Stimuli-Responsive Drug-Delivery Systems Based on Supramolecular Nanovalves

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From motor proteins to molecular machines, supramolecular chemistry has been revealed as a remarkable link to bridge the gap between biology, chemistry, and materials. Taking inspiration from the dynamic, reversible, and directional manner of non-covalent interactions that can respond to diversiform external stimuli, supramolecular nanovalves installed on the surface of inorganic or hybrid nanocarriers have received extensive attention in stimuli-responsive delivery of small drug molecules, implying their outspread bioapplications in cancer/gene therapy, biomedical application, and antimicrobial regulations. The state of supramolecular nanovalves could be well regulated by switching the conformation or the assembled/disassembled state of the assemblies. This tutorial review lays the foundation for a better understanding of the significant and typical intelligent drug-delivery systems immobilized with supramolecular polymers or supramolecular pseudorotaxanes as the gating entities of nanovalve-based molecular machines, by showing their chemical structures, operation modes, and release modalities triggered by various actuations at molecular scale. In particular, relevant perspectives of supramolecular therapeutics will also be elaborated upon.

Introduction
Supramolecular chemistry continues to scale new heights in science on account of the profound insight into the microscopic world for the advancement of healthcare and frontier science.1,2 The past few decades have marked the advent of artificial molecular machines and smart supramolecular devices equipped with fascinating mechanical and reversible properties and capable of desirable stimuli responsiveness based on macrocyclic chemistry and host-guest chemistry, and accordingly great impetus has been given to the development of materials science, such as biomedical materials.3–6 One appealing type of supramolecular assemblies refers to the gated devices serving for the security and escape of cargos.7,8 As an essential player in supramolecular chemistry, reversible non-covalent interactions—which include electrostatic interactions, π-π stacking interactions, hydrophobic effects, van der Waals interactions, and hydrogen-bonding interactions—could effectively organize matching pieces together by molecular recognition to produce ordered supramolecular nanoarchitectures with tailorable size, morphology, and functions, such as micelles, nanoparticles (NPs), vesicles, and hydrogels.9–13 The environment-operable properties that could respond to external changes are realized via dynamic association and dissociation of component parts in such supramolecular assemblies.14–16

Depending on the flexible modular strategy, supramolecular therapeutics directed by synthetic knowledge has been proposed, especially in the fabrication of...
supramolecular drug-delivery systems. To date, drug therapeutics is still the most typical and dominant method in dealing with health problems, which has made great advances toward refractory diseases. However, two major challenges that drug therapeutics would encounter involve unfavorable invasions toward normal tissues caused by unspecific aggressivity and the difficulty in realizing sustained release within diseased cells. Motivated by the necessity of drug safety and efficacy, it follows that the gated materials have been extensively studied, mainly including supramolecular polymers and supramolecular pseudorotaxanes for stimuli-responsive drug delivery, which not only endow the delivery systems with flexible and robust attributes of non-covalent interactions but also meet the urgent need of human healthcare.

Drug-delivery systems immobilized with supramolecular nanovalves, emerging as a compelling topic of interest, have been realized in medical platforms of late. Such a functional delivery platform generally consists of porous inorganic or hybrid scaffolds and switchable gatekeepers installed on the surface of nanocarriers to block and unlock the pore entrances. Accordingly, research endeavor has been focused on supramolecular switches grafted on solid surfaces or biointerfaces. Supramolecular nanovalves could be switched on and off, triggered by external stimuli including light irradiation, pH, thermal, redox, competitive binding, magnetic field, chemical signals, and biological inputs.

On the basis of engineered nanomaterials, supramolecular nanovalves integrate different modalities and multilateral advantages into a simple platform with exquisite complexity. The adaptivity of supramolecular nanovalves is determined by the tailable building blocks, ready accessibility, and controllable assembly. Supramolecular switches have attracted tremendous interest due to the inherent dynamic properties derived from non-covalent interactions and their promise in dealing with specific targeted release at will. Combined with the sophisticated gating nanotechnology, a rational drug-delivery process could be divided into three parts: (1) loading drug molecules into the channels of nanocarriers, whose surface has been modified with stalks for interacting with gated bulky materials; (2) installing nanovalves to close pore orifices and prevent the leakage of cargos; and (3) introducing predefined stimuli to regulate/open gating entities and release cargos toward diseased cells. These feasible types of gatekeepers are required to improve the performance of traditional drug/gene delivery systems for enhancing the therapeutic effect by carefully selecting biocompatible building blocks and endogenous triggers, which has imparted the obtained assemblies with versatile stimuli responsiveness and holds considerable perspective in finely regulating the transport and tuning the movement of drug molecules or biochemical species.

Selecting biocompatible inorganic materials of high loading capacity as carriers is another important prerequisite in effective treatment. Therefore a broad scope of solid scaffolds, including mesoporous silica NPs (MSNs), metal-organic frameworks (MOFs), and other inorganic NPs, has been used to prepare organic-inorganic hybrid supramolecular drug-delivery systems. Taking advantage of their porous structures, large surface areas, considerable loading capacity, and easily modified surface, a huge number of drug molecules (i.e., chlorambucil, camptothecin, 5-fluorouracil [5-Fu], busulfan, cisplatin prodrug, gemcitabine, and doxorubicin) have been encapsulated into the carriers for further precise release within solid tumors. To further overcome the existing biological barriers, scientists have made great efforts to modify carriers with targeted biomarker species, allowing progress in supramolecular nanovalves and present their applications in cancer/gene therapy and antibacterial regulations.
for guided delivery and site-specific release. Current attention has been focused on both the smart gated devices with switchable ability and the applicable nanocarriers with good biocompatibility and easy degradability.

Supramolecular Pseudorotaxanes as Nanovalves

As representative mechanically interlocked structures, supramolecular (pseudo)rotaxanes, comprising at least one macrocyclic entity and a dumbbell-type or bar-shaped axle threaded through the macrocycles according to the pioneer work by Stoddart in 1991 (entitled “A Molecular Shuttle”), have expanded to a huge range of switchable gated devices. At a molecular level, the mechanical motion does occur in a relative movement of rod components with respect to the encircled rings without cleavage of intramolecular covalent bindings. Thus, complex motion could be modulated by dethreading and rethreading movements upon external energy supply. Host-guest interactions derived from the unique affinity between synthetic macrocyclic receptors and their guests are considered as the dominant toolbox in the formation of intelligent supramolecular gated materials for the realization of controllable release of circulating species in an activated and stimuli-responsive manner. In particular, supramolecular macrocycles are recognized as important movable encircled rings in supramolecular pseudorotaxanes and mechanically interlocked molecules. Along with the emergence of supramolecular macrocycles, including crown ethers, cyclodextrins, calixarenes, cucurbiturils, pillararenes, and metallo macrocycles, a variety of supramolecular pseudorotaxanes originating from the inclusion complexation have been established and explored based on host-guest chemistry. Their interior cavities with definite space, unique charge distribution, and hydrophobic parts could serve as versatile accommodations for suitable guests with good size selectivity and recognition specificity. Figure 1 shows...
some typical chemical structures of stalk components employed in supramolecular nanovalves. A number of supramolecular gatekeepers based on pseudorotaxanes have emerged. For instance, Hernandez and coworkers pioneered in demonstrating the earliest installation of pseudorotaxanes-based gates onto the surface of mesostructured silica for controlled release of luminescent cargos, in which 1,5-dioxynaphthalene derivatives (DNPD) acted as tethered gateposts to be further encircled by cyclobis-(paraquat-p-phenylene) (CBPQT$^{4+}$) rings to prepare [2]pseudorotaxanes denoted as [DNPD$^3$CBPQT]$^{4+}$. After attaching the obtained gated machines on the porous carriers, the loaded fluorescent tris(2,2-phenylpyridyl)iridium(III), Ir(ppy)$_3$ for short, were well regulated in the access to and out of containers upon the addition of NaCNBH$_3$ as a reducing reagent that could weaken the supramolecular interactions and induce the disassembly of pseudorotaxanes; therefore, Hernandez et al. named the gated devices nanovalves. This work put forward the concept of supramolecular gates and described several stages in operation procedures, which paves an advanced way for controlled cargo release.

In addition to the supramolecular drug-delivery systems supported on inorganic nanocarriers, synthetic macrocycle-derived supra-amphiphilic polypseudorotaxanes are rising stars as host-guest nanoplatforms in the field of cancer diagnosis and treatment. Such an amphiphilic structure could be easily prepared by dynamic non-covalent connection between hydrophilic and hydrophobic parts. Notably, in the mixture of water and organic solvent, a self-assembled process will occur driven by hydrophobic effect to form various supra-nanoarchitecture, such as vesicles and NPs. On the other hand, the obtained supra-assemblies relying on molecular recognition are capable of encapsulating drug molecules and achieving controllable stimuli-responsive release upon environmental variation, such as competitive agents, light irradiation, and thermal heating, to disassemble the delivery systems; this has opened new avenues for the development of supramolecular biomedicine.

The scope of this review will focus on the recent advances of supramolecular nanovalves and their applications in biomedical fields, represented by drug/gene delivery for tumor therapy and antimicrobial regulation. An advanced survey of newly reported switchable devices for the delivery of therapeutic payloads has also been delineated. For a better understanding of the release profile, we will highlight the construction of nanovalves and disassembly behaviors in response to different types of external stimuli. Figure 2 shows the recent progress of such supramolecular drug-delivery systems.

**MSN Nanocarriers for Stimuli-Responsive Drug Delivery**

One of the most heavily investigated inorganic nanocarriers are those based on porous silica materials. The advent of porous silica has marked a thriving advancement of drug delivery for cancer treatment since their first debut in 1952; however, its widespread application in biomedicine took place only after the discovery of MSNs in 1992. MSNs are a kind of porous silica material with ordered 2D hexagonal mesopores of a distribution from 2 nm to 50 nm. With diversified advantages, such as adjustable geometry, high drug-loading capacity, excellent rigidity, tailored surface functionalization, large specific surface area, and desirable biocompatibility, MSNs could serve as superior robust nanocarriers over other inorganic scaffolds. Due to their chemical inertness and well-defined surface properties, MSNs are recognized as ideal candidates for the ease of internalization with good resistance
toward microbial attack and denaturation. Another appealing point refers to the tunable pores in trapping various pharmaceutical agents for further triggered release. Incorporation of MSNs into the gated nanodevices not only endows the therapeutic platform with an enhanced permeability and retention effect, but also provides considerable potential for anchoring versatile functionalities as caps owing to their tunable particle size and switchable pore entrances.59–65

Nowadays, light provides many superiorities as a stimulus, depending on the easy operation spatially and temporally, remote responsiveness, and controllable properties, among which near-infrared (NIR) light is regarded as a superior alternative due to the deep tissue penetration and noninvasiveness. Photochemical pulses have proved to be an effective method for on-demand drug release based on the various photochemical mechanisms, including photoisomerization, photolysis, and photocleavage. Supramolecular nanovalves bearing light-triggered hydrophobic-to-hydrophilic switch has been developed for an NIR light-activated delivery of anti-cancer drug (doxorubicin [DOX]) in a core-shell nanoplatform (Figure 3A).60 By coating MSN shell on the surface of upconversion NPs (UCNPs) (NaYF4:Yb, Tm@NaYF4) core, the UCNP@MSN materials were obtained for further anchoring hydrophobic 2-diazo-1,2-naphthoquinone (DNQ) as guest stalks. DOX molecules were then loaded, and host molecules, i.e., β-cyclodextrins, were used as gatekeepers and the channels of UCNP@MSN materials were capped via the hydrophobic interactions between the hydrophobic cavity of β-cyclodextrin and hydrophobic DNQ stalks. On the basis of hydrophobic-to-hydrophilic transformation of DNQ induced by NIR light, hydrophilic product of 3-indenecarboxylic acid (ICA) could be generated and led to the dissociation of gated assembly, enabling the on-demand release of DOX. Upon irradiation with NIR light, the nanocomposite
material, UCNP@MSN-DNQ, displayed a new peak at 255 nm in its UV-visible absorption spectrum ascribed to ICA, in contrast with the pure MSN modified with DNQ, for which no spectral change could be detected, revealing the vital role of...

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Figure 3. Schematic Representation of Supramolecular Nanovalves Installed on the Surface of Mesoporous Silica Nanoparticles

(A) Illustrations of cyclodextrin-based supramolecular nanovalves triggered by near-infrared (NIR) light. Reproduced with permission from Han et al. Copyright 2018, American Chemical Society.
(B) CuS NPs modified by cyclodextrin as gatekeepers for the controlled release of doxorubicin (DOX) drug. Reproduced with permission from Li et al. Copyright 2017, American Chemical Society.
(C) Monoferrocene-functionalized cyclodextrin as gated materials for redox-triggered release of DOX. Reproduced with permission from Wang et al. Copyright 2015, American Chemical Society.
the UCNP core in facilitating the transformation of DNQ to ICA. Both in vitro and in vivo experimental results demonstrated that the DOX-loaded UCNP@MSN NPs exhibited efficient tumor inhibition ability in controllable killing of HeLa cells, which opens a new avenue for cancer therapy by NIR light regulation.

An aberrant tumor intracellular microenvironment, such as abnormal enzyme content and high acid pH levels in endosome and lysosome, could provide direct stimulus in opening the nanovalves and unlocking the pore entrances for drug release. In 2015, a dynamic nanovalve system based on cucurbit[7]uril was reported by our research group, in which a crosslinked supramolecular network derived from cucurbit[7]uril and protonated diamines was fabricated as supramolecular gatekeepers. In this work, poly(glycidyl methacrylate)s (PGMAs) modified with protonated diamines were grafted onto the surface of MSNs by disulfide bonds, then cucurbit[7]uril was introduced to seal DOX through the formation of a 1:2 host-guest complex with protonated diamines via ion-dipole interactions, leading to the formation of dynamic supramolecular crosslinked polymer chains as detachable porters. The hybrid material exhibited a good release performance in response to lower pH conditions and a high level of glutathione (GSH) concentration due to the destruction of host-guest complexation and the cleavage of disulfide bonds, and an obvious cell-growth inhibition effect was found in cancer A549 cell lines from an MTT assay.

A drug-delivery system capped by per-6-thio-β-cyclodextrin-modified ultrasmall CuS NPs (CD-CuS) was constructed by Li and coworkers in 2018. In this contribution, fluorescent AIEgen-embedded MSN (FMSN) as nanocarriers were modified by benzimidazole, followed by an anchoring process of CD-CuS via host-guest interactions, whereby CD-CuS acted not only as gatekeeper but also photothermal agent for synergetic chemo-photothermal cancer therapy (Figure 3B). Significantly, the obtained DOX-loaded FMSN@CuS displayed effective anticancer ability triggered by an acidic environment or 808-nm NIR irradiation due to the pH-responsiveness and photothermal properties of the nanovalves. Thereafter, drug-release performance was measured by UV-visible spectrophotometry and imaged by a fluorescence microscope, and the photothermal performance assessment was recorded under 808-nm laser irradiation at fixed time intervals. Finally, chemo-photothermal therapy was carried out toward a gastric cancer cell line (SGC-7901 cells), which revealed an efficient release for tumor treatment in the acidic environment through entering the nucleus and destroying DNA. This work combined photothermal effect, fluorescent biomarker for cell imaging, and acid stimuli-responsive drug release in one pot, demonstrating the great possibility of a multifunctional delivery platform in cancer therapy and cell imaging.

Wang and coworkers designed monofericocene-modified β-cyclodextrin (Fc-β-CD) as pH/redox dual-responsive supramolecular nanovalves as shown in Figure 3C. The release behaviors could be affected by pH and voltage activation due to the acid-cleavable ketal linkages and reversible redox-responsive transition between the self-complexation and self-dissociation in nanovalves. It is noteworthy that zero premature release at physiological pH (7.4) and on-demand release could be achieved in a programmed manner with two release modalities. In modality 1, successive exposure upon voltage and acid stimuli led to the controllable release of encapsulated drugs gemcitabine (GEM) and DOX in sequence, while in modality 2, GEM and DOX escaped from MSNs together under acidic conditions because of the acidic hydrolysis of ketal groups. This work provided an alternative for developing smart delivery systems to meet the different needs of drug release.
To tackle the limitation of tumor heterogeneity existed in anticancer therapy, in 2018 Liu et al. reported a nanoscale drug-delivery platform (DOX@PRMSNs) from the view of a modular strategy, which employed MSNs with pyridine-disulfide stalks as containers for DOX and poly(β-cyclodextrin)s (PCD) as gatekeepers.63 Subsequently, PCD capped orifices and prevented the cargo leakage through self-assembly between pyridine groups and the cavity of β-cyclodextrin, which could be disordered by low pH value due to the protonation and escape of pyridine. Furthermore, several adamantyl (Ad)-terminated entities containing targeted ligands or polyethylenimine cationic polymer were introduced for self-assembly between cyclodextrin and Ad moieties, conferring nanocomposites with precise release and gene codelivery function. The feasibility of this proposal has been confirmed by in vitro drug-release experiments and transfection activity assay.

For another instance, Huang et al. designed and reported a phosphonated pillar[5]arene-valved (PPA[5]) delivery system for chemo-photothermal tumor therapy in 2017.64 They installed choline or pyridinium stalks on the surface of gold nanorod (GNR)-embedded MSNs (GNR@MSNs) for further host-guest complexation with PPA[5] via ion pairing between quaternary ammonium and phosphonate moieties, as shown in Figure 3D. The opening of nanovalves could be induced by enriched Zn^{2+} ions or competitive methyl viologen due to the coordination and competitive binding with PPA[5]. The experimental results revealed an invaluable insight for developing intelligent multiple-response delivery systems.

Recently, we have applied a new magnetic nanovalve system in promoting the growth of plants, such as Arabidopsis thaliana and cabbages (Figure 4).65 We installed gated components comprising water-soluble carboxylatopillar[5]arene ammonium pillar[5]arene (WP[5]A) modified Fe_{3}O_{4} NPs (WP[5]A-Fe_{3}O_{4}) on hollow MSNs (HMSNs) with larger capacity to load gibberellic acid (GA_{3}) as plant hormones. This multifunctional delivery system displayed bidirectional pH-responsive release since the cargo could be released under both acidic and alkaline conditions. Thereafter, other external stimuli including 1,4-butanediamine (BDA) and ultrasound were also used to trigger the controllable release of GA_{3} in a sustained-release manner, which has provided a promising method for the agricultural industry.

### MOF Nanocarriers for Stimuli-Responsive Drug Delivery

MOFs, one emerging type of porous material under considerable attention, are derived from the marriage of organic linkers and metal ions or clusters. Based on the evolution of hybrid materials, MOFs have been regarded as rational candidates in building multifunctional nanodevices, showing astonishing potential in nanotechnology and materials science.30,66 Owing to the superior properties of MOFs, such as tailorable pore aperture, versatile functionality, high loading capacity, tunable structures, biodegradability, and diverse morphologies, abundant interest has been focused on applying MOFs as drug-delivery carriers for stimuli-responsive controlled release. Furthermore, more and more remarkable achievements have demonstrated the improvement of MOFs in nanomedical applications from the viewpoint of surface and inclusion chemistry. As of today, extensive efforts have been devoted toward the utilization of MOF-derived smart platforms for effective therapy and meet the demand for the complicated requirements, especially for drug delivery and tumor therapy.

Taking into account the improvement of biocompatibility and highly ordered porosity of MOFs, we built up a multifunctional Fe_{3}O_{4}@MOF core-shell nanocomposite integrated with stimulus responsiveness, sustained drug release, and magnetic
The Fe$_3$O$_4$@MOF material was prepared by coating UiO-66 Zr-MOF shell on Fe$_3$O$_4$ core to produce Fe$_3$O$_4$@UiO-66-NH$_2$ composites assisted by an *in situ* growth method, and water-soluble pillar[6]arene (WP6) was then installed on 1-(6-bromohexyl) pyridinium bromide (Py) stalks-modified and 5-Fu-encapsulated core-shell nanocomposites through forming a bulky pseudorotaxanes structure. Significantly, the movable WP6-gated Fe$_3$O$_4$@UiO-66@WP6 material endowed the theranostic nanoplatform with multiple responsiveness toward pH, temperature, and competitive agents due to the dynamic host-guest binding. The facile magnetic separation and MRI-guided properties arising from the magnetic core made the composites a multifunctional platform for tumor therapy. It is notable that the tight host-guest binding has prolonged the release time over 7 days for sustained cancer therapy.

In the same year, we continued in fabricating another pH/temperature dual-responsive pillar[6]arene-valved nanoplatform for multimodal chemo-photothermal therapy with desirable targeting ability (Figure 5). In light of the layer-by-layer assembly strategy and surface engineering concept, different modular components possessing specific functions were utilized, for example, polypyrrole NPs (PPy NPs) with desirable photothermal conversion capability performed as cores,
UiO-66 MOF scaffolds bearing high drug-loading capacity served as shells, and folic acid conjugated polyethyleneimine (PEI-Fa) acted as active targeting entity in the outermost layer via electrostatic interactions. The as-prepared nanohybrid of PPy NPs and UiO-66 was then equipped with pillar[6]arene-based pseudorotaxanes, followed by the modification of PEI-Fa to give PPy@UiO-66@WP6@PEI-Fa hybrid NPs (PUWPFa NPs). Upon irradiation of 808 nm, the photothermal effects arising from PPy NPs accelerated the release of the loaded 5-Fu drug for cancer therapeutics.
Other Supramolecular Assemblies for Stimuli-Responsive Drug Delivery

Supramolecular Vesicles

Nanomedicines expedite the development of supramolecular polymeric nanomaterials linked by responsive linkages, which have offered feasible options in overcoming the limitations of traditional polymeric medicines, including complicated metabolism and elimination processes, and potential adverse reactions, due to their robust covalent binding. Supramolecular vesicles driven by reversible connections have received much attention in the field of cargo delivery owing to the fascinating stimuli responsiveness. In particular, supramolecular macrocycles and host-guest interactions play leading roles in the recently proposed supramolecular vesicles with multiple biomedical functions. Supramolecular vesicles for drug delivery are generally arising from the coassembly of non-covalent connected amphiphile entities. Yu and coworkers designed an amphiphilic copolymer, Pt-PAZMB-b-POEGMA, integrated with an aggregation-induced emissive metallacycle for live cell imaging and four diblock arms with GSH-responsive properties, which could self-assemble into NPs or vesicles with distinct morphologies along with the variation in experimental conditions, as presented in Figure 6. It was found that both NPs and vesicles embedded with anticancer 3,6-bis[trans-Pt(PEt3)2]phenanthrene (PhenPt) could encapsulate DOX for synergistic antitumor outcomes. The amphiphility of polymers could be altered via GSH-triggered cascade elimination and the nanostructures disassembled for controlled release of cargos.

Researchers spare no effort to engage in the construction of nanostructured supramolecular polymers with directional linkages and reversible properties. Along this...
line, Yu and coworkers utilized β-cyclodextrin and camptothecin (CPT) with suitable size as building blocks bridged by disulfide bonds to form GSH-responsive supramolecular polymer theranostic NPs (Figure 7). Through the formation of a host-guest inclusion complex, CPT was well protected against the physiological conditions. In addition, CPT-PEG-RGD (camptothecin-polyethylene glycol-arginyl-glycylaspartic acid) with targeting ligand and PEG shell was then introduced for
the cooperative stabilization of supramolecular NPs with multiple hydrogen bonds, π-π stacking interaction, and host-guest interactions. The release behaviors were studied upon the exposure of this system to GSH, demonstrating a negligible release within the bloodstream or extracellular matrix and an immediate release in the treatment of GSH.

Jiang et al. have reported a representative case of carboxylate-substituted pillar[6] arene (CPA[6]) based supramolecular vesicles that can respond to five types of stimuli, which are closely related to the tumorous microenvironments (Figure 8). The amphiphile microstructures were fabricated from the host-guest assembly of CPA [6] and disulfide-linked benzimidazolium guests. Thereafter, the amphiphiles further coassembled into vesicles of ca. 165 nm. Inspired by the abnormal pathological processes, five types of stimuli were taken into account as activation means, namely pH, CO₂, Zn²⁺, hexanediamine (HDA), and GSH. Ru(bipy)₃Cl₂ and DOX were used as

Figure 8. Schematic Illustration of a Carboxylatopillar[6]arene-Based Supramolecular Vesicle
drug models for the investigation of controlled drug release. Accordingly, acid environment and high CO2 level led to the protonation of CPA[6] and broke the electrostatic interactions between macrocyclic cavity and benzimidazolium; meanwhile, the metallic chelation between Zn2+ and carboxylate groups also weakened the host-guest interactions. In addition, HDA holds promise in capturing CPA[6] via competitive binding with macrocyclic cavities and GSH is known for its ability in cutting the disulfide bond, both of which could cause the disassembly of vesicles as well as the release of drugs. This work opens a new perspective in the fabrication of smart supramolecular platforms with multiple responsiveness in dealing with complicated tumor environments.

Reactive oxygen species (ROS) are playing increasingly important roles in cancer therapy fields because they could damage DNA and proteins of tumor cells. In particular, mitochondria are susceptible to ROS, which include peroxides (·O2), superoxide (·O2-), the hydroxyl radical (·OH), and singlet oxygen (1O2).71,72 Photosensitizers are one kind of the most popular molecules for producing ROS. Fan’s group prepared a supramolecular vesicle based on pillar[5]arene and an NIR-absorbing diketopyrrolopyrrole (DPP)-based guest G, and finally the hypoxia-activated prodrug tirapazamine (TPZ) was encapsulated into the vesicle.71 Once the system was irradiated by 660-nm laser, 1O2 molecules were produced to treat cancer. Rui et al. designed a photodynamic therapy supramolecular vesicle.72 Photosensitizer-tetraphenylporphyrin-containing quaternary ammonium salts (TPP-QASs) serving as guests were used to bind with water-soluble pillar[5]arene to result in host-guest assemblies, which could release TPP-QASs in an acidic tumor microenvironment, thus generating 1O2 effectively under light irradiation for photodynamic therapy.

**Polymeric NPs**

Depending on the desired outcome, supramolecular polymer-based responsive NPs are promising for effective gene transfection and drug delivery by holding different modules together, especially for biomolecule-implanted polymers.35,37,73–75 The combination of supramolecular assembly technique and polymeric vectors is increasingly gaining importance on account of their quite low cytotoxicity and potential in getting over multiple extracellular and intracellular barriers. Supramolecular host-guest interactions have provided viable approaches in the integration of functional components and biomacromolecules with recognition entities for improved biocompatibility, degradability, and enhanced cellular internalization. Following the aforementioned attributes, in this section we focus on the supramolecular polymeric vectors in gene and drug delivery for cancer treatment and acquired genetic diseases.

By means of dynamic combinatorial chemistry, a simple supramolecular strategy was successfully conducted in fabricating thiol/acid dual-responsive polymer vehicle-based drug-delivery system originating from the self-assembly of adamantane (AD) containing polyacrylic acid bridged by disulfide bond (PAA-SS-AD), β-cyclo-dextrin-embedded polyacrylic acid (PAA-CD), and AD-conjugated PEG5000 (PEG-AD) (Figure 9).73 The prepared system loaded with DOX by electrostatic interactions could respond to acidic conditions within the endosomal environment and the cleavable dynamic disulfide bonds were sensitive toward the reducing environment. Significantly, the DOX-loaded NPs displayed lower systemic toxicity in comparison with free DOX, resulting from the general unspecific toxicity of DOX, which could be observed in typical viability assessment of zebrafish larvae tumor cells.
Covalent attachment of macrocycles provides reliable and robust protection to the therapeutic agents, and has been achieved in the recently proposed metal-organic polyhedron (MOP). With a metal-organic cage architecture, a MOP was built from the self-assembly of ligands and metal ions. By blending with supramolecular macrocycles, a cubo-octahedral MOP vehicle featuring multiple-response release profile was successfully constructed in the coexistence of cucurbit[7]uril-derived ligand 1, bis(pyridine) ligand 2, Pd(NO₃)₂, and specific guest molecules, such as 1,6-hexanedi-amine (HDA). The corresponding hydrophobic inner cavity of MOP vehicle was produced from the host-guest complexation of cucurbit[7]uril and HDA for trapping hydrophobic DOX or Nile red (NR). The dynamic host-guest property of cucurbit[7]uril rendered the given vehicle to be stimuli responsive; as a result, the introduction of adamantane ammonium for competitive binding with cucurbit[7]uril would lead to the destruction of the hydrophobic nanoenvironment, thus allowing the release of cargos. Interestingly, pH-chemical or pH-photochemical triggered release were further investigated (Figure 10), whereby the corresponding neutral adamantane carboxylic acid at pH 5.8 could displace the included guests within cucurbit[7]uril macrocycles. On the other hand, remote photochemical control was also realized by using photoisomerization of 4,4'-diaminostilbene from trans to cis within the cavities of macrocycles, resulting in the dissociation of previous host-guest complexation and the release of cargos. The proposed MOP exhibits a positive therapeutic profile determined by in vitro assessment with significant uptake characteristics by cells.

Inorganic Nanocarriers for Stimuli-Responsive Drug Delivery
There are multifarious emerging inorganic nanoplastforms currently experiencing a burgeoning development in drug transport. The emergence of other inorganic
nanocarriers, such as reduced graphene oxide (rGO), magnetic NPs, CuS NPs, rare-earth-doped UCNPs, and hollow zirconia nanospheres, has combined the high loading capacity and photochemistry or electrochemistry properties within the delivery systems. Similarly, in these systems, supramolecular assemblies could also serve to gate the carriers anchored with drug monomer and engage in the effective management of cargo discharge process.

Motivated by smart and powerful self-propelled nanotechnology, Khezri and co-workers described an intriguing micromachine, n-rGO/Pt, derived from catalytic Pt layer and reduced nanographene oxide (n-rGO) layer, which could convert electrochemical energy to mechanical motion for effective DOX release. Among all the attractive vehicles, carbon allotropes are competitive for their remarkable DOX-loading capacity driven by supramolecular π-π stacking, which reached up to 200% according to the work by Sadaf and Walder. It was reported that n-rGO/Pt could be constructed by electrodeposition of nanographene as outer layer and potentiometric deposition of Pt as inner layer, respectively, via a template-assisted strategy. Therefore, DOX could be readily loaded through physical adsorption based on π-π interactions between the aromatic structure of DOX and conjugated system of n-rGO/Pt without complicated surface functionalization. As performed

Figure 10. Schematic Representation of the Metal-Organic Polyhedron for Controlled Release
(A) Synthetic route to the monofunctionalized cucurbituril host and the chemical structures of host and guests. (B) pH-chemical and pH-photochemical responsive release processes. Reproduced with permission from Samanta et al. Copyright 2017, American Chemical Society.
by cyclic voltammetry scans, once the electrons were injected into DOX@n-rGO/Pt micromotors, the quinizarin part of DOX molecules underwent a reversible transformation from oxidation state (anthracenonetetrone) to reduction state (leucoquinizarin) by $2e^-\rightarrow 2H^+$. The successful expulsion of DOX was attributed to electron transfer from negatively charged rGO to drug molecules and eventually caused by electrostatic repulsion between rGO and DOX of the reduction state, which was further confirmed by the UV-visible spectra of electrolyte solution. The cytotoxicity experiment was carried out toward T47D cells with the treatment of DOX@n-rGO/Pt, and the cell shrinkage accompanied by fluorescence change demonstrated the applicable release.

UCNPs are regarded as rising stars in nanomedicine owing to their unique optical and biological properties, such as narrow emission bands, biocompatibility, negligible photodamage, and low autofluorescence, and meanwhile these features render them as promising candidates in fabricating multimode diagnostic and therapeutic nanoplatforms, involving drug delivery, MRI, and upconversion bioimaging. Very recently, a pH-responsive supramolecular nanovalve based on hydrophilic carboxylate-based pillar[5]arene (WPS) was installed on the surface of core-shell NaYF4:Yb/Er@NaGdF4 UCNPs constructed by coating a thin NaGdF4 shell on the outermost surface of NaYF4:Yb/Er NP.79 The surface of UCNPs was then modified with 15-carboxy-N,N,N-trialkylpentadecan-1-ammonium bromide as guest stalks, which could be further encircled by WPS. Driven by specific host-guest recognition between hydrophobic cavities of WPS and ammonium bromide moieties, the WPS rings were anchored onto UCNPs and produced the resultant nanohybrids for further loading with DOX as shown in Figure 11. Moreover, the protonated WPS, due to the addition of a series of PBS bearing different pH levels, led to the dissociation of host-guest complexation and subsequent release of DOX on demand. As visualized by upconversion luminescence (UCL) spectra, the overlap of emission of the resultant nanohybrids and the absorbance of DOX ensured the non-radiative energy transfer between UCNPs and DOX. Remarkably, the incorporation of the gadolinium-containing NaGdF4 shell imparted the overall nanohybrids with enhanced magnetic resonance signal in T1-weighted and color-mapped MR images, so that the nanohybrids performed with potential to be positive T1 MRI contrast agents for organisms. Moreover, HeLa cells were incubated with the prepared materials, both showing significant cell death (72%) in the presence of DOX-loaded nanohybrids, and the superior cell viability (96%) treated with blank vehicles without DOX has demonstrated that the obtained nanohybrids could serve as versatile platform for drug delivery.

We reported another multifunctional system based on UCNPs for controlled cargo release and cell imaging by introducing phosphoryl pillar[5]arenes to modify oleic acid-stabilized β-NaYF4:Yb/Er UCNPs (OA-UCNPs) via a ligand-exchange process (Figure 12).76 In this work, rhodamine B (Rhb) was chosen as loaded drug model through electrostatic and host-guest interactions. The nanomaterial exhibited considerable pH-responsive release efficiency due to the electrostatic repulsion between the COO− group of RhB and deprotonated phosphate groups. Thereafter, the biocompatibility and UCL cell-imaging ability of the nanosystem were also evaluated. This work has opened a new door for the employment of UCNPs functionalized with synthetic macrocycles in biomedical applications.

Indeed, CuS NPs display a good photothermal effect for creating hyperthermia, and could also be used as nanocarriers in targeted chemo-photothermal therapeutic platforms valved by carboxylate-pillar[5]arene. In a recent work by Yu’s group, our
own group, and other coworkers, pillar[5]arene rings were used to act as stabilizers in the synthesis of CuS NPs, followed by a simple supramolecular approach to anchor liver cancer-specific galactose ligands through host-guest recognition between the cavity of pillar[5]arene and pyridinium moiety of galactose to give the final material CuS@CPG. DOX was then loaded via electrostatic interactions on the surface of CuS@CPG. As a result, the multifunctional CuS@CPG-DOX has integrated target-specific release, chemotherapy, and photothermal therapy in one pot. HepG2 cells and HepG2 tumor-bearing nude mice were selected in the evaluation of cellular uptake, release performance, and chemo-photothermal therapy efficiency. Upon NIR irradiation at 808 nm for only 7 min, the temperature of cell culture could achieve 60°C rapidly for photothermal ablation. Notably, the amount of DOX release obviously increased with the decrease in pH due to the protonation of pillar[5]arene and the disassembly of host-guest complexation. In short, the desired synergistic therapeutic effects have proved the advantages of supramolecular assembly strategy and the related nanovalves.

On account of the extraordinary resistance against a hot alkaline environment, mechanized hollow mesoporous zirconia nanospheres (HMZNs) have been used in achieving dual-pH-responsive drug release by Wang and coworkers. Propanone bis(2-aminoethyl)ketal (PBAEK) stalks were successfully grafted on the surface of HMZNs. Supramolecular switches derived from cucurbit[7]uril macrocycles were then installed through an assembly procedure based on specific ion-dipole interactions between cucurbit[7]uril and PBAEK, forming bistable [2]pseudorotaxanes to...
block the entrance and entrap cargos. Accordingly, the alkali activation could lead to the destruction of ion-dipole interactions followed by the dethreading of cucurbit[7]uril rings; on the other hand, acid stimulus could result in the cleavage of ketal groups of stalks and unlock the pore orifices. Both alkaline and acidic ranges possessed feasibility to mediate and execute controlled release of drugs, as confirmed by the in vitro cell studies toward SMMC-7721 cell line. By virtue of the intrinsic advantages of HMZNs, this work has proposed a dual-pH mediation method for targeted drug delivery and chemotherapy from the viewpoints of structural design and selection of stalks and macrocycles.

**Supramolecular Switch for Antibacterial Application**

Bacterial infections continue to attract much attention because of the occurrence of bacterial resistance and the accumulation of antibiotic, which has been considered a severe threat to public health. Supramolecular antibiotic switches particularly stand out depending on their structural diversity and easy maneuverability. The antibacterial activity could be readily regulated via a supramolecular assembly/disassembly method without complicated modifications. Such a strategy has been verified by using cucurbit[7]uril to protect the antimicrobial entities’ quaternary ammonium within the cationic poly(-phenylene vinylene) derivative (PPV), where...
the interactions with bacteria could be “switched off” by encapsulating quaternary ammonium groups inside the cavities of cucurbit[7]uril rings (Figure 13). Researchers turned their attention to the antibacterial activity by using AD to competitively bind with cucurbit[7]uril whereby the antimicrobial entities could be exposed to the bacteria. The subsequent antibacterial experimental results with high killing efficiency of 70% against Escherichia coli confirmed the feasibility of this strategy.

Together with Wu and coworkers, we used a layer-by-layer self-assembly strategy to construct another antibacterial platform by coating lysozyme (Lys), hyaluronic acid (HA), and 1,2-ethanediamine (EDA)-modified PGMA on the outside of MSNs which were loaded with amoxicillin (AMO) as antibiotics (Figure 14A). In this system, Lys and cationic PGMA acted as multivalent interaction providers to contact with bacterial membrane. The resultant hybrid material MSN-Lys-HA-PGMA possesses a good antimicrobial effect toward Gram-positive Staphylococcus aureus with hyaluronic-dase-responsive behaviors for antibacterial AMO release. Subsequently, we proposed a new supramolecular nanoassembly in 2017, which could detect bacteria and cause bacterial elimination simultaneously (Figure 14B) through layer-by-layer self-assembly of EDA-modified PGMA, cucurbit[7]uril, and an AIEgen tetraphenylethylene carboxylate derivative, TPE-(COOH)4, on the surface of MSNs. The interactions between bacteria and nanoassembly weakened the connections between cationic PGMA and TPE-(COOH)4 layer and led to a decrease in fluorescent emission of the TPE entity. Furthermore, the addition of AD created competitive binding with cucurbit[7]uril and resulted in the release of loaded AMO. As a result, this nanoassembly exhibited responsive antibacterial activity against pathogenic S. aureus and E. coli. This work has developed a dual-function-assisted antibacterial nanoplat- form for bacterial elimination and detection.

Figure 13. Schematic Description of Supramolecular Switch for Antimicrobial Regulations
Conclusions

In summary, we have reviewed in detail the most recent progress of supramolecular theranostics by showing various types of drug-delivery systems gated by supramolecular macrocycle-based entities. For earlier examples, one can refer to our previously published review articles. A principal goal of nanomedicine is to effectively minimize premature release in terms of reducing severe side effects toward normal organs, which could be achieved by employing supramolecular gating techniques due to their many advantages including stimuli responsiveness, dynamic and reversible connections, flexibility, and controllability. As already mentioned, supramolecular nanovalves may be divided into two categories:

1. Conformational valves, gated on the surface of porous and solid supports such as MSNs and MOFs, are the earliest supramolecular gated materials studied by researchers.
2. Conceptual valves perform a switching function; however, they also participate in the fabrication of carriers instead of installing on the outside of delivery systems.

Recent advancements are focused on fulfilling multilateral requirements in medical treatment, and supramolecular nanovalves with good mechanical behaviors have been proved to be a stronger helper in regulating access to small drug molecules in a responsive manner. Abnormal physiological conditions in tumor tissues could be used as favorable endogenous stimuli to avoid undesirable damage caused by external stimuli. These representative examples have demonstrated that supramolecular theranostics possess competitive superiorities over other existing means, especially in realizing site-specific release and dealing with biological barriers.
Despite these exciting achievements in the field of supramolecular theranostics, there are few multifunctional nanoplatforms reported so far that are able to integrate diagnosis, treatment, and tracing in one system. In this sense, multidisciplinary cooperation is highly required to expand the applications into clinical trials, especially by scientists, engineers, and clinicians in those closely related disciplines such as materials science, chemistry, biology, pharmacology, nanotechnology, and engineering. Moreover, as unforeseen difficulties could arise in in vivo and clinical models, investigations on the stability, biodistribution, biodegradability, metabolic pathways, and biosafety of these supramolecular theranostic systems at all levels should be strengthened. From the viewpoint of long-standing challenges in human healthcare, we believe that supramolecular theranostics could provide a comprehensive toolbox for the advancement of therapeutic methodology.

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AUTHOR CONTRIBUTIONS

REFERENCES


