-47] graphenes,[48,49] quantum dots (QDs),[50,51] clays[52,53]) or metal nanostructures (*e.g.*, gold nanoparticles,[54,55] silver nanoparticles[56]) in the cross-linked networks. In this regard, these rigid inorganic and metal substances generally serve as multivalent cross-linking sites, thus greatly improving the mechanical properties and biostability of hydrogels. In addition, the incorporation of these functional compounds also leads to new, unexpected functionalities including fluorescent performance, electrical conductivity, chiroptical property, and antibacterial activity.

Properties and functions

As a novel class of water-compatible noncovalent cross-linked polymeric materials, supramolecular hydrogels display not only some basic physicochemical properties similar to covalent polymeric hydrogels, such as water-retention ability, drug loading capacity, biodegradability and biocompatibility, biostability, and mechanical property, but also the stimuli responsiveness and processability inherent to the noncovalent cross-linkages in 3D hydrogel networks that can endow the resulting hydrogels with the ability to efficiently switch their physicochemical properties under exposure to certain external stimuli. Besides, supramolecular hydrogels can be facilely modified with a wide range of functional components, thereby achieving expected functions, such as optoelectronic property and bioactive property, and such functions mainly derive from the intrinsic molecular structures of exogenous substances. Meanwhile, the dynamic/switchable nature of supramolecular cross-linked networks leads to unexpected functions beyond the molecular structures, including self-healing ability and shape memory ability.

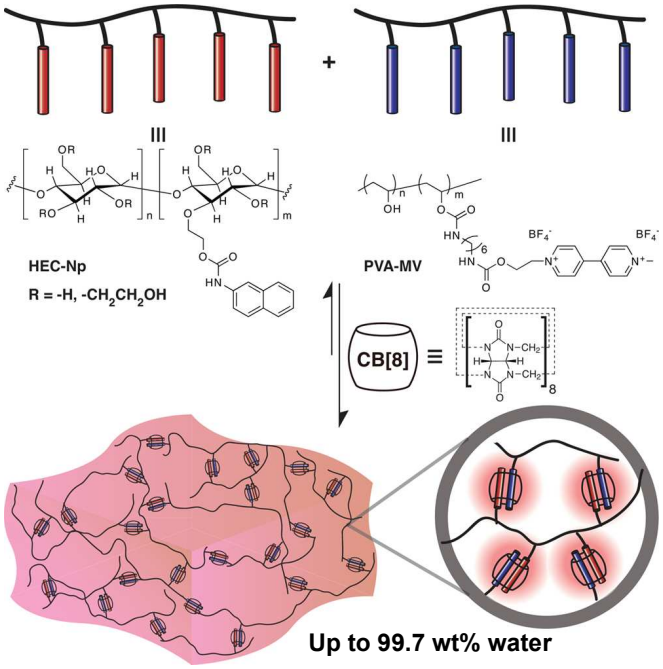

Fig. 3 Schematic illustration of a supramolecular polymeric hydrogel formed through addition of CB[8] to a mixture of a naphthyl-functionalized cellulose (HEC-Np) and a methyl viologen-functionalized poly(vinyl alcohol) (PVA-MV) in water. Reproduced with permission from ref. 57. Copyright 2012, American Chemical Society.

Water-retention ability and drug loading capability

As a typical class of soft materials, supramolecular hydrogels with 3D cross-linked networks can be formed by either the supramolecular cross-linking of hydrophilic polymeric building blocks or the physical entanglement of supramolecular nanofibers assembled from amphiphilic molecules, which have the ability to retain large volumes of water, further leading to the swelling of the hydrogel networks in aqueous solution. In

general, the extent of swelling and the content of water retained in hydrogels are greatly dependent on the hydrophilicity of the polymer chains and the cross-linking density. To date, the majority of supramolecular hydrogels have been reported to contain less than 98 wt% water. In order to improve the water-retention ability of supramolecular hydrogels, Scherman et al.[57] recently utilized commercially available commodity polymers such as poly(vinyl alcohol) and renewable cellulosic derivatives along with facile, rapid, and scalable conjugation techniques based on the CB[8] ternary complex system to prepare ultrahigh-water-content supramolecular hydrogels (up to 99.7 wt% water) (Fig. 3). Importantly, the water-retention ability endows the supramolecular hydrogels with the aqueous compatibility that is an essential prerequisite to supramolecular polymeric materials for various biomedical applications, while the retained water accounts for the hydrogel's lubricity and also serves as the primary conduit for diffusion of solutes into the hydrogel networks. Additionally, owing to their 3D cross-linked structure, supramolecular hydrogels can offer an ideal environment to load a variety of pharmaceutical agents (*e.g.*, drug, gene, protein, growth factor) as well as functional nanostructures, including carbon nanotubes, graphenes, QDs, gold nanoparticles/nanorods, *etc*.

Biodegradability, biocompatibility and biostability

The non-biodegradable or non-metabolizable external materials will gradually accumulate in the human body, which is very harmful to one's health or even one's life. Therefore, the biodegradability and biocompatibility are of great significance for the exploitation of new physiologically friendly biomaterials. Different from covalent hydrogels, supramolecular hydrogels, which can be spontaneously degraded or metabolized in variable physiological environment of the human body due to the noncovalent cross-linkages in the hydrogel networks, show more prominent biodegradability and biocompatibility *in vitro* and *in vivo*. These hydrogels could be promising injectable biomaterials with adjustable degradation properties to control both the cellular behavior as a regenerative cell matrix and the drug release behavior as a drug delivery vehicle.[58] Presently, biodegradable and biocompatible supramolecular hydrogels can be formed by either the self-assembly of natural biomolecule-containing amphiphiles or by the multivalent cross-linking of host-/guest-functionalized biodegradable and biocompatible synthetic polymers in aqueous media. Meanwhile, the biostability is also an essential requisite for supramolecular hydrogels for application in the diagnosis and treatment of human cancers. In order to improve the biostability of supramolecular hydrogels, Xu et al. designed a new type of hydrogelators based on the bioconjugates of nucleobases and short peptides, which could self-assemble in water to generate supramolecular hydrogels upon a pH- or enzymatic trigger.[59] The resulting hydrogels displayed high resistance to a powerful protease: proteases K, and thus it promises to serve as new biomaterial for applications that require long-term biostability. Also, the DOPA-Fe^{3+} complexation was found to provide strong, yet reversible cross-linking at physiological pH, thereby rendering the resultant hydrogels the resistance against oxidative degradation.[60]

Mechanical property

The conventional polymer hydrogels having covalent cross-linkages, are often brittle, have poor transparency, and lack the ability to self-heal. In contrast, the 3D noncovalent cross-linked networks of supramolecular hydrogels show unique mechanical properties, including both stiffness/toughness and elasticity/flexibility to keep the hydrogel structure. However, most of supramolecular hydrogels are mechanically weak and prone to fracture due to the existence of inhomogeneities that serve as crack initiation points, greatly restricting their applications as structural biomaterials such as cartilage. The macroscopic mechanical properties of hydrogels are highly correlated to the cross-link density. Increasing the cross-link density of hydrogel networks results in an increase in the storage and loss moduli of the hydrogels, and can be accomplished by either increasing the concentration of cross-linkers, or by decreasing the ratio of mechanically inactive cross-links.[61]

Currently, several strategies to improve hydrogel toughness have been introduced, such as the addition of chemical cross-linker to provide permanent cross-linked network, the combined use of multiple noncovalent interactions to enhance the cooperative effect between the cross-linkages, and the introduction of inorganic nanomaterials to produce organic-inorganic hybrid cross-linked structure. As a typical example, Gong and coworkers reported that polyampholytes, polymers bearing randomly dispersed cationic and anionic repeat groups, form tough and viscoelastic hydrogels with a combination of multiple mechanical properties including stiffness, strength, toughness, damping, fatigue resistance and self-healing, along with biocompatibility.[62] In this system, the strong bonds serve as permanent cross-links, imparting elasticity, whereas the weak bonds reversibly break and reform, dissipating energy. These supramolecular hydrogels can be tuned to alter multiple mechanical properties over wide ranges by using diverse ionic combinations. Also, the introduction of the additional hydrophobic interaction into a host-guest hydrogel system efficiently regulated the resultant hydrogel stiffness, strength, and structural recovery rate: a very important parameter for injectable hydrogels.[63] More recently, hybridization of polymers with clay nanosheets has been shown to yield mechanically tough and transparent supramolecular hybrid hydrogels.[52,53]

Stimuli-responsiveness

The noncovalent nature of these supramolecular hydrogels affords them with highly tunable mechanical properties, and the dynamics of the supramolecular cross-linked networks allows the hydrogels to rapidly respond to a multitude of external stimuli, including physical (*e.g.*, temperature, light, voltage, magnetic field) and chemical (*e.g.*, pH, ionic strength, redox agent, glucose, enzyme, competitive host/guest) parameters of the surrounding environment. In general, these external stimuli have a remarkable impact on the cross-linkages, further leading to the swelling or dissociation of the cross-linked hydrogel networks. With proper design of the hydrogels, the swelling degree and gel-sol transition behavior of these hydrogels can be effectively controlled. Due to the responsiveness to external stimuli, such supramolecular hydrogels show great potential as promising mediators for biosensor and modulated drug delivery. In particular, molecular hydrogels consisting of low-molecular-weight hydrogelators, such as peptide amphiphiles, are easily broken down upon exposure to certain physiological stimuli (*e.g.*, pH, redox agents, enzyme),[28-31] making them as smart vehicles to deliver therapeutic agents to targeted tumor sites for efficient cancer therapy. Among these stimuli-responsive properties, enzyme-response is of great interest to supramolecular biomaterials for site-specific cancer therapy,

because a large amount of disease-related enzymes are usually found in elevated concentrations in cancer cells or tissues. In addition, gel-sol transition is also shown to be triggered by other bio-relevant metal ions such as Al^{3+}, Ga^{3+} and Cu^{2+}, which allows for regulation of the release and dissolution profiles with potential application as injectable delivery systems.[60] As compared to single stimuli-responsive hydrogels, multiple stimuli-responsive supramolecular hydrogels can not only simultaneously respond to multiple external stimuli, but also adapt to complex and volatile physiological environment *in vivo*, thus showing great potential in clinical diagnosis and treatment.[38,57,64,65]

Optoelectronic property

Optoelectronic supramolecular hydrogels containing organic/inorganic π-conjugated components or metal nanostructures show typical photo-/electro-luminescence properties and photo-/electro-conductivity, making it excellent candidate for applications in organic optoelectronics and biomedical fields. The desirable optoelectronic performance of supramolecular hydrogels highly depends on the primary molecular structure of π-conjugated components and their intermolecular interactions in hydrogels.[9,66] Hitherto, the optoelectronic supramolecular hydrogels can be formed by either molecular self-assembly of organic π-conjugated molecule-containing building blocks, or the incorporation of inorganic components or metal nanostructures into cross-linked networks to yield supramolecular hybrid hydrogels. Furthermore, the optoelectronic properties of these supramolecular hydrogels can be effectively modulated under exposure to a suitable external stimulus.

For the former, light-emitting supramolecular hydrogels with different wavelengths in the visible region have been widely developed by using a variety of π-conjugated amphiphiles via various noncovalent interactions such as hydrogen bonding, π-π stacking, metal-ligand coordination, electrostatic interaction, host-guest interaction.[67-70] Most striking, the light-emitting properties (*e.g.*, wavelength, intensity) of these supramolecular hydrogels can be readily tuned by either applying a suitable external stimulus or altering the internal composition. Very recently, a white-light-emitting hydrogel was produced by the co-assembly of melamine, blue-light-emitting 6,7-dimethoxy-2,4[1H,3H]-quinazolinedione, green-light-emitting riboflavin and red-light-emitting dye (rhodamine B) in a requisite proportion.[67] In the resultant co-assembled hydrogel, the addition of rhodamine B resulted in fluorescence resonance energy transfer from riboflavin to rhodamine B, and white light emission was achieved by varying the molar ratio of rhodamine B and riboflavin in the hydrogel system.

For the latter, a number of supramolecular hybrid hydrogels containing inorganic constituents (*e.g.*, carbon nanotubes, graphenes/graphene oxides, QDs) or metal nanoparticles show interesting optoelectronic properties. Currently, a large number of graphene- and graphene oxide-based hydrogels have been intensively developed, and the incorporation of graphenes and graphene oxides renders these hybrid hydrogels both outstanding mechanical properties and high electrical conductivity, making them suitable for application in catalysis, energy conversion, fuel cells, and chemical sensors.[48,49] As a large family of inorganic nano-crystals with quantum-confined physical properties, QDs have also been used to construct optoelectronic hybrid hydrogels.[50,51] In an example, a dual-responsive supramolecular hybrid hydrogel composed of an azobenzene end-functionalized block copolymer (PDMA-*b*-PNIPAM) and β-CD-modified CdS QDs has been reported by Jiang and coworkers.[50] Initially, the β-CD/azobenzene host-guest interaction drove the formation of a hybrid inclusion complex that could be further converted to the predesigned hybrid hydrogels upon heating. This hybrid hydrogel displayed not only dual reversibility but also excellent photophysical properties originating from QDs. The integration of QDs with supramolecular hydrogels provides a new generation of fluorescence markers for potential biological assay. In addition, Jung and coworkers[54] demonstrated the chiral supramolecular assembly of achiral gold nanoparticles using helical nanofiber templates to yield hybrid hydrogels with customizable chiroptical properties, which have promising applications to photonics and sensing (Fig. 4).

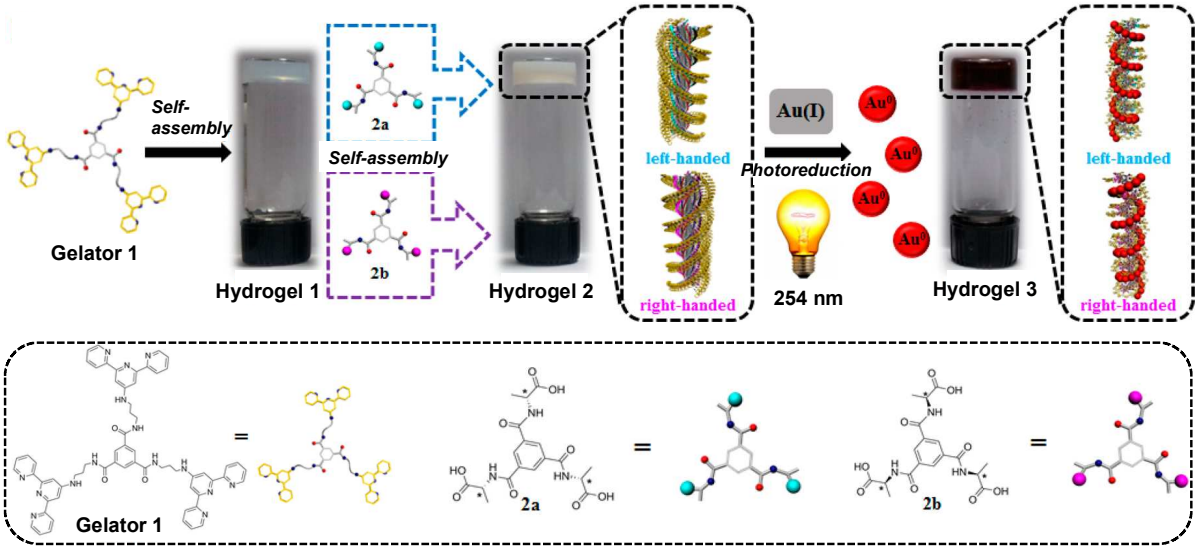

Fig. 4 Schematic representation of the formation of supramolecular hybrid hydrogels resulting from controlled assembly of nanofibers with tunable helicity by addition of chiral **2a** or **2b** components, and further addition of Au(I) followed by UV exposure to produce helically templated gold nanoparticle superstructures. Reproduced with permission from ref. 54. Copyright 2014, American Chemical Society.

Bioactive property

The supramolecular hydrogels formed by the self-assembly of bioactive functional molecules (*e.g.*, peptide, protein, carbohydrate) can be used as either promising vehicles for delivering pharmaceutical agents to specific tumor sites or biomaterials for tissue engineering applications. The resultant bioactive supramolecular hydrogel systems display several advantages, such as facile functionalization, smart responsiveness to various external stimuli, and specific recognition ability towards cell surface receptors.

Peptides and proteins having biological activities play a key role in metabolic regulation and modulation. Because of their versatile structures and excellent biocompatibility, peptide- or protein-based amphiphiles consisting of hydrophilic peptide or protein segments covalently bonded to hydrophobic segments, have been widely utilized to produce bioactive supramolecular materials. The groups of Hamachi,[28,29,71] Xu,[30] and others[31,72] have exploited a variety of bioactive supramolecular hydrogels by the aqueous self-assembly of peptide-based amphiphiles, which underwent a reversible gel-sol phase transition in response to various physiological stimuli in tumor cells and tissues (*e.g.*, pH, redox agents, enzyme), making them promising biomaterials suitable for numerous bioapplications, such as cellular scaffolds, site-specific drug delivery, and biosensing.

In parallel, Hamachi et al. employed amphiphilic peptide scaffolds to construct stimuli-responsive supramolecular hydrogels that were capable of sensing a variety of biological substances.[28,29,71] For example, on the basis of the redox-controlled self-assembly of a BAmoc-peptide-based hydrogelator, they built OR and AND logic gate into the enzyme-containing hybrid hydrogels responses towards several disease-related biomarkers including glucose, lactose, uric acid, choline, acetylcholine and sarcosine.[28] The intelligent supramolecular hybrid hydrogels could be used not only to detect the presence of various biomarkers in solution with the naked eye, but also to regulate logically the release of therapeutic antibodies, showing great potential as advanced soft materials for the diagnosis and treatment of various diseases in future.

In nature, living things always interact with each other for signal communication and specific recognition. As one of the most important functional biomolecules, carbohydrates often play an extremely important role in a wide range of basic biological phenomena through carbohydrate-mediated multivalent interactions. At present, carbohydrate-based supramolecular hydrogels have begun to emerge as valuable scaffolds for multivalent carbohydrate recognition,[73-75] showing tight and specific binding to host cells. A recent series of studies have demonstrated the clear dependence of carbohydrate-mediated multivalent interactions on the structure and morphology of hydrogels.

Self-healing

As a new class of supramolecular smart materials, self-healing supramolecular hydrogels that have the ability to spontaneously/autonomously repair their damage and recover their performance in aqueous media upon exposure to a suitable external stimulus, have attracted much attention recently due to the automatic healing nature and their wide applications in various fields. In striking contrast to covalent polymeric hydrogels, the reversible nature of noncovalent interactions conceptually impart the resulting supramolecular hydrogels with the capacity to achieve repeated healing at the molecular level to fully restore the original material properties.

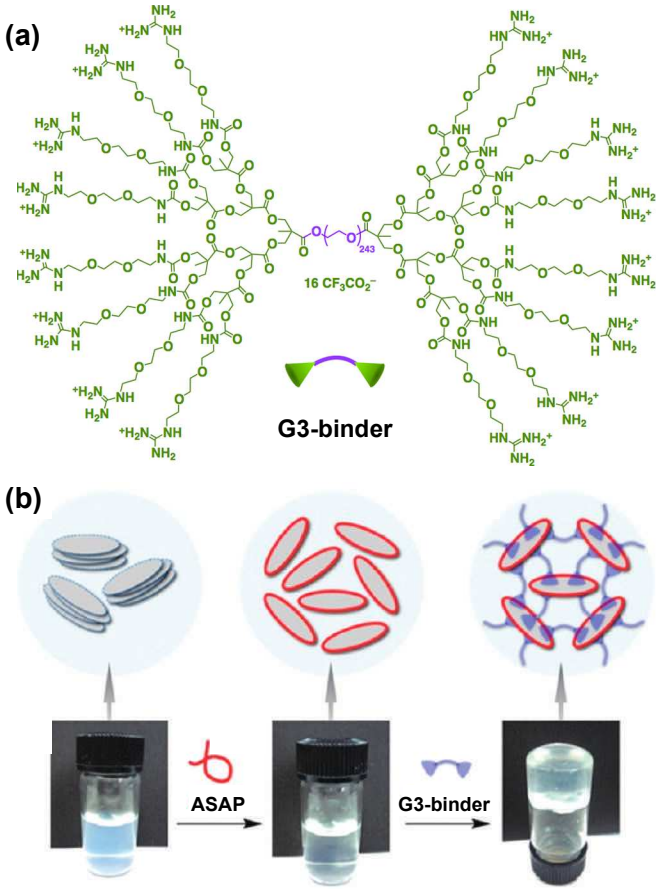

Fig. 5 (a) Chemical structure of a G3 dendritic binder. (b) The preparation process of supramolecular hybrid hydrogels upon addition of a G3 dendritic binder into anionic sodium polyacrylate (ASAP) treated clay nanosheets in water. Photographs show the evolution of the systems upon addition of these components. Reproduced with permission from ref. 52. Copyright 2010, Nature Publishing Group.

In recent years, CD-based host-guest pairs were widely used to design self-healable supramolecular hydrogels.[76-78] For example, Harada demonstrated the formation of a redox-responsive self-healing supramolecular hydrogel by *in situ* noncovalent cross-linking of a β-CD-containing poly(acrylic acid) (pAA) host polymer with a ferrocene-modified pAA guest polymer in water under ambient conditions.[76] Redox-stimuli was shown to induce a sol-gel phase transition in the supramolecular hydrogel and regulate self-healing behaviors such as re-adhesion between fractured surfaces. Differently, a supramolecular carbohydrate hydrogel system consisting of a cellulose polymer randomly functionalized with adamantane side groups and a β-CD vesicle was exploited recently using the β-CD vesicle as 3D multivalent junctions.[78] The resulting hydrogel showed typical shear-thinning and self-healing behaviors, making it highly suitable for applications that require injectability. Additionally, the CB[8]-based host-guest chemistry has proven to be a powerful tool for constructing versatile dynamically cross-linked materials.[79,80] By the utilization of CB[8] ternary complexes, Scherman prepared a

series of physically cross-linked polymeric hydrogels showing a range of binding, cross-linking and dynamics.[79] The results demonstrated that the mechanical strength of the resultant hydrogels was highly correlated with a high energetic barrier to dissociation of the CB[8] ternary complex, whereas rapid and efficient self-healing required a low energetic barrier to ternary complex association.

The incorporation of inorganic components[47,48,52] or metal nanostructures[54] to a hydrogel system often brings about a whole new set of interesting properties and functions. As a typical example, Aida and coworkers[52] reported the preparation of a supramolecular polymer/clay hybrid hydrogels by mixing anionic sodium polyacrylate treated clay nanosheets and telechelic poly(ethylene glycol)s (PEGs) polymers bearing multivalent guanidinium dendridic endgroups (G3 dendritic binder) (Fig. 5). The hybrid hydrogels exhibited several structural/functional advantages, including high water-content (96~98 wt%), very high mechanical strength (10^4-10^6 Pa), rapid self-healing ability, stimuli responsiveness, the ease to be moulded into shape-persistent, free-standing macroscopic objects, and can offer a proper environment for retaining and transporting biological activities. Besides, the graphene oxide nanosheets[48] and carbon nanotubes[47] have also been used as multivalent functional cross-linkers to build a number of environmental-responsive supramolecular hybrid hydrogels with autonomous self-healing properties that have great application potential in sensors, actuators, *etc*.

Shape memory

Shape-memory supramolecular hydrogels represent a newly emerging class of smart materials, which are capable of undergoing reversible change from a temporary fixed shape to a permanent pre-programmed shape under exposure to various external stimuli (*e.g.*, solvent exposure, pH, heat, light, redox agent).[81-85] The permanent shape is typically generated from a deformable soft matrix by either physical or chemical cross-links defining an equilibrium conformation. Shape recovery is driven by the entropic gain from chain relaxation, which can be accelerated appreciably above T_g or T_m.

While the stimuli-responsiveness of supramolecular hydrogels fulfills phase-transition role for the preparation of shape-memory hydrogels, the encoded instructive shape-memory element is thereupon missing. Luo recently designed and programmed two enzyme processes to produce a novel DNA meta-hydrogel that undergoes gel to quasi-solid transitions.[81] In this system, polymerase-woven long DNA strands were swollen by water in shaped molds to afford shaped hydrogels. The subsequent removal of water led to the collapse of the fixed shape into a quasi-solid structure, which could return to their original shapes following the reintroduction of water. Moreover, Willner et al. further tailored pH-switchable DNA hydrogels having unusual shape-memory features by the self-assembly of nucleic acid-functionalized acrylamide copolymers via cooperative duplex DNA and *i*-motif bridging units.[82] In their design, cytosine-rich nucleic-acid strands assembled into an *i*-motif structure at pH 5.0 to form shaped hydrogel materials, and the hydrogel subsequently dissolved into a "quasi-liquid" at pH 8.0 by the dissociation of the *i*-motif units, where the duplex DNA network offered the shape-memory code for the recovery of the shaped hydrogel at pH 5.0. Upon the periodic switching of the pH between 5.0 and 8.0, the hydrogel underwent reversible shape transitions between predesigned shaped structures and quasi-liquids. Very recently, Meijer and coworkers described the preparation of tough supramolecular hydrogels with thermally or water activated shape memory behavior consisting of a multiblock PEG-based copolymer matrix based on the 2-ureido-4[1H]-pyrimidinone (UPy) hydrogen-bonding interactions.[83] Specifically, the physical cross-links in this system benefit greatly from both the hydrogen-bonding UPy motif and a hydrophobic effect. The resulting hydrogels exhibited high mechanical strength and resilience upon deformation.

In addition, CDs and their derivatives have been extensively employed to construct diverse host-guest supramolecular hydrogels with stimuli-responsive shape-memory property across length scales and to engineer functional supramolecular materials. As an example, Harada et al. reported a photo-responsive actuator-like supramolecular hydrogel by radical copolymerization of a mixture of α-CD-modified acrylamide, azobenzene acrylamide and other functional components.[84] The external photostimulus was able to induce trans/cis isomerization of the azobenzene groups in a hydrogel, thereby achieving the reversible swelling-shrinking of the supramolecular hydrogel by controlling the formation of an inclusion complex. Using β-CD/ferrocene host-guest pair, they further developed a redox-stimulated supramolecular hydrogel actuator, which swells and shrinks by dissociating and reforming supramolecular cross-links in response to redox stimulus.[85]

Biomedical applications

As discussed above, supramolecular hydrogels not only show unique physicochemical properties and specific functions, but also have the ability to undergo reversible swelling and gel-sol transition in response to various environmental stimuli, making them ideal biomaterials for applications in a variety of biomedical fields. In this section, we focus on the application of supramolecular hydrogels in disease diagnosis and therapy such as bioimaging, biodetection, drug delivery, gene transfection, protein delivery and tissue engineering.

Bioimaging

Bioimaging aims at using sophisticated probes to visualize specific molecular pathways *in vivo*, in particular, those that play a key role in disease processes, and it facilitates the integration of complicated biological phenomena into the rapid visualization process at the molecular level, further extending the applications into cancer diagnosis and therapy.[86,87] To date, numerous bioimaging techniques have been widely used for clinical cancer diagnosis, such as fluorescent probes for optical imaging, paramagnetic agents for magnetic resonance imaging (MRI), radiolabeled probes for nuclear imaging and acoustically active nanostructures for ultrasound imaging. In view of molecular structures, bioimaging probes may be classified into three major types, including small-molecule compounds, conventional polymers, and supramolecular polymers. Among them, supramolecular polymer-based bioimaging probes, in particular, those bioimaging probes based on supramolecular hydrogels show great potential in cancer diagnosis owing to their 3D cross-linked structure, excellent biodegradability and biocompatibility, and smart response to physiological stimuli.

As one type of nanoscale supramolecular hydrogels, supramolecular nanohydrogels that can be facilely endocytosed into cells, have proved to be promising biological carriers to load versatile bioimaging agents (*e.g.*, fluorescent dyes, QDs,

contrast agents, radioactive isotopes) for *in vitro* or *in vivo* bioimaging. For example, Tseng[27] developed a flexible and modular synthetic approach for the preparation of size-controlled ^{64}Cu-labeled supramolecular nanoparticles suitable for microPET/CT imaging based on β-CD/AD host-guest interaction. The resultant supramolecular nanoparticles with different sizes (30 or 100 nm) were injected into the front footpad of mice to investigate the lymph node trafficking. The whole-body biodistribution and lymph node drainage results demonstrated that the sizes of these supramolecular nanoparticles remarkably affected their *in vivo* characteristics. They subsequently utilized a similar strategy to prepare a novel class of Gd^{3+}-containing supramolecular nanoparticle, which could serve as MRI agents for diagnosis of cancer metastasis in future.[88] Using a "bricks and mortar" strategy, we fabricated a novel class of calcein-based supramolecular fluorescent nanoparticles through the aqueous self-assembly of β-CD-grafted branched polyethylenimine (PEI), AD-functionalized calcein, AD-functionalized PEG derivative, and AD-functionalized folate (Fig. 6a).[24] These supramolecular nanoparticles possessed controllable size, size-dependent fluorescent behavior, good biostability under physiological conditions, and smart tumor-targeting ability originating from the folate receptor, thereby achieving excellent bioimaging efficacy in HeLa cells. In addition, Xu and coworkers[89-91] recently reported a series of biofunctional, fluorescent supramolecular hydrogels using amphiphilic peptide-based hydrogelators attached with a fluorophore, which showed potential as fluorescent probes for targeted cancer cell imaging and diagnostics (Fig. 6b).

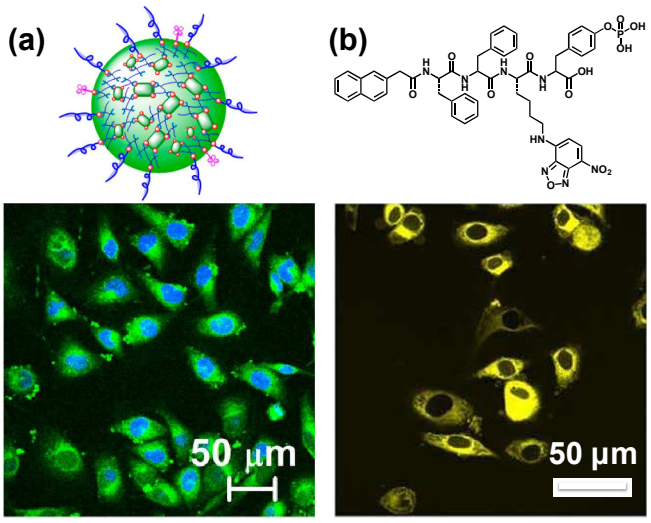

Fig. 6 Fluorescent confocal microscope images of HeLa cells that incubated with (a) calcein-based supramolecular nanohydrogels with folate, and (b) 4-nitro-2,1,3-benzoxadiazole (NBD)-modified peptide hydrogels. (a) Reproduced with permission from ref. 24. Copyright 2012, American Chemical Society. (b) Reproduced with permission from ref. 91. Copyright 2012, Nature Publishing Group.

Currently, the rational design of multifunctional supramolecular nanoparticles for both therapeutic and diagnostic purposes has become one of the most exciting and challenging topics in nanomedicine.[51,90] In one example, Li[51] reported a novel multifunctional supramolecular hybrid nanocarrier composed of a red-fluorescence QD core and a β-CD-OEI star-shaped cationic polymer shell suitable for cooperative co-delivery of DNA and antitumor drug paclitaxel as well as simultaneous cellular imaging. The imaging function of this hybrid nanocarrier offered the self-tracking ability to allow the localization of the co-delivery system in both transfected and untransfected cells.

Biodetection

The development of biodetection techniques for the diagnosis of diseases and environmental analysis of biological agents is an extremely crucial problem. By a combination of biological recognition elements and signal conversion elements into a biodetection system, biosensors have been developed for a wide variety of biodetection applications, showing the advantages of increased speed and ease of use compared to traditional detection methods. As is known to all, many bioactive molecules in human body play extremely significant roles in various disease-related biological events. Therefore, the development of rapid, convenient, and high-throughput sensing systems for detecting such disease-related biomarkers is keenly desirable not only for basic science advancement but also for diagnostic applications. Because of their high biocompatibility and rapid gel-to-sol transition in response to a variety of bio-related stimuli (*e.g.*, enzymatic reactions and biological molecules), supramolecular hydrogels with the rational design of nanostructures have great potential for biodetection applications.[1]

In recent years, a large number of optical, mechanical supramolecular hydrogel-based sensors have been actively constructed for detecting and sensing diverse bio-relevant molecules or species, such as glycosidases, alkaline phosphatase, glycoconjugates, proteins, polyanions, polyamines, cancer cells, and bacteria. In an example, Hamachi recently succeeded in fabricating supramolecular hydrogel capsule by co-assembly of a prostate specific antigen (PSA)-cleavable additive with glycolipid-based stiff and stable hydrogel matrix (Fig. 7).[92] The obtained functionalized capsule showed the PSA-responsive release of a prostate-specific membrane antigen (PSMA) binding fluorescent substance (3), allowing us not only to assay the PSA activity, but also to selectively sense and target prostate cancer (PCa) cells. Furthermore, the released fluorescent substance was delivered and internalized into PCa cells, mediated by the tethered ligand targeting a membrane-bound protein PSMA overexpressed on the PCa cell surface. This work might further expand the general utility of flexibly switchable supramolecular hydrogels as nanostructured functional biomaterials for applications such as intelligent controlled release and cell culture matrices and actuators. In addition, Yang et al. reported the interfacial self-assembly of an environment-sensitive fluorophore-vancomycin conjugate initiated by specific peptide-antibiotic interaction to yield fluorescent supramolecular nanohydrogels, which could be applied for simultaneous bacterial detection and inhibition.[93]

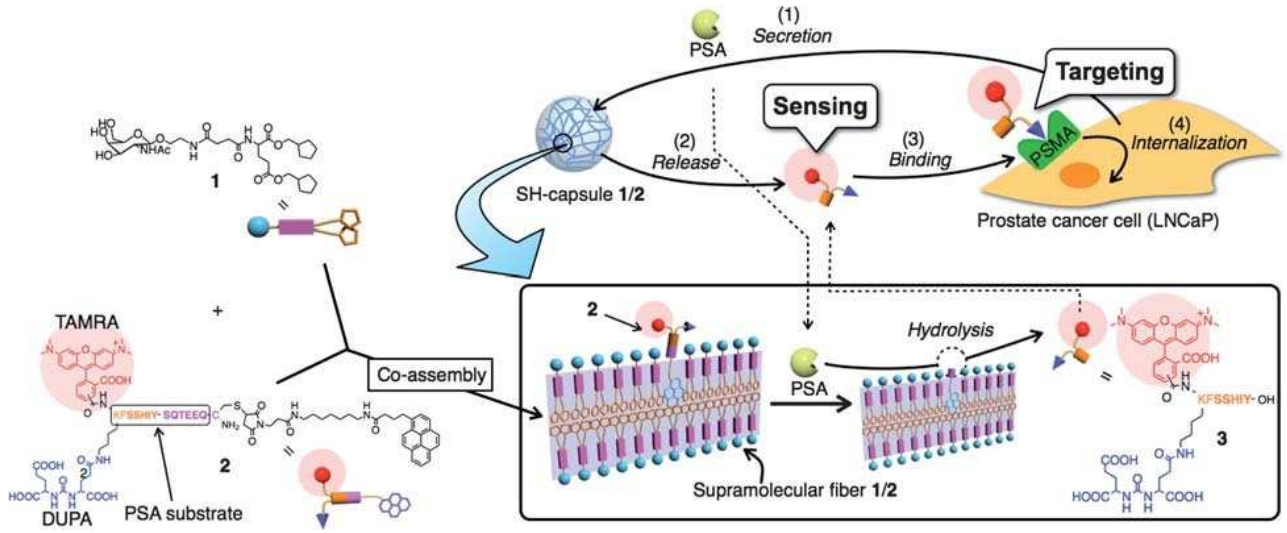

Fig. 7 Schematic illustration of supramolecular hydrogel capsule **1**/**2** for sensing and targeting PCa cells. Supramolecular nanofibers **1**/**2** can release a PSMA binding substance (3) in response to hydrolytic cleavage by PSA secreted from a prostate cancer cell (LNCaP). The released substance 3 can bind selectively to PSMA on the cell surface of LNCaP, and subsequently internalize into the cell. Reproduced with permission from ref. 92. Copyright 2010, Royal Society of Chemistry.

By contrast, it is becoming more important to exploit easy to use, inexpensive, portable, user-friendly naked eye biosensing systems to detect ultralow concentrations of analytes for biomedical, environmental, and national security applications. The group of Hamachi has done excellent works on the design and development of supramolecular hydrogel-based fluorescent biosensors for detecting various biomarkers with the naked eye. For example, Hamachi reported a polyanion-selective fluorescent supramolecular hybrid sensor consisting of a supramolecular hydrogel, a phosphatase, and an aminoethyl-modified mesoporous silica particles (NH_2-MCM41) loading an anionic fluorescent dye as a probe.[94] In this system, the semi-wet supramolecular hydrogel not only served as an immobilization matrix, but also played an active role in converting signals of the fluorescent dye. The rational combination of the anion-exchange ability of NH_2-MCM41 and the supramolecular hydrogel matrix generated peculiar sensing materials with three distinct orthogonal domains including cationic nanopores, hydrophobic nanofibers, and aqueous bulk gel phase. The coupling of anion-selective probe release from NH_2-MCM41 with the enzymatic dephosphorylation catalyzed by phosphatase in the system efficiently regulated the sensing efficiency and selectivity of the hybrid hydrogel materials to polyanions such as heparin, chondroitin sulfate, sucrose octasulfate, and so forth. Recently, they described the hybridization of a supramolecular hydrogel with an anionic layered montmorillonite host adsorbing a cationic fluorescent dye, which gave rise to a fluorocolorimetric sensor for spermine and spermidine in artificial urine, achieving rapid, sensitive and user-friendly naked-eye detection suitable for cancer diagnosis and clinical usage.[95] In addition, bola-amphiphilic glycolipid-based supramolecular hydrogels showing rapid color change in response to glycosidases could be used to construct a colorimetric sensor array chip for detecting glycosidases with the naked eye.[96]

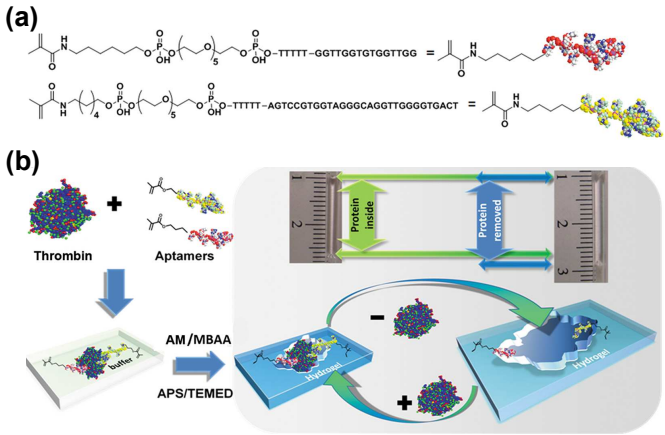

Fig. 8 (a) Two different aptamers modified with a polymerizable methacrylamide terminus linked to the aptamer via a linker incorporating five thymidine units, six ethylene oxide units, and six methylene units. (b) Scheme of the biomolecular imprinting used to produce superaptamer thrombin-responsive hydrogels along with macroscopic volume change. Reproduced with permission from ref. 97. Copyright 2013, American Chemical Society.

As a unique alternative, Spivak's group exploited a new type of mechanical sensor systems based on the aptamer-based hydrogels with specific response to target proteins (Fig. 8).[97] This superaptamer assembly offered an example of utilizing protein-specific aptamers to produce volume-changing hydrogels with amplified response to the target protein. These superaptamer hydrogels showed a remarkable volume shrinking that was visible to the naked eye down to femtomolar concentrations of protein. This dramatic macromolecular amplification could be attributed to a complex interplay between protein-aptamer supramolecular cross-links and the sequential reduction in excluded volume of the hydrogel. Thus, the visibility of the hydrogel response in this biomarker detection provided an alternative to traditional analytical

techniques that require sophisticated instrumentation and highly trained personnel, making them ideal for portable or point-of-care applications.

Therapeutic delivery

Therapeutic delivery refers to the kind of approaches, formulations, and technologies that utilize versatile vehicles to deliver therapeutic agents including chemotherapeutic drugs, genes, and proteins, into pathological tissues for safely achieving its desired therapeutic effect.[98,99] Various types of supramolecular polymeric systems are widely used in therapeutic delivery applications.[100-102] As a type of 3D cross-linked supramolecular materials, supramolecular hydrogels show numerous advantages, such as high water content for the diffusion of entrapped molecules, unique mechanical property similar to that of human tissues, the ease of degradation *in vivo*, *in situ*-forming a hydrogel in contact with tissues, and facile incorporation of functional components, which can be used as promising carriers for improving the water-solubility and bioavailability, prolonging the circulation time, inducing the preferential accumulation at tumor sites through the enhanced permeability and retention (EPR) effect, and reducing the systemic side effects of therapeutic agents.[8,103] Especially, supramolecular hydrogels have the ability to undergo reversible swelling and gel-sol transition in response to the bio-related stimuli such as pH, oxidizing or reducing agents, enzymes, and other biomolecules, thereby enabling the programmable and controllable delivery of loaded therapeutic agents into the tumor sites.

To date, a variety of supramolecular hydrogel-based drug carriers have been widely developed for clinical cancer therapy. In particular, self-assembling peptide hydrogels that are highly sensitive to environmental pH variation, have been proved to be promising vehicles for pH-controlled drug delivery in acidic tumor tissues. A range of peptide-based drug-delivery supramolecular hydrogels have been prepared by the aqueous self-assembly of amphiphilic peptide derivatives, which undergoes a gel-to-sol phase transition upon exposure to lower pH, leading to the controlled release of kanamycin,[104] taxol,[105,106] anti-inflammatory agents (*e.g.*, 5-aminosalicylic acid, naproxen),[107,108] and anti-HIV prodrugs[109]. These works illustrate an unprecedented approach for designing functional supramolecular biomaterials for site-specific drug delivery. In particular, prodrug-based supramolecular hydrogels were also reported as peculiar self-delivery scaffords for efficiently inhibiting tumor growth.[107-109] Because of their excellent biocompatibility, weak immunogenicity, and selective inclusion capability, CDs and their derivatives have been widely used to exploit numerous injectable and biodegradable host-guest hydrogels suitable for cancer therapy.[110-113] These supramolecular hydrogels often exhibited a thixotropic or thermo-reversible nature, and thereby could be applied for relatively long-term sustained and controlled delivery of drugs as an injectable formulation. In comparison to conventional polymeric carriers, these supramolecular hydrogels presented much faster release rate while arriving at the pathological sites, thereby achieving the enhancement of the therapeutic efficacy and the reduction of drug resistance.

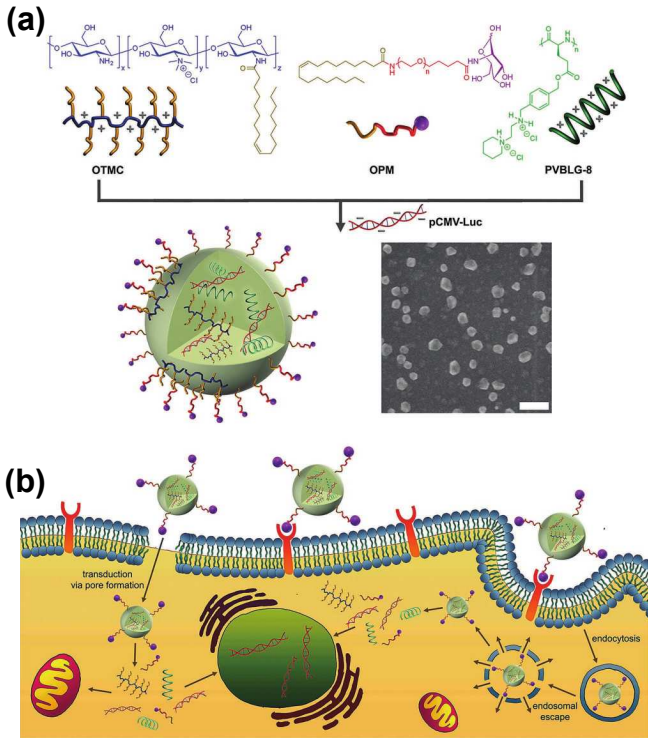

Fig. 9 (a) Formation of SSANs via electrostatic as well as hydrophobic interactions among individual components, and SEM image of the resulting SSANs. The scale bar represents 200 nm. (b) Schematic illustration of the endocytosis, direct diffusion, and escape from endosomes of SSANs, as well as the transfer of the DNA into the nuclei to allow gene transfection. Reproduced with permission from ref. 116. Copyright 2013, Wiley-VCH.

Cationic supramolecular hydrogels have the ability to condense and transfer exogenous nucleic acids to specific tumor cells or tissues, which can serve as potential nonviral vectors for *in vitro* or *in vivo* gene therapy. During the past five years, diversified supramolecular hydrogel-based gene delivery vehicles have been successfully designed and developed for gene delivery, showing equivalent or even higher transfection efficiency compared to covalent ones. Owing to their controlled size, switchable structure and morphology, as well as the ease of surface functionalization, supramolecular nanohydrogels, namely, nanoscale supramolecular hydrogels, are regarded as transfection reagents for safe and efficient gene delivery.[22] For example, by a combination of a supramolecular synthetic approach and an automated digital microreactor, Wang and Tseng reported a rapid developmental pathway for producing superb nanohydrogel-based gene delivery systems.[114] With the help of the digital microreactor, wide structural and functional diversity could be programmed into a library of DNA-loaded supramolecular nanohydrogels by systematically changing the mixing ratios of molecular building blocks and a plasmid DNA. *In vitro* transfection studies demonstrated that the optimal 40-nm DNA-loaded supramolecular nanohydrogels showed dramatically enhanced transfection efficiency in a collection of cell lines including NIH/3T3, HeLa, A549, U87, and IMR-90, which could be attributed to cooperative effects of structures and surface chemistry of supramolecular DNA complexes. Similarly, Ma et al. utilized CD/AD host-guest interaction to construct multifunctional core-shell structured supramolecular nanoparticles for simultaneous drug delivery and gene

therapy.[115] Also, Chen[116] described the preparation of supramolecular self-assembled nanocomplexes (SSANs) as nonviral gene vectors via electrostatic and hydrophobic interactions between oleyl-conjugated trimethyl chitosan (OTMC), poly(γ-(4-((2-(piperidin-1-yl)ethyl) aminomethyl) benzyl-L-glutamate) (PVBLG-8), oleyl-PEG-mannose (OPM) with mammalian cell-targeting ability, and plasmid DNA encoding luciferase (pCMV-Luc) (Fig. 9a). In this system, the hydrophobic OTMC was expected to achieve greatly enhanced transfection efficacy by promoting cellular internalization and endosomal escape (Fig. 9b). In contrast, the macroscopic supramolecular hydrogels also have tremendous potential as nonviral vectors for efficient delivery of plasmid DNA, VEGF-siRNA, and microRNA into different live cell lines.[117-119]

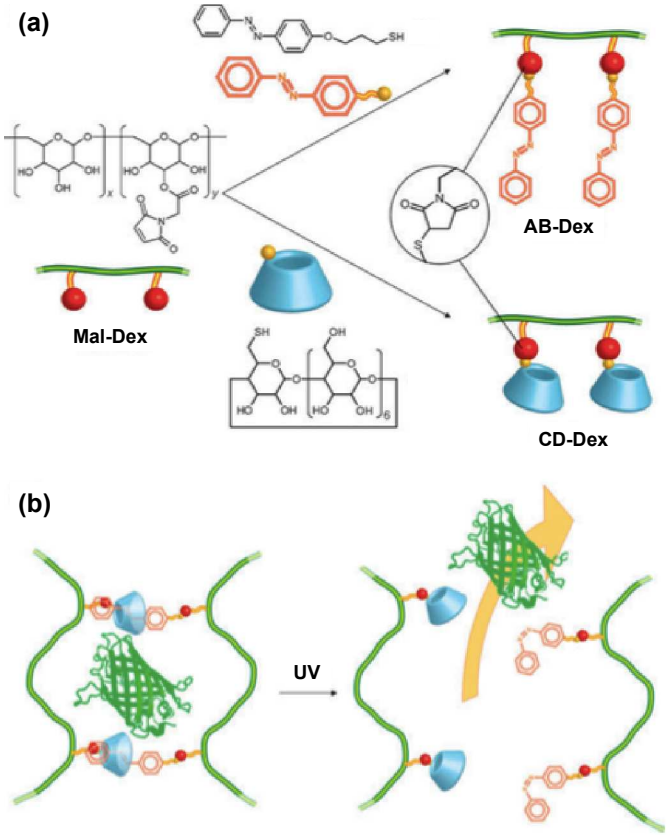

Fig. 10 (a) Preparation of azobenzene-modified dextran (AB-Dex) and cyclodextrin-modified dextran (CD-Dex). (b) Photo-responsive protein release from the supramolecular hydrogels. Reproduced with permission from ref. 121. Copyright 2010, Royal Society of Chemistry.

As we know, protein-based biotherapeutics are easily cleared by proteolytic digestion and renal excretion.[120] Thus, a variety of supramolecular hydrogel-based protein-delivery carriers have been successfully reported to improve the stability against proteases as well as reduce the immunogenicity of protein therapeutics. As a class of 3D smart biomaterials, supramolecular hydrogels can be utilized as emerging carriers for encapsulation and release of proteins. In an example, Scherman et al.[57] exploited cellulose-based supramolecular hydrogels with high-water-content of up to 99.5% self-assembled from naphthyl-functionalized cellulose derivative, viologen-modified poly(vinyl alcohol) polymer, and CB[8]. Most strikingly, an extremely sustained-release profile of bovine serum albumin was observed over the course of up to 160 days from supramolecular hydrogels with a polymer content of only 1.5 wt%, making them suitable for sustained therapeutic applications. Recently, a photo-responsive supramolecular hydrogels was reported by Kros based on the host-guest interaction between β-CD-modified dextran and azobenzene-carrying dextran, which could be used for light-triggered protein release (Fig. 10).[121] After UV light irradiation, trans-azobenzene groups in this hydrogel were transformed into the cis-form, leading to the dissociation of the cross-linking network and the release of entrapped green fluorescent protein (GFP) into the media. Additionally, supramolecular hydrogels have also been widely employed as protein carriers for *in vitro* and *in vivo* protein delivery. As a typical example, Tseng and coworkers[122] reported a novel supramolecular nanohydrogel system that was capable of delivering intact transcription factor (TF) with high transduction efficacy. In their design, an anionic TF-DNA complex was firstly formed using a plasmid DNA with a matching recognition sequence specific to a TF, which was subsequently encapsulated into supramolecular nanohydrogels to form TF-containing supramolecular complexes via electrostatic interaction. The resultant TF-containing supramolecular complexes showed much higher delivery efficacy than that of TAT-TF as a standard method for TF delivery. Very recently, Meijer and Dankers[123,124] have prepared a novel class of hierarchical self-healing supramolecular hydrogels using quadruple hydrogen-bonded supramolecular polymers, which showed great potential as modular injectable delivery vehicles for *in vivo* growth-factor delivery.

Differently, Xu recently reported unique supramolecular hydrogel/nanonets in the pericellular space formed by enzyme-instructed self-assembly of a small $_D$-peptide derivative.[125] The resultant pericellular hydrogel networks have the ability to selectively form around the cancer cells that overexpress surface and secretory phosphatases, which effectively prevent cellular mass exchange, thereby inducing apopotosis of cancer cells. This work offers a new way that enriches and regulates secretome of cells for modulating and controlling cellular microenvironment.

Tissue engineering

Tissue engineering aims at achieving local regeneration of lost or malfunctioning tissues and organs by culturing a patient's own cells on a polymer matrix.[126,127] The biological environment and cell-biomaterial interaction play an important role in the functioning of the implanted biomaterials. Supramolecular hydrogels not only effectively combine tunable mechanical properties with regulation of the degradability, but also have the ability to afford excellent biological environments for encapsulating bioactive moieties such as growth factors and cells, showing great potential as biocompatible scaffolds in tissue engineering for supporting, guiding, and stimulating the sustainable growth of tissues. During the past decade, a wide range of supramolecular hydrogel-based biomaterials for tissue engineering have been constructed from bioactive building blocks via highly directional, reversible, non-covalent interactions such as hydrogen bonding and host-guest interactions.

In particular, peptide-based supramolecular hydrogels with outstanding bioactivity are promising as dynamic biomaterials for tissue-engineering applications.[5,128] Stupp and Zhang pioneered relevant studies on the design and development of peptide hydrogel-based tissue engineering scaffolds from peptide amphiphiles. For example, Stupp synthesized an

amphiphilic pentapeptide epitope derivative (IKVAV) found in neurite-promoting laminin, which could self-assemble into supramolecular hydrogels in water. The resultant hydrogels could encapsulate neural progenitor cells and induce selective differentiation of the cells into neurons due to the high epitope density in the supramolecular hydrogels.[129] In parallel, Zhang utilized β-sheet-forming peptides to generate supramolecular hydrogel scaffolds, which could be used for entrapment and differentiation of neural cells.[130,131] Recently, Xu[132] designed and synthesized a new type of naphthalene-containing oligopeptides as hydrogelators, which could rapidly form supramolecular hydrogels *in vivo* using a kinase/phosphatase switch. The obtained hydrogels showed excellent biocompatibility in mice. Yang and coworkers[133] also demonstrated that a naphthalene-containing tripeptide hydrogelator could selectively self-assemble into a thin-layered hydrogel at the surface of platelets, further inhibiting human platelet aggregations induced by various agonists. Very recently, a photodegradable hydrogel assembled from a phototrigger-modified short peptide was used as biomaterial scaffolds to modulate cellular microenvironments.[134]

In addition, other types of peptide-containing supramolecular hydrogels have also been successfully applied for tissue engineering. As an example, Meijer and coworkers prepared hydrogen bonded supramolecular hydrogels by simply mixing UPy-modified oligocaprolactones with Upy-functionalized cell-adhesion-promoting UPy-Gly-Arg-Gly-Asp-Ser and synergistic UPy-Pro-His-Ser-Arg-Asn peptide sequences.[135] These obtained biomaterials showed excellent biodegradability and biocompatibility, favorable mechanical properties, and strong, specific binding ability to fibroblast cells, thereby facilitating the proliferation of fibroblast cells. They subsequently reported a new class of supramolecular copolymer hydrogels composed of bifunctional and chain-extended UPy-modified oligocaprolactones, which displayed a gentle *in vivo* tissue response along with the thin capsule formation upon implantation.[136] Thus, this supramolecular copolymer hydrogel will be an ideal scaffold material for soft-tissue engineering. Additionally, Akashi utilized a multi-armed PEG terminally functionalized with a collagen mimetic peptide $(POG)_{10}$ (P = proline, O = hydroxyproline, G = glycine) (PEG-$(POG)_{10}$), to produce a collagen-specific injectable hydrogel when mixed with fibrous collagens due to the triple-helix association.[137] This multi-armed PEG-$(POG)_{10}$ hydrogelator could be advantageous as a tissue cross-linker for the cornea, skin, cartilage, and bone tissue engineering.

Saccharides and their glycol-conjugates are naturally abundant in extracellular matrices in the form of glycoproteins and proteoglycans, which play a key biological role in intercellular communication and cell differentiation. Thus, saccharide-based supramolecular hydrogels also show great advantage for tissue engineering and various cell culture applications. Hamachi demonstrated that the glyco-lipid mimics with saccharides in the hydrophilic head and two alkyl chains in the hydrophobic tail could form stable and sufficiently strong supramolecular hydrogels.[138] More importantly, the addition of polystyrene nanobeads greatly facilitated the homogeneous 3D dispersion of the supramolecular hydrogel networks. The resultant hybrid supramolecular hydrogels could be used as a unique matrix for the immobilization and encapsulation of live Jurkat cells in three dimensions under physiological conditions.

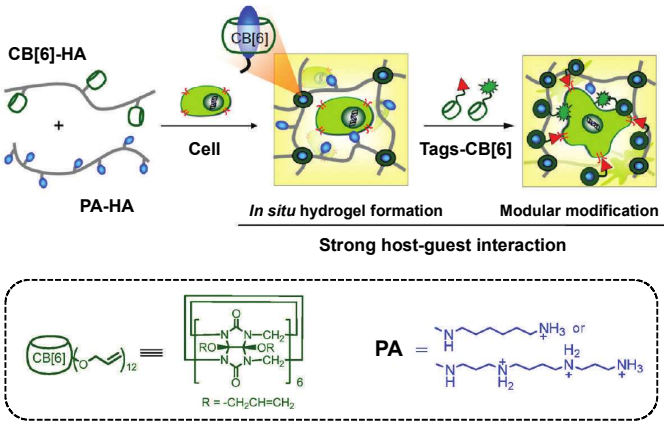

Fig. 11 Schematic representations for *in situ* formation of supramolecular biocompatible hydrogel and its modular modification using highly selective and strong host-guest interactions. The simple mixing of CB[6]-HA and PA-HA in the presence of cells led to the formation of cell-entrapped supramolecular hydrogels, which was further modularly modified with various tags-CB[6]. Reproduced with permission from ref. 139. Copyright 2012, American Chemical Society.

The diversity and specificity of host-guest interactions endow the host-guest supramolecular hydrogels with unique biological properties and tunable functions, making them as smart scaffolds for tissue engineering. For example, Kim and coworkers[139,140] constructed biocompatible supramolecular hyaluronic acid hydrogels by the self-assembly of CB[6]-conjugated hyaluronic acid (CB[6]-HA), polyamine-conjugated HA (PA-HA), and tags-CB[6] using strong and selective CB[6]/PA host-guest interaction (Fig. 11). In this system, the 3D microenvironment of supramolecular hydrogels could be readily regulated by the incorporation of various multifunctional tags-CB[6]. The supramolecular assembly of CB[6]-HA and PA-HA in the presence of cells led to the *in situ* formation of cell-entrapped supramolecular hydrogels, thus rendering this hydrogel system great promise as an artificial extracellular matrix for 3D cellular engineering. Besides, CD-based host-guest supramolecular hydrogels have been widely exploited as promising tissue engineering materials.[141,142] As an example, Elisseeff reported a simple modular supramolecular strategy to the preparation of multifunctional PEG hydrogels for cell culture and tissue engineering.[141] In this design, functional α-CD nanobeads threaded onto the PEG chains resulted in the formation of hydrogels with highly controlled biophysical and biochemical properties for cell culture and tissue engineering to probe stem cell function and stimulate stem cell differentiation. This work provided an accessible platform for the independent switch of mechanics, cell adhesion properties, and chemical functionality of the hydrogels without any chemical modification of the PEG backbone.

Summary and outlook

In this review, we provided an overview of the synthesis of supramolecular hydrogels and their use in disease diagnostics and therapeutics over the past five years. As a perfect mimic of soft biological tissues, supramolecular hydrogels have been widely employed as intelligent biomaterials for programmed drug delivery and *in situ* tissue repair and regeneration. In summary, considerable progress has been made in this emerging area of supramolecular hydrogel-based biomedical materials. However, current studies on supramolecular

hydrogels are still at a very preliminary stage, and many fundamental problems still remain unsolved before supramolecular hydrogels can be put into clinical diagnosis and treatment.

From a structural perspective, the internal microstructures such as the cross-linking density and the distribution of cross-links play a very crucial role in determining macroscopic physiological properties and functions (*e.g.*, mechanical strength, bioactivity) of the resultant supramolecular hydrogels. However, most of the existing supramolecular hydrogels have irregular internal microstructures due to uncontrolled cross-linking behavior driven by multivalent noncovalent interactions. Therefore, it is necessary to rationally select driving forces and self-assembly techniques to form spatially ordered supramolecular hydrogels such as hierarchical self-assembly with well-defined amphiphilic molecular building blocks.[143] In addition, the size of supramolecular hydrogels has an important effect on their biological behaviors in cells or tissues, such as cytotoxicity, internalization pathways, and therapeutic efficacy. However, multivalent supramolecular cross-linking often facilitates continuous propagation of the cross-linked networks, thereby leading to the formation of macrohydrogels. The development of convenient, flexible, and modular synthetic approach for the control of the hydrogel size has become urgent. For example, the introduction of competitive solvation groups can facilely regulate the equilibrium between the propagation/aggregation and capping/solvation of the cross-linked network fragments, allowing arbitrary control over the sizes of hydrogels.[24,27]

From an application perspective, numerous supramolecular hydrogel-based delivery vehicles and tissue-engineered scaffolds show limited clinical therapeutic efficacy and serious side effects owing to low drug loading efficiency, uncontrollable drug release rates, and high cytotoxicity originated from toxic degradation products. Thus, there are permanent requirements for superior delivery platforms in order to improve the curative effect and reduce the side effects of therapeutic agents. At present, the notion of "self-delivery" molecular hydrogels without passive components or matrices provides a powerful approach for improving the entrapment efficiency, localization at the specific target, precise control of release rates for prolonged circulation times, and the control of biodegradability.[109,144,145] To this end, it is requested for the design and development of therapeutic agent-containing hydrogelators without impairing their biological activity and antitumor efficacy. In addition, the hybrid self-assembly method provides a promising platform for exact control over spatial organization of components in 3D, further pushing forward into new hydrogel research in order to tackle the challenges described above.

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Notes and references

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1. R. A. Siegel, Y. Gu, M. Lei, A. Baldi, E. E. Nuxoll and B. Ziaie, *J. Control. Release*, 2010, **141**, 303.
2. M. Choi, J. W. Choi, S. Kim, S. Nizamoglu, S. K. Hahn and S. H. Yun, *Nat. Photonics*, 2013, **7**, 987.
3. A. Singh and N. A. Peppas, *Adv. Mater.*, 2014, **26**, 6530.
4. J.-A. Yang, J. Yeom, B. W. Hwang, A. S. Hoffman and S. K. Hahn, *Prog. Polym. Sci.*, 2014, **39**, 1973.
5. F. Zhao, M. L. Ma and B. Xu, *Chem. Soc. Rev.*, 2009, **38**, 883.
6. B. Rybtchinski, *ACS Nano*, 2011, **5**, 6791.
7. E. A. Appel, J. del Barrio, X. J. Loh and O. A. Scherman, *Chem. Soc. Rev.*, 2012, **41**, 6195.
8. J. Zhang and P. X. Ma, *Adv. Drug Deliver. Rev.*, 2013, **65**, 1215.
9. S. S. Babu, V. K. Praveen and A. Ajayaghosh, *Chem. Rev.*, 2014, **114**, 1973.
10. O. Wichterle and D. Lim, *Nature*, 1960, **185**, 117.
11. H. Zhang, L. Bré, T. Zhao, B. Newland, M. Da Costa and W. Wang, *J. Mater. Chem. B*, 2014, **2**, 4067.
12. Y. Dong, W. U. Hassan, R. Kennedy, U. Greiser, A. Pandit, Y. Garcia and W. Wang, *Acta Biomater.*, 2014, **10**, 2076.
13. J. Li, *NPG Asia Mater.*, 2010, **2**, 112.
14. T. Aida, E. W. Meijer and S. I. Stupp, *Science*, 2012, **335**, 813.
15. X. Yan, F. Wang, B. Zheng and F. Huang, *Chem. Soc. Rev.*, 2012, **41**, 6042.
16. R. Dong, Y. Zhou and X. Zhu, *Acc. Chem. Res.*, 2014, **47**, 2006.
17. R. Dong, Y. Zhou, X. Huang, X. Zhu, Y. Lu and J. Shen, *Adv. Mater.*, 2015, **27**, 498.
18. D. Wang, G. Tong, R. Dong, Y. Zhou, J. Shen and X. Zhu, *Chem. Commun.*, 2014, **50**, 11994.
19. R. Hogg and R. G. Wilkins, *J. Chem. Soc.*, 1962, 341.
20. M. A. C. Stuart, B. Hofs, I. K. Voets and A. de Keizer, *Curr. Opin. ColloidInterface Sci.*, 2005, **10**, 30.
21. M. Oishi and Y. Nagasaki, *Nanomedicine*, 2010, **5**, 451.
22. M. M. Yallapu, M. Jaggi and S. C. Chauhan, *Drug Discov. Today*, 2011, **16**, 457.
23. Y. Chen, Y. Pang, J. Wu, Y. Su, J. Liu, R. Wang, B. Zhu, Y. Yao, D. Yan, X. Zhu and Q. Chen, *Langmuir*, 2010, **26**, 9011.
24. R. Dong, H. Chen, D. Wang, Y. Zhuang, L. Zhu, Y. Su, D. Yan and X. Zhu, *ACS Macro Lett.*, 2012, **1**, 1208.
25. L. Meng, B. Ji, W. Huang, D. Wang, G. Tong, Y. Su, X. Zhu and D. Yan, *Macromol. Biosci.*, 2012, **12**, 1524.
26. W. Jiang, B. Y. S. Kim, J. T. Rutka and W. C. W. Chan, *Nat. Nanotechnol.*, 2008, **3**, 145.
27. H. Wang, S. Wang, H. Su, K.-J. Chen, A. L. Armijo, W.-Y. Lin, Y. Wang, J. Sun, K.-i. Kamei, J. Czernin, C. G. Radu and H.-R. Tseng, *Angew. Chem. Int. Ed.*, 2009, **4**8, 4344.
28. M. Ikeda, T. Tanida, T. Yoshii, K. Kurotani, S. Onogi, K. Urayama and I. Hamachi, *Nat. Chem.*, 2014, **6**, 511.
29. T. Yoshii, M. Ikeda and I. Hamachi, *Angew. Chem. Int. Ed.*, 2014, **53**, 7264.
30. J. Zhou, X. Du, Y. Gao, J. Shi and B.Xu, *J. Am. Chem. Soc.*, 2014, **136**, 2970.
31. L. E. R. O'Leary, J. A. Fallas, E. L. Bakota, M. K. Kang and J. D. Hartgerink, *Nat. Chem.*, 2011, **3**, 821.
32. W. Deng, H. Yamaguchi, Y. Takashima and A. Harada, *Angew. Chem. Int. Ed.*, 2007, **46**, 5144.
33. I. Hwang, W. S. Jeon, H.-J. Kim, D. Kim, H. Kim, N. Selvapalam, N. Fujita, S. Shinkai and K. Kim, *Angew. Chem. Int. Ed.*, 2007, **46**, 210.
34. B. J. Cafferty, I. Gaĺlego, M. C. Chen, K. I. Farley, R. Eritja and N. V. Hud, *J. Am. Chem. Soc.*, 2013, **135**, 2447.
35. Z. Sun, Z. Li, Y. He, R. Shen, L. Deng, M. Yang, Y. Liang and Y. Zhang, *J. Am. Chem. Soc.*, 2013, **135**, 13379.
36. R. K. Castellano, R. Clark, S. L. Craig, C. Nuckolls and J. Rebek, *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 12418.
37. Q. Zhang, D.-H. Qu, X. Ma and H. Tian, *Chem. Commun.*, 2013, **49**, 9800.
38. C. Ma, T. Li, Q. Zhao, X. Yang, J. Wu, Y. Luo and T. Xie, *Adv. Mater.*, 2014, **26**, 5665.
39. Y. Chen, X.-H. Pang and C.-M. Dong, *Adv. Funct. Mater.*, 2010, **2**0, 579.
40. X. Liao, G. Chen, X. Liu, W. Chen, F. Chen and M. Jiang, *Angew. Chem. Int. Ed.*, 2010, **49**, 4409.
41. S. Tamesue, Y. Takashima, H. Yamaguchi, S. Shinkai and A. Harada, *Angew. Chem. Int. Ed.*, 2010, **49**, 7461.
42. Z.-X. Zhang, K. L. Liu and J. Li, *Angew. Chem. Int. Ed.*, 2013, **5**2, 6180.
43. E. A. Appel, F. Biedermann, U. Rauwald, S. T. Jones, J. M. Zayed and O. A. Scherman, *J. Am. Chem. Soc.*, 2010, **132**, 14251.
44. W. Cao, X. Zhang, X. Miao, Z. Yang and H. Xu, *Angew. Chem. Int. Ed.*, 2013, **52**, 6233.
45. T. Ogoshi, Y. Takashima, H. Yamaguchi and A. Harada, *J. Am. Chem. Soc.*, 2007, **129**, 4878.
46. Z. Tan, S. Ohara, M. Naito and H. Abe, *Adv. Mater.*, 2011, **23**, 4053.
47. R. Du, J. Wu, L. Chen, H. Huang, X. Zhang and J. Zhang, *Small*, 2014, **10**, 1387.
48. D. Han and L. Yan, *ACS Sustainable Chem. Eng.*, 2014, **2**, 296.
49. J. Liu, G. Chen and M. Jiang, *Macromolecules*, 2011, **44**, 7682.
50. J. Liu, G. Chen, M. Guo and M. Jiang, *Macromolecules*, 2010, **43**, 8086.
51. Y.-L. Wu, H. Yin, F. Zhao and J. Li, *Adv. Healthcare Mater.*, 2013, **2**, 297.

52. Q. Wang, J. L. Mynar, M. Yoshida, E. Lee, M. Lee, K. Okuro, K. Kinbara and T. Aida, *Nature*, 2010, **463**, 339.
53. S. Tamesue, M. Ohtani, K. Yamada, Y. Ishida, J. M. Spruell, N. A. Lynd, C. J. Hawker and T. Aida, *J. Am. Chem. Soc.*, 2013, **135**, 15650.
54. S. H. Jung, J. Jeon, H. Kim, J. Jaworski and J. H. Jung, *J. Am. Chem. Soc.*, 2014, **136**, 6446.
55. B. Adhikari, A. Biswas and A. Banerjee, *Langmuir*, 2012, **28**, 1460.
56. D. Ma, X. Xie and L.-M. Zhang, *J. Polym. Sci. Polym. Phys.*, 2009, **47**, 740.
57. E. A. Appel, X. J. Loh, S. T. Jones, F. Biedermann, C. A. Dreiss and O. A. Scherman, *J. Am. Chem. Soc.*, 2012, **134**, 11767.
58. N. Q. Tran, Y. K. Joung, E. Lih, K. M. Park and K. D. Park, *Biomacromolecules*, 2010, **11**, 617.
59. X. Li, Y. Kuang, H.-C. Lin, Y. Gao, J. Shi and B. Xu, *Angew. Chem. Int. Ed.*, 2011, **50**, 9365.
60. M. S. Menyo, C. J. Hawker and J. H. Waite, *Soft Matter*, 2013, **9**, 10314.
61. M. M. E. Koenigs, A. Pal, H. Mortazavi, G. M. Pawar, C. Storm and R. P. Sijbesma, *Macromolecules*, 2014, **47**, 2712.
62. T. L. Sun, T. Kurokawa, S. Kuroda, A. B. Ihsan, T. Akasaki, K. Sato, Md. A. Haque, T. Nakajima and J. P. Gong, *Nat. Mater.*, 2013, **12**, 932.
63. K. L. Liu, J.-L. Zhu and J. Li, *Soft Matter*, 2010, **6**, 2300.
64. H. Komatsu, S. Matsumoto, S.-i. Tamaru, K. Kaneko, M. Ikeda and I. Hamachi, *J. Am. Chem. Soc.*, 2009, **131**, 5580
65. A. Saeed, N. Francini, L. White, J. Dixon, T. Gould, H. Rashidi, R. C. A. Ghanami, V. Hruschka, H. Redl, B. R. Saunders, C. Alexander and K. M. Shakesheff, *Adv. Mater.*, 2014, DOI: 10.1002/adma.201403626.
66. R. Dong, Y. Bo, G. Tong, Y. Zhou, X. Zhu and Y. Lu, *Nanoscale*, 2014, **6**, 4544.
67. P. Bairi, B. Roy, P. Chakraborty and A. K. Nandi, *ACS Appl. Mater. Interfaces*, 2013, **5**, 5478.
68. A. Griffith, T. J. Bandy, M. Light and E. Stulz, *Chem. Commun.*, 2013, **49**, 731.
69. E. Elmalem, F. Biedermann, M. R. J. Scherer, A. Koutsioubas, C. Toprakcioglu, G. Biffid and W. T. S. Huck, *Chem. Commun.*, 2014, **50**, 8930.
70. S. Mukherjee, T. Kar and P. Kumar Das, *Chem. Asian J.*, 2014, **9**, 2798.
71. M. Ikeda, T. Tanida, T. Yoshii and I. Hamachi, *Adv. Mater.*, 2011, **23**, 2819.
72. H. Guo, J. Zhang, T. Xu, Z. Zhang, J. Yao and Z. Shao, *Biomacromolecules*, 2013, **14**, 2733.
73. Y. Koshi, E. Nakata, H. Yamane and I. Hamachi, *J. Am. Chem. Soc.*, 2006, **128**, 10413.
74. Z. M. Yang, G. L. Liang, M. L. Ma, A. S. Abbah, W. W. Lu and B. Xu, *Chem. Commun.*, 2007, 843.
75. S. Nandi, H.-J. Altenbach, B. Jakob, K. Lange, R. Ihizane, M. P. Schneider, U. Gun and A. Mayer, *Org. Lett.*, 2012, **14**, 3826.
76. M. Nakahata1, Y. Takashima, H. Yamaguchi and A. Harada, *Nat. Commun.*, 2011, **2**, 511.
77. T. Kakuta, Y. Takashima, M. Nakahata, M. Otsubo, H. Yamaguchi and A. Harada, *Adv. Mater.*, 2013, **25**, 2849.
78. S. Himmelein, V. Lewe, M. C. A. Stuart and B. J. Ravoo, *Chem. Sci.*, 2014, **5**, 1054.
79. E. A. Appel, R. A. Forster, A. Koutsioubas, C. Toprakcioglu and O. A. Scherman, *Angew. Chem. Int. Ed.*, 2014, **53**, 10038.
80. J. R. McKee, E. A. Appel, J. Seitsonen, E. Kontturi, O. A. Scherman and O. Ikkala, *Adv. Funct. Mater.*, 2014, **24**, 2706.
81. J. B. Lee, S. Peng, D. Yang, Y. H. Roh, H. Funabashi, N. Park, E. J. Rice, L. Chen, R. Long, M. Wu and D. Luo, *Nat. Nanotechnol.*, 2012, **7**, 816.
82. W. Guo, C.-H. Lu, R. Orbach, F. Wang, X.-J. Qi, A. Cecconello, D. Seliktar and I. Willner, *Adv. Mater.*, 2014, DOI: 10.1002/adma.201403702.
83. M. Guo, L. M. Pitet, H. M. Wyss, M. Vos, P. Y. W. Dankers and E. W. Meijer, *J. Am. Chem. Soc.*, 2014, **136**, 6969.
84. Y. Takashima, S. Hatanaka, M. Otsubo, M. Nakahata, T. Kakuta, A. Hashidzume, H. Yamaguchi and A. Harada, *Nat. Commun.*, 2012, **3**, 1270.
85. M. Nakahata, Y. Takashima, A. Hashidzume and A. Harada, *Angew. Chem. Int. Ed.*, 2013, **52**, 5731.
86. J. H. Kim, K. Park, H. Y. Nam, S. Lee, K. Kim and I. C. Kwon, *Prog. Polym. Sci.*, 2007, **32**, 1031.
87. Q. Zhu, F. Qiu, B. S. Zhu and X. Y. Zhu, *RSC Adv.*, 2013, **3**, 2071.
88. K. J. Chen, S. M. Wolahan, H. Wang, C. H. Hsu, H. W. Chang, A. Durazo, L. P. Hwang, M. A. Garcia, Z. K. Jiang, L. Wu, Y. Y. Lin and H. R. Tseng, *Biomaterials*, 2011, **32**, 2160.
89. Y. Zhang, B. Zhang, Y. Kuang, Y. Gao, J. Shi, X. X. Zhang and B. Xu, *J. Am. Chem. Soc.*, 2013, **135**, 5008.
90. J. Li, Y. Gao, Y. Kuang, J. Shi, X. Du, J. Zhou, H. Wang, Z. Yang and B. Xu, *J. Am. Chem. Soc.*, 2013, **135**, 9907.
91. Y. Gao, J. Shi, D. Yuan and B. Xu, *Nat. Comm.*, 2012, **3**, 1033.
92. M. Ikeda, R. Ochi, A. Wada and I. Hamachi, *Chem. Sci.*, 2010, **1**, 491.
93. C. Ren, H. Wang, X. Zhang, D. Ding, L. Wang and Z. Yang, *Chem.Commun.*, 2014, **50**, 3473.
94. A. Wada, S.-i. Tamaru, M. Ikeda and I. Hamachi, *J. Am. Chem. Soc.*, 2009, **131**, 5321.
95. M. Ikeda, T. Yoshii, T. Matsui, T. Tanida, H. Komatsu and I. Hamachi, *J. Am. Chem. Soc.*, 2011, **133**, 1670.
96. R. Ochi, K. Kurotani, M. Ikeda, S. Kiyonaka and I. Hamachi, *Chem. Commun.*, 2013, **49**, 2115.
97. W. Bai, N. A. Gariano and D. A. Spivak, *J. Am. Chem. Soc.*, 2013, **135**, 6977.
98. R. Langer, *Nature*, 1998, **392**, 5.
99. K. Kataoka, A. Harada and Y. Nagasaki, *Adv. Drug Delivery Rev.*, 2001, **47**, 113.
100. R. Dong, L. Zhou, J. Wu, C. Tu, Y. Su, B. Zhu, H. Gu, D. Yan and X. Zhu, *Chem. Commun.*, 2011, **47**, 5473.
101. S. Yu, J. Chen, R. Dong, Y. Su, B. Ji, Y. Zhou, X. Zhu and D. Yan, *Polym. Chem.*, 2012, **3**, 3324.
102. R. Dong, Y. Su, S. Yu, Y. Zhou, Y. Lu and X. Zhu, *Chem. Commun.*, 2013, **49**, 9845.
103. M. E. Davis and M. E. Brewster, *Nat. Rev. Drug Discovery*, 2004, **3**, 1023.
104. Z. Yang, Y. Kuang, X. Li, N. Zhou, Y. Zhang and B. Xu, *Chem. Commun.*, 2012, **48**, 9257.

105. Y. Gao, Y. Kuang, Z.-F. Guo, Z. Guo, I. J. Krauss and B. Xu, *J. Am. Chem. Soc.*, 2009, **131**, 13576.
106. C. Yang, M. Bian and Z. Yang, *Biomater. Sci.*, 2014, **2**, 651.
107. X. Li, J. Li, Y. Gao, Y. Kuang, J. Shi and B. Xu, *J. Am. Chem. Soc.*, 2010, **132**, 17707.
108. J. Li, Y. Kuang, Y. Gao, X. Du, J. Shi and B. Xu, *J. Am. Chem. Soc.*, 2013, **135**, 542.
109. J. Li, X. Li, Y. Kuang, Y. Gao, X. Du, J. Shi and B. Xu, *Adv. Healthcare Mater.*, 2013, **2**, 1586.
110. D. Ma and L.-M. Zhang, *Biomacromolecules*, 2011, **12**, 3124.
111. N. Lin and A. Dufresne, *Biomacromolecules*, 2013, **14**, 871.
112. W. Ha, J. Yu, X. Song, J. Chen and Y. Shi, *ACS Appl. Mater. Interfaces*, 2014, **6**, 10623.
113. Z. Liu and P. Yao, *Polym. Chem.*, 2014, **5**, 1072.
114. H. Wang, K. Liu, K.-J. Chen, Y. Lu, S. Wang, W.-Y. Lin, F. Guo, K.-i. Kamei, Y.-C. Chen, M. Ohashi, M. Wang, M. A. Garcia, X.-Z. Zhao, C. K.-F. Shen and H.-R. Tseng, *ACS Nano*, 2010, **4**, 6235.
115. J. Zhang, H. Sun and P. X. Ma, *ACS Nano*, 2010, **4**, 1049.
116. L. Yin, Z. Song, K. H. Kim, N. Zheng, N. P. Gabrielson and J. Cheng, *Adv. Mater.*, 2013, **25**, 3063.
117. Z. Li, H. Yin, Z. Zhang, K. L. Liu and J. Li, *Biomacromolecules*, 2012, **13**, 3162.
118. S. P. Patil, H. S. Jeong and B. H. Kim, *Chem. Commun.*, 2012, **48**, 8901.
119. J. Li, R. Kooger, M. He, X. Xiao, L. Zheng and Y. Zhang, *Chem. Commun.*, 2014, **50**, 3722.
120. F. Wurm, J. Klos, H. J. Räder and H. Frey, *J. Am. Chem. Soc.*, 2009, **131**, 7954.
121. K. Peng, I. Tomatsu and A. Kros, *Chem. Commun.*, 2010, **46**, 4094.
122. Y. Liu, H. Wang, K.-I. Kamei, M. Yan, K.-J. Chen, Q. Yuan, L. Shi, Y. Lu and H.-R. Tseng, *Angew. Chem. Int. Ed.*, 2011, **50**, 3058.
123. P. Y. W. Dankers, T. M. Hermans, T. W. Baughman, Y. Kamikawa, R. E. Kieltyka, M. M. C. Bastings, H. M. Janssen, N. A. J. M. Sommerdijk, A. Larsen, M. J. A. van Luyn, A. W. Bosman, E. R. Popa, G. Fytas and E. W. Meijer, *Adv. Mater.*, 2012, **24**, 2703.
124. M. M. C. Bastings, S. Koudstaal, R. E. Kieltyka, Y. Nakano, A. C. H. Pape, D. A. M. Feyen, F. J. van Slochteren, P. A. Doevendans, J. P. G. Sluijter, E. W. Meijer, S. A. J. Chamuleau and P. Y. W. Dankers, *Adv. Healthcare Mater.*, 2014, **3**, 70.
125. Y. Kuang, J. Shi, J. Li, D. Yuan, K. A. Alberti, Q. Xu and B. Xu, *Angew. Chem. Int. Ed.*, 2014, **53**, 8104.
126. R. Langer and J. P. Vacanti, *Science*, 1993, **260**, 920.
127. L. G. Griffith and G. Naughton, *Science*, 2002, **295**, 1009.
128. A. Altunbas and D. J. Pochan, *Top Curr. Chem.*, 2012, **310**, 135.
129. G. A. Silva, C. Czeisler, K. L. Niece, E. Beniash, D. A. Harrington, J. A. Kessler and S. I. Stupp, *Science*, 2004, **303**, 1352.
130. C. E. Semino, J. Kasahara, Y. Hayashi and S. G. Zhang, *Tissue Eng.*, 2004, **10**, 643.
131. T. C. Holmes, S. de Lacalle, X. Su, G. S. Liu, A. Rich and S. G. Zhang, *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 6728.
132. Z. Yang, G. Liang, L. Wang and B. Xu, *J. Am. Chem. Soc.*, 2006, **128**, 3038.
133. W. Zheng, J. Gao, L. Song, C. Chen, D. Guan, Z. Wang, Z. Li, D. Kong and Z. Yang, *J. Am. Chem. Soc.*, 2013, **135**, 266.
134. M. He, J. Li, S. Tan, R. Wang and Y. Zhang, *J. Am. Chem. Soc.*, 2013, **135**, 18718.
135. P. Y. W. Dankers, M. C. Harmsen, L. A. Brouwer, M. J. A. van Luyn and E. W. Meijer, *Nat. Mater.*, 2005, **4**, 568.
136. P. Y. W. Dankers, E. N. M. van Leeuwen, G. M. L. van Gemert, A. J. H. Spiering, M. C. Harmsen, L. A. Brouwer, H. M. Janssen, A. W. Bosman, M. J. A. van Luyn and E. W. Meijer, *Biomaterials*, 2006, **27**, 5490.
137. M. Matsusaki, R. Amekawa, M. Matsumoto, Y. Tanaka, A. Kubota, K. Nishida and M. Akashi, *Adv. Mater.*, 2011, **23**, 2957.
138. M. Ikeda, S. Ueno, S. Matsumoto, Y. Shimizu, H. Komatsu, K.-i. Kusumoto and I. Hamachi, *Chem. Eur. J.*, 2008, **14**, 10808.
139. K. M. Park, J.-A Yang, H. Jung, J. Yeom, J. S. Park, K.-H. Park, A. S. Hoffman, S. K. Hahn and K. Kim, *ACS Nano*, 2012, **6**, 2960.
140. H. Jung, J. S. Park, J. Yeom, N. Selvapalam, K. M. Park, K. Oh, J.-A Yang, K. H. Park, S. K. Hahn and K. Kim, *Biomacromolecules*, 2014, **15**, 707.
141. A. Singh, J. Zhan, Z. Ye and J. H. Elisseeff, *Adv. Funct. Mater.*, 2013, **23**, 575.
142. H. Cui, L. Cui, P. Zhang, Y. Huang, Y. Wei and X. Chen, *Macromol. Biosci.*, 2014, **14**, 440.
143. S. Pedron, E. Becka and B. A. Harley, *Adv. Mater.*, 2014, DOI: 10.1002/adma.201404896.
144. Y. Shen, E. Jin, B. Zhang, C. J. Murphy, M. Sui, J. Zhao, J. Wang, J. Tang, M. Fan, E. V. Kirk and W. J. Murdoch, *J. Am. Chem. Soc.*, 2010, **132**, 4259.
145. P. Huang, D. Wang, Y. Su, W. Huang, Y. Zhou, D. Cui, X. Zhu and D. Yan, *J. Am. Chem. Soc.*, 2014, **136**, 11748.

Table of Contents Entry

Supramolecular hydrogels: Synthesis, properties and their biomedical applications

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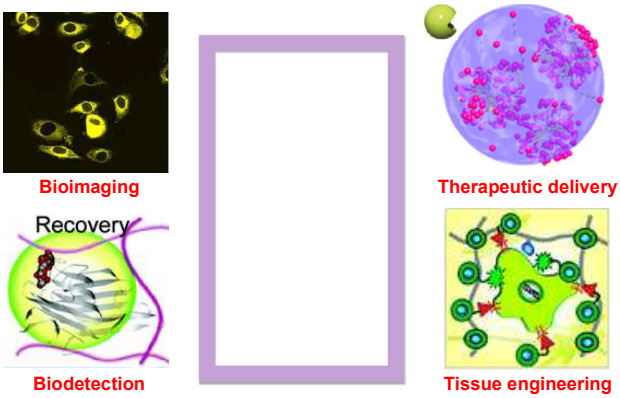

The recent progress in synthesis, properties and biomedical applications of supramolecular hydrogels have been reviewed.