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Supramolecular chemotherapy based on host–guest molecular recognition: a novel strategy in the battle against cancer with a bright future

Jiong Zhou, Guocan Yu* and Feihe Huang *

Chemotherapy is currently one of the most effective ways to treat cancer. However, traditional chemotherapy faces several obstacles to clinical trials, such as poor solubility/stability, non-targeting capability and uncontrollable release of the drugs, greatly limiting their anticancer efficacy and causing severe side effects towards normal tissues. Supramolecular chemotherapy integrating non-covalent interactions and traditional chemotherapy is a highly promising candidate in this regard and can be appropriately used for targeted drug delivery. By taking advantage of supramolecular chemistry, some limitations impeding traditional chemotherapy for clinical applications can be solved effectively. Therefore, we present here a review summarizing the progress of supramolecular chemotherapy in cancer treatment based on host–guest recognition and provide guidance on the design of new targeting supramolecular chemotherapy combining diagnostic and therapeutic functions. Based on a large number of state-of-the-art studies, our review will advance supramolecular chemotherapy on the basis of host–guest recognition and promote translational clinical applications.

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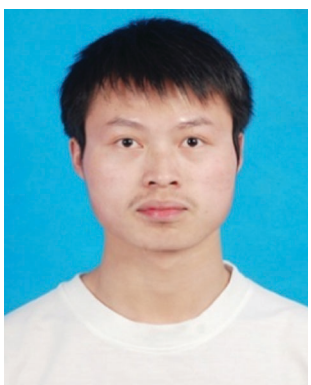
1. Introduction

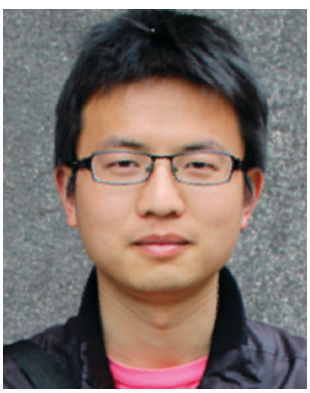
Of the many challenges in medicine, none has had a more controversial beginning and none has experienced more hard-fought progress than the treatment and cure of cancer.[1] On a global level, cancer is now one of the world's most pressing health challenges. Seven out of every 10 cancer deaths occur in Africa, Asia, and Central and South America. By the year 2030, these cancer deaths will increase globally by as much as 80%, according to WHO estimates.[2,3] The scientific community is working hard to avert this grim projection. With care that aims to balance the effectiveness of treatment alongside the importance of quality of life, more patients than ever are not

State Key Laboratory of Chemical Engineering, Center for Chemistry of High-Performance & Novel Materials, Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China. E-mail: guocanyu@zju.edu.cn, fhuang@zju.edu.cn; Fax: +86-571-8795-3189; Tel: +86-571-8795-3189



Jiong Zhou

Jiong Zhou was born in Hubei, China, in 1992. He received his BS degree in polymer materials and engineering from Anhui University under the supervision of Prof. Ru Xia in 2014. Then he joined the laboratory of Prof. Feihe Huang at Zhejiang University to pursue his PhD degree in chemistry. He was a visiting scholar in Prof. Timothy R. Cook's group at the University at Buffalo-SUNY (November 2016 to May 2017). His current research interests are focused on responsive self-assembly, supramolecular coordination complexes and functional materials based on host–guest chemistry.



Guocan Yu

Guocan Yu was born in Zhejiang, China, in 1987. He received his PhD degree from Zhejiang University in 2015 under the direction of Prof. Feihe Huang. He is currently a postdoctoral fellow in Dr Xiaoyuan (Shawn) Chen's research group at National Institutes of Health (NIH). His research interests are focused on the construction of functional supramolecular theranostics and stimuli-responsive biomaterials.

just living longer but able to lead full lives. Clinical research is the bedrock of progress against cancer and discoveries are moving from the bench to the bedside faster than ever.

With regards to systemic anticancer therapy, conventional chemotherapy agents or cytotoxic agents are the first agents in the armamentarium for the war on cancer.[4,5] Chemotherapy, working by stopping or slowing the growth of cancer cells, is a treatment that uses drugs to destroy cancer cells. Sometimes, chemotherapy is used as the only cancer treatment. But more often, patients receive chemotherapy along with surgery, radiation therapy or biological therapy.[6–8] Chemotherapy can:

(a) Make a tumor smaller before surgery or radiation therapy. This is called neo-adjuvant chemotherapy.

(b) Destroy cancer cells that may remain after surgery or radiation therapy. This is called adjuvant chemotherapy.

(c) Help radiation therapy and biological therapy work more effectively.

(d) Destroy cancer cells that come back (recurrent cancer) or spread to other parts in the body (metastatic cancer).

However, conventional chemotherapy has drawbacks ranging from poor solubility/stability of the drugs in physiological environments to limited efficacy, drug resistance and severe treatment-related side effects to healthy tissues, greatly limiting its clinical applications. On the other side, the processes of translocation, activation and excretion of the drugs are hardly able to be tracked *in vitro* and *in vivo*, because most anticancer drugs are intrinsically non-fluorescent or weakly fluorescent, such as cisplatin, gemcitabine and paclitaxel. New methods that can specifically deliver drugs to tumor tissues are urgently desired.[9–12]

Supramolecular chemistry is ''chemistry beyond the molecule''.[13] In contrast to molecular chemistry, which is predominantly based on the covalent bonding of atoms, supramolecular chemistry is based upon intermolecular interactions, *i.e.* on the association of two or more building blocks, which are held together by intermolecular bonds. The dynamic and reversible nature of the non-covalent interactions endows the resultant supramolecular architectures with excellent stimuli-responsive features and infinite possibilities.[14–18] Among various non-covalent interactions, including hydrogen bonding, π–π stacking interactions, host–guest interactions, electrostatic interactions and charge-transfer interactions, host–guest interactions are attracting more and more attention arising from their distinctive properties by introducing macrocylic hosts into supramolecular systems.[19–21] Macrocylic molecules, such as crown ethers, cyclodextrins, calixarenes, cucurbiturils and pillararenes, usually have hydrophobic cavities in which the guests can be embedded.[22–25] These magnificent macrocycles provide ideal platforms for the fabrication of supramolecular chemotherapeutic agents through host–guest molecular recognition. By taking advantage of host–guest chemistry, some limitations impeding traditional chemotherapy for clinical applications can be solved effectively (Fig. 1). For example, the solubility/stability of the poorly soluble anticancer drugs can be significantly improved in physiological environments upon formation of host–guest complexes.[26,27] High accumulation of the anticancer drug in tumors can be achieved benefiting from supramolecular self-assembly, remarkably enhancing the efficacy of the supramolecular chemotherapeutic agents and reducing the side effects towards normal tissues.[28–30] Furthermore, functional groups can be easily integrated into supramolecular chemotherapeutic systems by simply modifying the building blocks, such as targeting ligands, imaging agents or even therapeutic drugs, endowing them with multi-functional theranostic properties.[31–34] Most importantly, the release of the loaded drugs/prodrugs in the tumor can be precisely controlled, because the binding affinity of the host–guest linkages can be adjusted according to different environments between the tumor and normal tissues (such as pH, redox, enzymes).[35–37] The dynamic nature of non-covalent interactions makes supramolecular chemotherapy more versatile than traditional chemotherapy and nanomedicines that have a shortage of stimuli-responsiveness.

In this critical review, we summarize the progress achieved in supramolecular chemotherapy for cancer treatment based on host–guest interactions and provide guidance on the design of new targeting supramolecular chemotherapy combining diagnostic and therapeutic functions. Supramolecular chemotherapy based on host–guest molecular recognitions between macrocyclic hosts/biomolecules and drugs/prodrugs, supramolecular nanovehicles, supramolecular organic–inorganic hybrid materials, metal-coordination and combination with other treatments for cancer therapy are well elucidated in sequence. Research directions of supramolecular chemotherapy in the future are also proposed. As this topic is at the interface of nanotechnology, supramolecular chemistry, biology and materials science, it unifies multiple disciplines to provide exciting new strategies that can be used to explore smart supramolecular theranostics. We hope to raise more interest from materials scientists, chemists, oncologists and pharmacologists to advance supramolecular chemotherapy and promote translational clinical applications.

Feihe Huang

Feihe Huang was born in China in 1973. He obtained his degree of Doctor of Philosophy in Chemistry from Virginia Polytechnic Institute and State University (VT) under the guidance of Prof. Harry W. Gibson in March 2005. Then he joined Prof. Peter J. Stang's group at the University of Utah as a postdoctor. He became a Professor of Chemistry at Zhejiang University in December 2005. His current research interests are supramolecular polymers and pillararene supramolecular chemistry. The awards he has received up to now include the Chinese Chemical Society AkzoNobel Chemical Sciences Award, the Cram Lehn Pedersen Prize in Supramolecular Chemistry, and the 2016 Royal Society of Chemistry Polymer Chemistry Lectureship award.

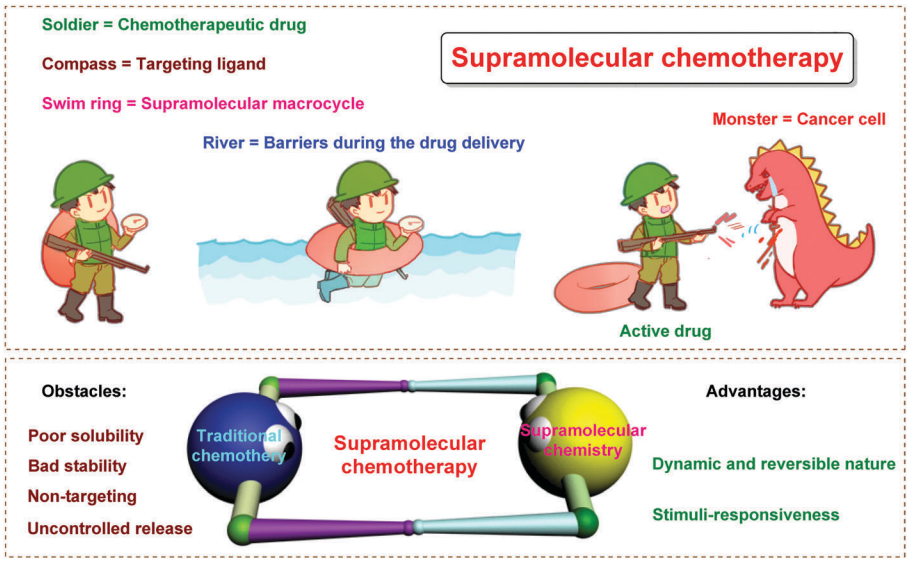


Fig. 1 Top: Cartoon representation of supramolecular chemotherapy. Bottom: Schematic illustration of supramolecular chemotherapy integrating traditional chemotherapy with supramolecular chemistry. The obstacles of traditional chemotherapy to clinical applications and the advantages of supramolecular chemistry are provided.

2. Supramolecular chemotherapy based on host–guest molecular recognition between macrocyclic hosts and drugs/prodrugs

For most anticancer drugs/prodrugs, their solubility and stability in physiological environments are poor, greatly decreasing their efficacy.[38,39] In a typical host–guest inclusion complex, a host molecule affords a cavity to encapsulate a guest molecule through non-covalent interactions.[40–43] For pharmaceutical applications, the most common case is to encapsulate hydrophobic drug molecules into hydrophobic cavities of macrocyclic molecules in aqueous media.[44–46] Such host–guest complexes have relatively high stability, solubility and bioavailability, providing robust and reliable connections for the fabrication of supramolecular drugs. Several types of major macrocyclic hosts including cyclodextrins, calixarenes, cucurbiturils and pillararenes used for the fabrication of supramolecular chemotherapeutic agents are discussed in this section.

2.1 Cyclodextrin-based supramolecular chemotherapy

Discovered coincidentally by the French scientist Villiers from natural products in 1891, cyclodextrins (CDs) are a family of water-soluble macrocyclic oligosaccharides composed of D-glucose units that are connected by α-1,4-glucosidic linkages.[47] The most commonly used CD subtypes are α-, β- and γ-CD, which consist of six, seven and eight D-glucose units, respectively (Fig. 2).[48] The three dimensional structure of CDs can be considered as a truncated cone-like molecular container with a hydrophobic interior cavity and hydrophilic external surface. CDs can trap or encapsulate suitably sized guest species with different binding affinities *via* hydrophobic and van der Waals interactions between CDs and guest molecules in aqueous media.[49,50] Due to the high stability, excellent biocompatibility and facile modification of the parental structure of CDs, various CD derivatives and CD-based nano-systems have been applied in biomedical fields and pharmaceutical applications.[51–53]

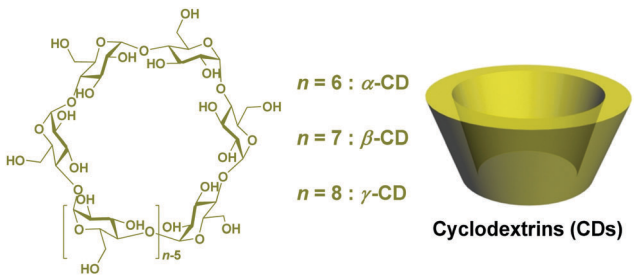


Fig. 2 Chemical structure and cartoon illustration of cyclodextrins (CDs). n = 6, 7 and 8 represent α-, β- and γ-CD, respectively.

An important aspect resting on the saccharide nature of CDs is their non-toxicity toward humans. Several CD-containing pharmaceutical products have successfully been approved by regulatory agencies, such as the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe.[54,55] CDs have emerged as useful functional excipients in pharmaceutical formulation to improve the apparent solubility, rate of dissolution and chemical stability of poorly water-soluble drugs.[56] By forming host–guest inclusion complexes between hydrophobic drugs and CDs (or CD derivatives), the solubility, stability and safety of drugs can be improved, thereby enhancing the drug availability in biological systems. In particular, CDs have been used as carriers to encapsulate anticancer drugs such as doxorubicin (DOX), paclitaxel (PTX) and camptothecin (CPT), resulting in the enhancement of their solubility, stability and bioavailability.[57,58]

Liposomes are small, spherical and enclosed compartments separating an aqueous medium from another by a phospholipid bilayer.[59,60] Loading drugs into liposomes can increase the therapeutic performance by reducing drug concentrations in normal tissues and raising the concentrations in tumors by fully taking advantage of the enhanced permeability and retention (EPR) effect.[61–64] For example, Doxil is a commercially used anticancer drug, which can be used to increase the blood circulation time of DOX and reduce its cardiac toxicity.[65,66] However, it is hard to load poorly soluble anticancer drugs into the hollow cavity of liposomes. The hydrophobic membrane of liposomes is able to encapsulate poorly soluble drugs, but the stability is disappointing, and the sturctures easily aggregate or disassemble. By the formation of CD⊃drug host–guest inclusion complexes, the water-soluble complexes can be easily encapsulated by liposomes. Based on this, Vogelstein and co-workers designed ionizable β-CDs containing weakly basic or acidic functional groups on their solvent-exposed surfaces to encapsulate poorly soluble chemotherapeutic agents (BI-2536 and PD-0325901).[67] The CD⊃drug complexes were remotely loaded into liposomes *via* pH gradients. This incorporation not only dramatically increased the aqueous solubility of these compounds but also afforded the loaded liposomes with less toxicity and greater activity. The supramolecular strategy makes the impossible possible, which provides an extremely novel method to prepare nanomedicines using anticancer drugs that have already failed in the clinical due to their troublesome formulations, causing dead drugs to come back to life.

Gu and co-workers developed a transformable liquid–metal nanomedicine for drug delivery based on a core–shell nanosphere composed of a liquid-phase eutectic gallium–indium core and a thiolated polymeric shell.[68] This formulation can be simply produced through a sonication-mediated method with bioconjugation flexibility. β-CDs provided faithful loading sites for DOX. The resulting nanoparticles loaded with DOX subsequently fuse and degrade under mildly acidic conditions, which facilitated the release of DOX in acidic endosomes after cellular internalization. Equipped with hyaluronic acid, a tumour-targeting ligand, the formulation displayed enhanced tumor suppression. This liquid metal-based drug delivery system (DDS) with fusible and degradable behaviour under physiological conditions provided a new strategy for engineering supramolecular therapeutic agents with low toxicity.

2.2 Calixarene-based supramolecular chemotherapy

Calix[*n*]arenes (C[*n*]As) have been considered as the third generation of macrocyclic host molecules next to crown ethers and CDs in supramolecular chemistry.[69,70] Generally, C[*n*]As are produced by chemical synthesis between phenols and formaldehyde with phenolic units linked by methylene groups at the *meta*-positions. C[*n*]As possess corn-like shape with a hollow hydrophobic cavity, as well as two rims at the primary and secondary sides (Fig. 3). C[*n*]As have flexible conformational isomers and variable cavity dimensions according to the number of incorporated phenolic units (generally composed of 4, 5, 6 or 8 phenolic units). C[*n*]As and their derivatives have

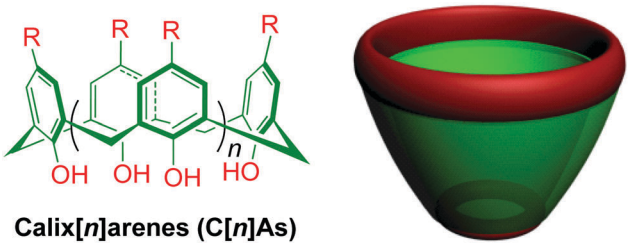


Fig. 3 Chemical structure and cartoon illustration of calix[*n*]arenes (C[*n*]As).

been reported to exhibit anticancer, antibacterial, antiviral, antitubercular and antifungal activity.[71–73] As potential drug carriers and therapeutic modifiers, water-soluble C[*n*]As have been made through sulfonation of the upper rim, coupling carboxylic acid groups to the lower rim or attaching polar functional groups to the molecular edge.[74] Small molecule drugs and biological molecules can be incorporated into the cavity at both rims of C[*n*]As, including ions, sugars, proteins, amino acids, peptides, hormones and nucleic acids.[75–78] Such inclusion complexes are stabilized by various forces, such as the hydrophobic effect, ion–dipole interaction and hydrogen-bonding.

Coleman and co-workers patented C[4]A derivatives as anticancer agents and illustrated their anticancer effects on different tumor cells.[79] In particular, C[4]A dihydrophosphonic acid exhibited an effective antitumor activity on fibrosarcoma, melanoma and leukemic cells due to the pharmaceutical composition. Ferreira-Halder and co-workers revealed the mechanisms by which C[6]A overcame the aggressiveness of a human pancreatic cancer cell line.[80] C[6]A abolished signal transduction of tyrosine kinase receptors localized in different cellular compartments, resulting in cell cycle arrest, down-regulation of pro-survival mediators, endoplasmatic reticulum stress and cell death by autophagy.

2.3 Cucurbituril-based supramolecular chemotherapy

Cucurbit[*n*]urils (CB[*n*]s) are macrocyclic containers prepared by acid-catalyzed condensation between glycoluril and formaldehyde. The first CB[*n*] was synthesized by Behrend and co-workers in 1905 and confirmed by Mock and co-workers in 1981.[81,82] The CB[*n*] family mainly includes CB[5], CB[6], CB[7], CB[8] and CB[10] (Fig. 4). The defining structural features of CB[*n*]s are their highly symmetric pumpkin-like structure, with negatively charged carbonyl lined portals and a central hydrophobic cavity. CB[*n*]s have been shown to form 1 : 1 as well as 1 : 2 host–guest complexes with a variety of organic and inorganic guest molecules by encapsulating them in the hydrophobic cavities of CB[*n*]s. The complexes are stabilized by hydrogen bonding, van der Waals forces and/or ion–dipole interactions with the CB[*n*] portals.[83–87]

Platinum-based anticancer drugs, including cisplatin, carboplatin and oxaliplatin (OX), have been widely used for the treatment of numerous human cancers, such as bladder, head/neck, lung, ovarian and testicular cancers. Their modes of action have been linked to their ability to intra-/inter-strand crosslink with the purine bases on DNA, thus interfering with

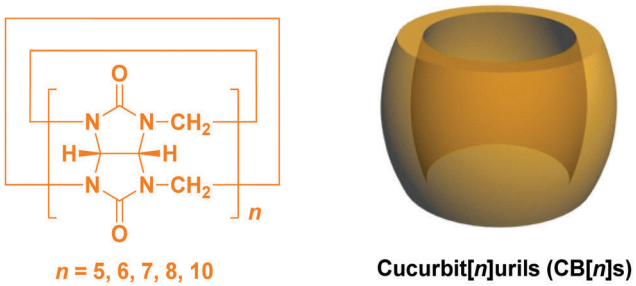


Fig. 4 Chemical structure and cartoon illustration of cucurbit[*n*]urils (CB[*n*]s).

DNA repair mechanisms, causing DNA damage and subsequently inducing apoptosis. However, platinum-based anticancer chemotherapy is associated with severe side effects and multidrug resistance (MDR).[88] Plumb, Wheate and co-workers encapsulated cisplatin in CB[7] to achieve enhanced anticancer efficacy towards human ovarian carcinoma cell lines.[89] The inclusion complex was stabilized by four hydrogen bonds between the ammine hydrogen atoms on cisplatin and the carbonyl oxygen atoms of CB[7]. *In vivo* study revealed that the CB[7]⊃cisplatin complex could be used for the treatment of drug resistant human cancer. The enhanced pharmacokinetic effect of the CB[7]⊃cisplatin complex was responsible for overcoming the cisplatin drug resistance.

Very recently, Sun, Zhang and co-workers used the clinical antitumor drug OX to form a host–guest complex with CB[7] (CB[7]⊃OX) and studied its competitive release and replacement by spermine.[90] The cytotoxicity of OX to the normal colorectal cell can be significantly decreased by the formation of the CB[7]⊃OX complex. More importantly, CB[7]⊃OX exhibited higher antitumor activity than OX itself, because the release of OX from CB[7]⊃OX and simultaneous consumption of spermine by CB[7] resulted in cooperatively enhanced anticancer performance.

In addition to the enhancement of water solubility, Scherman and co-workers encapsulated tomozolomide (TMZ), a primary chemotherapeutic agent against gliobalstoma multiforme (GBM), into the hydrophobic cavity of CB[7], which effectively decreased the degradation rate of TMZ and thus prolonged its lifetime in the physiological environment.[91] The supramolecular formulation was conducive to increasing its penetration of the blood–brain barrier and cellular absorption, dramatically improving the drug's activity against primary GBM cell lines. This interesting work emphasized that supramolecular drugs could potentially lead to the increase of the drug's propensity to cross the blood–brain barrier and be absorbed into the GBM cells by fully taking advantage of host–guest chemistry, thereby enhancing anticancer efficacy.

Briken, Isaacs and co-workers prepared a targeted monofunctionalized CB[7] derivative **1**, which featured a covalently attached biotin ligand on its convex surface (Fig. 5a, I).[92] Container **1** was capable of forming complexes with a wide variety of chemotherapeutic agents, such as OX, camtothecin, tamoxifen, temezolomide, albendazole and irinotecan. The introduction of a biotin ligand in CB[7] endowed the resultant host–guest complexes with excellent targeting ability, which could be uptaken by murine lymphocytic leukemia cells (L1210FR) overexpressing biotin receptors (Fig. 5a, II). The targeted container⊃drug complex (**1**⊃OX) showed approximately

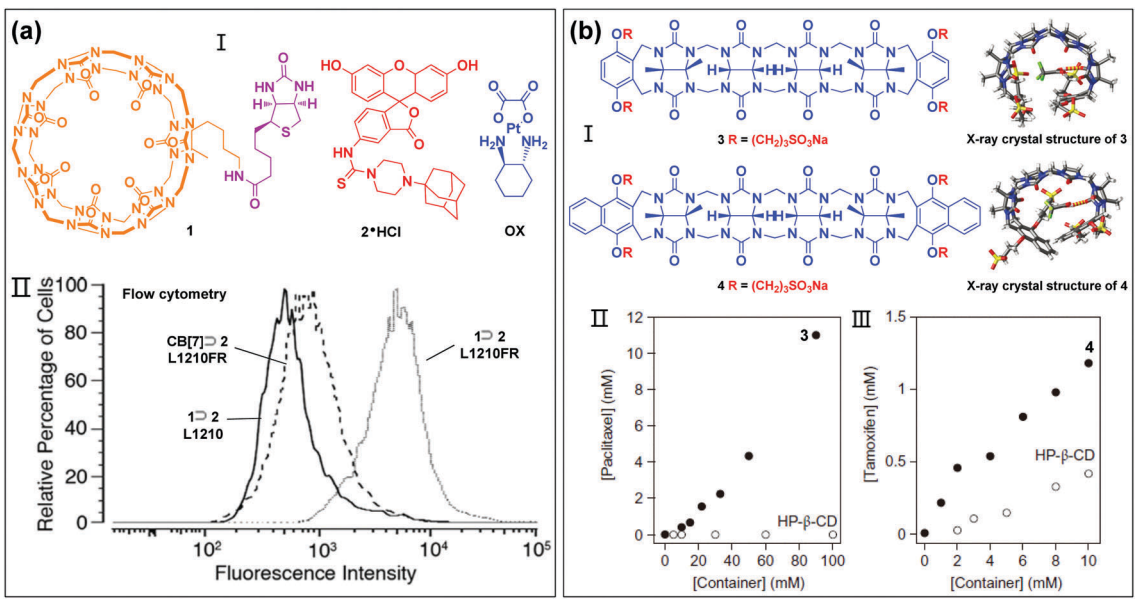


Fig. 5 (a) Chemical structures of biotin-functionalized CB[7] derivative **1**, fluorescent adamantane derivative **2**, and OX (I). Murine lymphocytic leukemia cells overexpressing biotin receptors (L1210FR) and expressing normal levels of biotin receptors (L1210) showed target-specific binding of **1**⊃**2** (II) (reproduced with permission of John Wiley & Sons, Inc. from ref. 92). (b) Chemical structures and X-ray crystal structures of acyclic CB[*n*] containers **3** and **4** (I). Phase solubility diagram for paclitaxel in the presence of molecular containers **3** (filled circles) and HP-β-CD (open circles) (II). Phase solubility diagram measured for tamoxifen in the presence of molecular containers **4** (filled circles) and HP-β-CD (open circles) (III) (reproduced with permission of Nature Publishing Group from ref. 96).

an order of magnitude higher cytotoxicity than untargeted CB[7]⊃OX in 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) bioactivity assays. Specific delivery of therapeutic drugs to cancer cells can be achieved without altering their efficacy through this supramolecular strategy, greatly avoiding redundant chemical modifications.

Acyclic macrocycles, such as acyclic CB[*n*]-type receptors that consist of central C-shaped glycoluril oligomers, are amenable to a more straightforward synthetic modification which allows diversification. It can retain the essential molecular recognition feature and have excellent solubility characteristics to solubilize insoluble pharmaceutical agents in water.[93–95] Briken, Isaacs and co-workers studied the syntheses and molecular recognition properties of acyclic CB[*n*]-type containers **3** and **4** (Fig. 5b, I).[96] Compounds **3** and **4** featured a central glycoluril tetramer, two terminal aromatic rings and four sodium sulfonate groups, which dramatically enhanced their solubility in water. Containers **3** and **4** were preorganized into a C-shaped conformation and were not significantly self-associated in water. Significantly, the acyclic nature of **3** and **4** and the flexibility of the glycoluril tetramer backbone allowed these compounds to flex like a hand to accommodate guests of different sizes. Containers **3** and **4** greatly enhanced the water solubility (from 23-fold to 2750-fold) of a number of insoluble drugs (*e.g.*, paclitaxel, melphalan, clopidogrel, amiodarone and camptothecin, Fig. 5b, II and III). Acyclic CB[*n*]-type container **3** did not display significant cytotoxicity toward kidney (HepG2), liver (HEK 293) and human monocyte (THP-1) cells. *In vivo* (Swiss Webster mice) studies indicated that the maximum tolerated dose (MTD) of **3** was as high as 1.23 g kg^{-1}, confirming the excellent biocompatibility of the acyclic host. Treatment of HeLa cells with **3**⊃PTX resulted in enhanced cytotoxicity compared to free PTX. This study established a proof-of-principle for use of acyclic CB[*n*]-type containers for drug solubilization and delivery.

2.4 Pillararene-based supramolecular chemotherapy

Pillar[*n*]arenes (P[*n*]As), a new type of macrocyclic host molecules introduced by Ogoshi and co-workers in 2008, are a rising star in the supramolecular chemistry community.[97] Compared with the basket-shaped structure of *meta*-bridged calixarenes, P[*n*]As are connected by methylene (–CH_2–) bridges at the *para*-positions of 1,4-dialkoxybenzene units, forming a unique rigid pillar-shaped architecture. Fig. 6 shows several schematic representations of P[5]A and P[6]A. Because of their highly symmetrical structures and easy functionalization, P[*n*]As have been utilized to construct various interesting supramolecular systems.[98–105] Water-soluble P[*n*]As bearing carboxylate, trimethylammonium or imidazolium units have been prepared, which can encapsulate diverse drug molecules in aqueous media to form supramolecular containers, resulting in the enhancement of solubility of chemotherapeutic agents mainly driven by hydrophobic or electrostatic interactions.

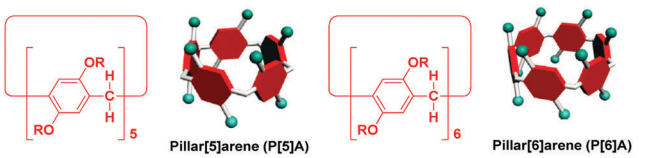


Fig. 6 Chemical structures and cartoon illustrations of representative pillar[5,6]arenes.

Wheate and co-workers examined the potential of water-soluble carboxylated pillar[*n*]arenes (**WP[*n*]As**, n = 6 or 7) with respect to their application in drug delivery and biodiagnostics (Fig. 7a).[106] Both **WP[*n*]As** formed host–guest complexes with memantine, chlorhexidine hydrochloride and proflavine. Binding was stabilized by hydrophobic effects within the cavities, hydrogen bonding and electrostatic interactions at the portals. The **WP[*n*]As** were relatively nontoxic to cells except at high doses and after prolonged continuous exposure.

Very recently, Sessler, Meng, Li and co-workers designed a pH-responsive DDS for OX based on the direct host–guest encapsulation of OX by a water-soluble pillar[6]arene (**WP6A**) (Fig. 7b, I).[107] The inclusion complex was stabilized by the electrostatic interactions between the anionic host and the cationic Pt^{II}. The association constant of **WP6A** for OX at pH 7.4 was 24 times larger than that at pH 5.4. Encapsulation of OX within the **WP6A** cavity did not affect its *in vitro* cytotoxicity as inferred from comparison studies carried out on several cancer cells (*e.g.*, A549, HepG-2 and MCF-7 cell lines) (Fig. 7b, II). On the other hand, complexation by **WP6A** served to increase the inherent stability of OX in plasma by a factor of 2.8 over a 24 h incubation period (Fig. 7b, III). The formation of a **WP6A**⊃OX host–guest complex enhanced the ability of OX in inhibiting the regrowth of sarcoma 180 (S180) tumors (Fig. 7b, IV). The improved antitumor activity *in vivo* was attributed to the combined effects of enhanced stability of the host–guest complex and the pH-responsive release of OX.

2.5 Supramolecular chemotherapy based on other macrocyclic hosts

In addition to the above-discussed macrocyclic hosts, other macrocycles can also be applied in supramolecular chemotherapy. Furthermore, functional groups can be introduced into these hosts, endowing the obtained supramolecular systems with interesting properties.[108–112]

Kohnke and co-workers reported the use of a *meso*-*p*-aminophenyl calix[4]pyrrole-*trans*-platinum(II) conjugate as a DDS to increase the drug/DNA coordination interactions (Fig. 8a, I and II).[113] Transfer of Pt(II) from *trans*-**6** to AMP could be promoted by the host–guest interactions between the phosphate group on DNA and the calix[4]pyrrole core through pyrrole N–H···anion hydrogen bonds. A standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay involving the A2774, OVCAR3 and SKOV3 ovarian carcinoma cell lines provided evidence that the calix[4]pyrrole skeleton in combination with the coordinated Pt(II) played a key role in modulating the reactivity of the bound cation (Fig. 8a, III). In particular, it was found that both *trans*-**6** and a dipyrromethane model complex (*trans*-**8**) exhibited good antiproliferative effects, whereas the corresponding free ligands (**5** and **7**) displayed little or insignificant activity. The results indicated that the

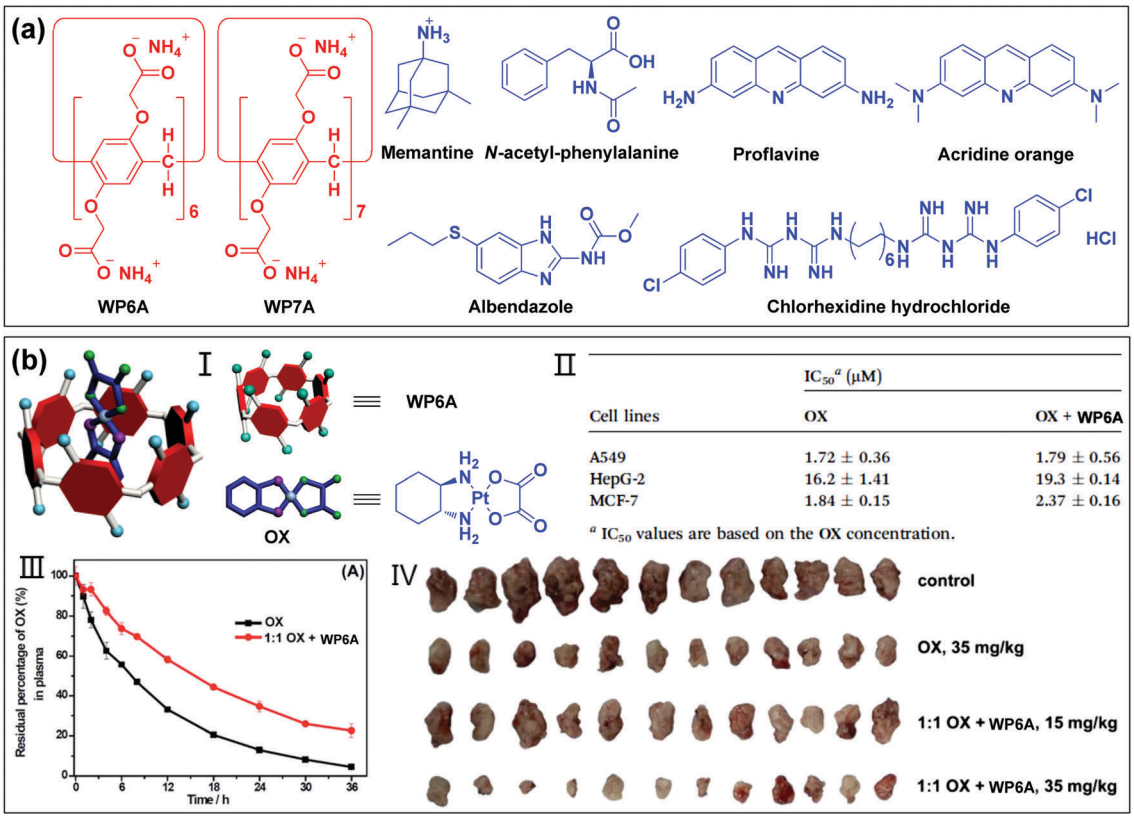


Fig. 7 (a) Chemical structures of water-soluble pillar[*n*]arenes (**WP[*n*]As**, *n* = 6 or 7) and bio-relevant compounds. (b) Molecular structure and model of OX and a potential binding mode of the anticancer drug OX with **WP6A** (I). Cytotoxicity profiles of OX and a 1 : 1 mixture of OX and **WP6A** against the A549, HepG-2 and MCF-7 cell lines (II). *In vitro* stability of OX in the absence and presence of 1.0 equiv. of **WP6A** (III). Pictures of the tumors excised from S180 xenograft mice treated with saline (control), free OX and a 1 : 1 mixture of OX and **WP6A** at an OX dose of 15 or 35 mg kg^{-1} in *in vivo* antitumor experiments (IV) (reproduced with permission of The Royal Society of Chemistry from ref. 107).

calixpyrrole unit had considerable advantages for the development of new anticancer *trans*-Pt(II) drugs.

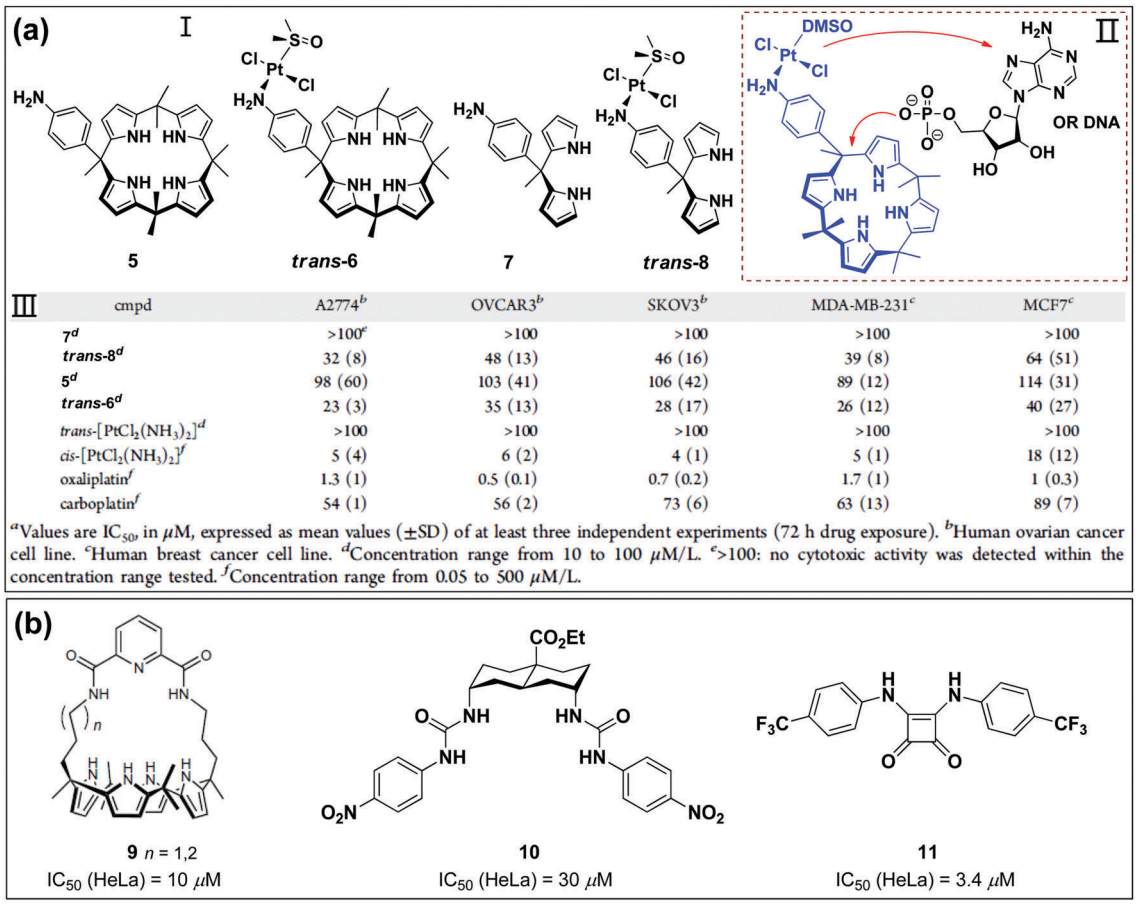
Anion transporters based on small molecules have received attention as therapeutic agents because of their potential in disrupting cellular ion homeostasis. Gale, Sessler, Shin and co-workers designed two pyridine diamide-strapped calix[4]-pyrroles **9** that facilitated chloride transport in liposomal model membranes and in mammalian cells (Fig. 8b).[114] The ion transporters induced the sodium chloride influx, which led to an increased concentration of reactive oxygen species and the release of cytochrome *c* from the mitochondria, resulting in cell death *via* caspase-dependent apoptosis. Subsequently, Sheppard, Davis and co-workers synthesized bis-(*p*-nitrophenyl) ureidodecalin **10** which could functionalize as an anion transporter without affecting cell viability.[115] Very recently, Sessler, Gale, Shin and co-workers showed that besides promoting caspase-dependent apoptosis, squaramide-based ion transporter **11** also served to increase the lysosomal pH, leading to autophagy disruption.[116]

2.6 Biomolecule-based supramolecular chemotherapy

Biomolecules, like proteins and DNA, can be regarded as natural delivery devices to specifically and non-covalently bind a wide variety of drugs mainly driven by hydrophobic, electrostatic and π–π stacking interactions. Owing to their excellent biocompatibility and programmability and high loading capability, various protein and DNA nanostructures have been constructed for cancer therapy applications.[117–120]

Albumin, the major component of serum proteins, is an excellent drug delivery platform because of its abundance, stability, long circulatory half-life and inherent binding capacity.[121] PTX is able to bind with human serum albumin (HSA) *via* hydrophobic interaction between the drug molecule and the hydrophobic domain on HSA. The formed HSA–PTX nanodrug (trade name Abraxane) has already been approved by the FDA for the treatment of metastatic breast cancer, non-small cell lung cancer and a few others.[122]

In an effort to capitalize on the ability of HSA to act as a drug delivery vehicle, Lippard and co-workers designed a platinum(IV) prodrug containing a fatty acid that HSA is known to bind (Fig. 9a, I).[123] The complex *cis*,*cis*,*trans*-$[Pt(NH_3)_2Cl_2(O_2CCH_2CH_2COOH)$-$(OCONHC_{16}H_{33})]$ (**Pt-C16**) interacted non-covalently with HSA in a 1 : 1 stoichiometry. The Pt(IV) prodrug **Pt-C16** completely inhibited proliferation in A2780 cancer cells at concentrations as low as 0.2 μM (Fig. 9a, II). Fluorescence quenching and modeling studies suggested that the platinum complex was buried beneath the surface of the protein and this encapsulation inhibited reduction by ascorbic acid. Compared with cisplatin or satraplatin, significant enhancement in



III cmpd	A2774[b]	OVCAR3[b]	SKOV3[b]	MDA-MB-231[c]	MCF7[c]
7[d]	>100[e]	>100	>100	>100	>100
trans-8[d]	32 (8)	48 (13)	46 (16)	39 (8)	64 (51)
5[d]	98 (60)	103 (41)	106 (42)	89 (12)	114 (31)
trans-6[d]	23 (3)	35 (13)	28 (17)	26 (12)	40 (27)
trans-$[PtCl_2(NH_3)_2]$[d]	>100	>100	>100	>100	>100
cis-$[PtCl_2(NH_3)_2]$[f]	5 (4)	6 (2)	4 (1)	5 (1)	18 (12)
oxaliplatin[f]	1.3 (1)	0.5 (0.1)	0.7 (0.2)	1.7 (1)	1 (0.3)
carboplatin[f]	54 (1)	56 (2)	73 (6)	63 (13)	89 (7)

[a]Values are IC_{50}, in μM, expressed as mean values (±SD) of at least three independent experiments (72 h drug exposure). [b]Human ovarian cancer cell line. [c]Human breast cancer cell line. [d]Concentration range from 10 to 100 μM/L. [e]>100: no cytotoxic activity was detected within the concentration range tested. [f]Concentration range from 0.05 to 500 μM/L.

Fig. 8 (a) Molecular structures of **5** and **7** and their Pt(II) conjugates *trans*-**6** and *trans*-**8** (I). Schematic representation showing transfer of Pt(II) from *trans*-**6** to AMP (II). *In vitro* cytotoxicity of compounds **7** and **5** and their Pt(II) derivatives *trans*-**8** and *trans*-**6**, compared with that of *trans*- and *cis*-$[PtCl_2(NH_3)_2]$, OX and carboplatin in a human cancer cell-line panel as assessed by MTT cell viability assay[a] (III) (reproduced with permission of John Wiley & Sons, Inc. from ref. 113). (b) Chemical structures of anion transporters **9**, **10** and **11**.

blood stability was realized by forming a protein/prodrug complex (Fig. 9a, III). Very recently, Lippard and co-workers showed that high-mobility group box protein 4, a protein preferentially expressed in testes, uniquely blocked excision repair of cisplatin–DNA adducts, 1,2-intrastrand cross-links, to potentiate the sensitivity of testicular germ cell tumors to cisplatin chemotherapy.[124]

Based on rolling circle replication, Tan and co-workers reported an aptamer-integrated DNA nanostructure termed as DNA nanoflowers (NFs) (Fig. 9b).[125] NFs were exceptionally resistant to nuclease degradation, denaturation, or dissociation at extremely low concentration, presumably resulting from the dense DNA packaging in NFs. The resultant multifunctional NFs were further implemented for targeted anticancer drug delivery by incorporating with drug-loading sequences. Many other types of aptamer-integrated DNA nanostructures, such as aptamer-tethered DNA nanotrains, Y-shaped DNA functional domains and aptamer–micelles, have also been developed for targeted anticancer drug delivery.[126,127]

Ferritin is a spherical iron storage protein composed of 24 subunits of two types, heavy-chain ferritin (HFn) and light-chain ferritin (LFn).[128] Ferritin proteins self-assemble naturally into a hollow nanocage with an outer diameter of 12 nm and an inner diameter of 8 nm. The cavity is a useful template for synthesizing highly crystalline and monodisperse nanoparticles. Yan and co-workers developed a natural H-ferritin (HFn) nanocarrier that specifically delivered high doses of DOX to tumor cells (Fig. 9c, I).[129] Cryo-electron microscopy (Cryo-EM) analysis showed that the DOX-loaded HFn (HFn-DOX) was monodispersed in solution with a well-defined spherical morphology (Fig. 9c, II). HFn-DOX significantly inhibited tumor growth with a single-dose treatment while also displaying excellent biocompatibility and safety profiles. Compared with the clinically approved liposomal DOX (Doxil), HFn-DOX exhibited longer median survival times and lower toxicity (Fig. 9c, III).

Zhu, Chen and co-workers reported a transformative nanomedicine of amphiphilic CPT prodrug for enhanced tumor-targeted drug delivery (Fig. 9d).[130] CPT was conjugated with an albumin-binding Evans blue (EB) derivative *via* a redox-responsive disulfide linker. The resulting amphiphilic CPT-ss-EB prodrug self-assembled into nanostructures in aqueous solution, thus conferring high solubility and stability. By binding CPT-ss-EB to endogenous albumin, the 80 nm CPT-ss-EB nanoparticles rapidly transformed into 7 nm albumin/prodrug nanocomplexes.

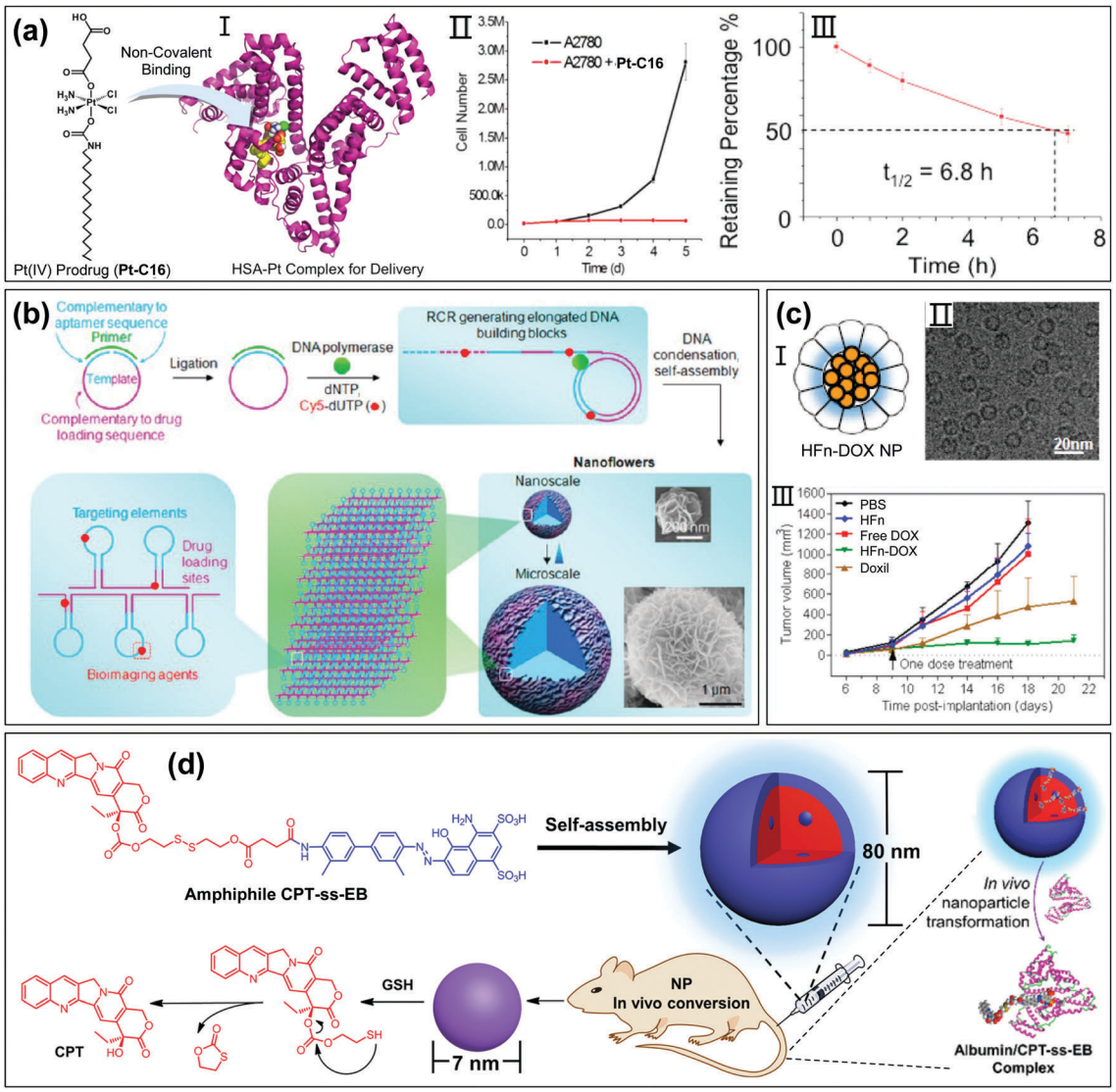


Fig. 9 (a) A platinum(IV) prodrug designed to bind non-covalently to human serum albumin (HSA) for drug delivery (I). Cellular response of A2780 cancer cells treated with **Pt-C16** (II). Stability of **Pt-C16** in whole human blood showing a half-life of 6.8 h (III) (reproduced with permission of the American Chemical Society from ref. 123). (b) Schematic illustration of noncanonical self-assembly of multifunctional DNA nanoflowers (reproduced with permission of the American Chemical Society from ref. 125). (c) Schematic illustration of H-ferritin-nanocaged doxorubicin nanoparticles (HFn-DOX NPs) (I). Cryo-electron microscopy (Cryo-EM) image of HFn-DOX NPs (II). Antitumor activity of HFn-DOX NPs (III) (reproduced with permission of the National Academy of Sciences from ref. 129). (d) Schematic illustration of transformative nanoparticles of amphiphilic CPT prodrug for enhanced tumor-targeted drug delivery (reproduced with permission of the American Chemical Society from ref. 130).

CPT-ss-EB was efficient at intracellular delivery into cancer cells, released intact CPT in a redox-responsive manner, and exhibited cytotoxicity as potent as CPT. The albumin/CPT-ss-EB nanocomplex exhibited remarkably long blood circulation (130-fold greater than CPT) and efficient tumor accumulation (30-fold of CPT), which consequently contributed to excellent therapeutic efficacy.

3. Supramolecular chemotherapy on the basis of supramolecular nano-vehicles

Nanotechnology is the creation and utilization of materials, devices and systems through the control of matter on the nanometer-length scale, *i.e.*, at the level of atoms, molecules and supramolecular structures.[131] Nanocarriers based on the rapid development of nanotechnology and biomaterials have shown distinct advantages in the field of anticancer drug delivery, such as improved drug bioavailability, promoted accumulation of anticancer drugs in tumor tissues *via* the EPR effect, inhibited absorption by proteins or the reticuloendothelial system (RES), active targeting to tumors by appropriate modifications and controlled drug release.[132–134]

Supramolecular nano-structures, including micelles, vesicles, nanoparticles, nanofibers and even hydrogels, provide sophisticated platforms to load anticancer drugs.[135–137] By taking advantage of supramolecular chemistry, various biodegradable polymers

such as poly(glycolic acid) (PGA), poly(D,L-lactic acid) (PLA), poly(D,L-lactic-*co*-glycolic acid) (PLGA) and poly(ethylene glycol) (PEG) can be introduced into these supramolecular DDSs, avoiding very time-consuming organic syntheses.[138–140] The most intriguing property of supramolecular materials is the stimuli-responsiveness, which is favorable to achieve controlled release. By precisely controlling the release of drugs in tumor sites, the injected dose can be decreased and the side effects can be effectively inhibited. In this section, supramolecular assemblies on the basis of host–guest molecular recognition motifs are classified by the types of macrocyclic hosts involved.

3.1 Supramolecular chemotherapy on the basis of supramolecular nano-vehicles formed from cyclodextrin-based host–guest molecular recognition

CDs have been approved by the FDA and widely used in drug formulations. Macrocyclic CD molecules have good water solubility and show prominent host–guest interactions with guest species. The host–guest recognition can serve as the linkage to fabricate various kinds of supramolecular assemblies with abundant stimuli-responsiveness, making it possible to release the loaded drugs/prodrugs in the tumor under control.[141–148] The modification of CDs is relatively easy, and mono- or multi-functional CDs can be synthesized on a large scale. As a consequence, linear, brush or dendrimeric polymers containing CD groups are obtained, which can be used as drug delivery vehicles.

CRLX101 (previously IT-101) comprising a β-CD-containing polymer conjugated to CPT is currently being investigated in a number of phase II clinical trials for cancer.[149,150] Conjugation of CPT to β-CD increases its solubility by roughly 3 orders of magnitude and prevents inactivation through spontaneous lactone ring opening, which can occur rapidly at physiological pH. Davis and co-workers reported the formation of supramolecular nanoparticles (SNPs) stabilized by multiple supramolecular host–guest interactions between CPT and β-CD of a single polymer strand (Fig. 10a).[151] Self-assembly of the β-CD- and CPT-functionalized polymer in aqueous solution resulted in the formation of SNPs with sizes of 30–40 nm. CRLX101 showed long-term *in vivo* circulation to provide extended time for the nanoparticles to extravasate into solid tumors *via* the leaky vasculature. The CPT lactone form (the antitumor active form) can be maintained by using host–guest complexation. The release of CPT depended on the hydrolysis of the ester bond (independent of enzyme activity), and the presence of lipoprotein complexes like low-density lipoprotein (LDL) further assisted the disassembly of CRLX101.[152]

Zhang, Li, Li and co-workers developed a series of α-CD materials for PTX delivery (Fig. 10b, I).[153] These pH-responsive materials could be conveniently fabricated by a facile acetonation process, and were further processed into nanoparticles (NPs) with controllable size (Fig. 10b, II). These nanoplatforms exhibited pH-controlled hydrolysis profiles that could be easily modulated by using materials with various acetal types resulting from different acetalation times. Both *in vitro* and *in vivo* experiments revealed the good biocompatibility of these newly engineered nanocarriers. Incorporation of PTX into pH-sensitive acetalated α-CD (Ac-aCD) nanosystems led to nanotherapeutics with significantly improved activity against tumor cells (Fig. 10b, III). More importantly, the formulated nanomedicines could effectively reverse MDR to PTX. Furthermore, Ac-aCD materials showed more effective drug loading, better antitumor activity and lower side effects, in comparison with two other pH-responsive counterparts of acetalated dextran (Ac-Dex) and poly(cyclohexane-1,4-diyl acetone dimethylene ketal) (PCADK) for tumor therapy.

Kim and co-workers reported a nano-assembled DDS formed from multivalent host–guest interactions between a polymer-CD (pCD) conjugate and a polymer-PTX (pPTX) conjugate (Fig. 10c, I).[154] The CD and PTX molecules were conjugated to the polymeric backbone of maleic anhydride by degradable ester groups. Driven by multiple host–guest interactions, pPTX/pCD self-assembled into small ellipsoidal nanoparticles, where the host–guest complexes acted as non-covalent crosslinkers, greatly stabilizing the NPs and reducing the hemolysis rates (Fig. 10c, II). The pPTX/pCD nano-assembly not only showed good water solubility due to the negative carboxylate ions on both pCD and pPTX, but also exhibited high stability in the blood due to the multivalent host–guest interactions. Compared with PTX/pCD, pPTX and free PTX, pPTX/pCD showed the highest cytotoxicity towards MCF-7, HeLa and HCT-8 cell lines (Fig. 10c, III), which was attributed to its high aqueous solubility, readily degradable ester bonds and resultant increase in the release of PTX. Conjugation of AP-1 peptide to the pPTX/pCD nano-assembly enhanced targeting ability and reduced non-specific organ accumulation, greatly reducing toxicity towards normal tissues (Fig. 10c, IV). The AP-1-conjugated nano-assembly demonstrated high *in vivo* antitumor efficacy as a result of the EPR effect followed by receptor-mediated endocytosis.

3.2 Supramolecular chemotherapy on the basis of supramolecular nano-vehicles formed from cucurbituril-based host–guest molecular recognition

By employing the host–guest interaction strategy, supramolecular vesicles or nanoparticles based on CB[*n*]s have shown several advantages in biomedical applications, such as ease of fabrication, targeted drug/prodrug delivery and responsive release.[155,156] For example, CB[8] can be used as a ''molecular handcuff'' to join two molecules together in a non-covalent fashion due to its large cavity volume (479 Å^3), forming a dynamic 1:1:1 ternary complex. Given its unique host–guest binding properties, this molecular recognition can be fully employed to prepare smart stimuli-responsive supramolecular assemblies for the fabrication of supramolecular chemotherapeutic drugs just by decorating with specific polymers.[157,158]

Kim and co-workers introduced a redox-responsive disulfide unit into the amphiphilic CB[6] to prepare reduction-sensitive vesicles (SSCB[6]VC) for targeted drug delivery (Fig. 11a, I).[159] The characteristic hollow-spherical morphology of SSCB[6]VC was observed by transmission electron microscopy (TEM), which showed an average diameter of 170 ± 30 nm and a membrane thickness of 6 ± 1 nm (Fig. 11a, II). Taking advantage of the

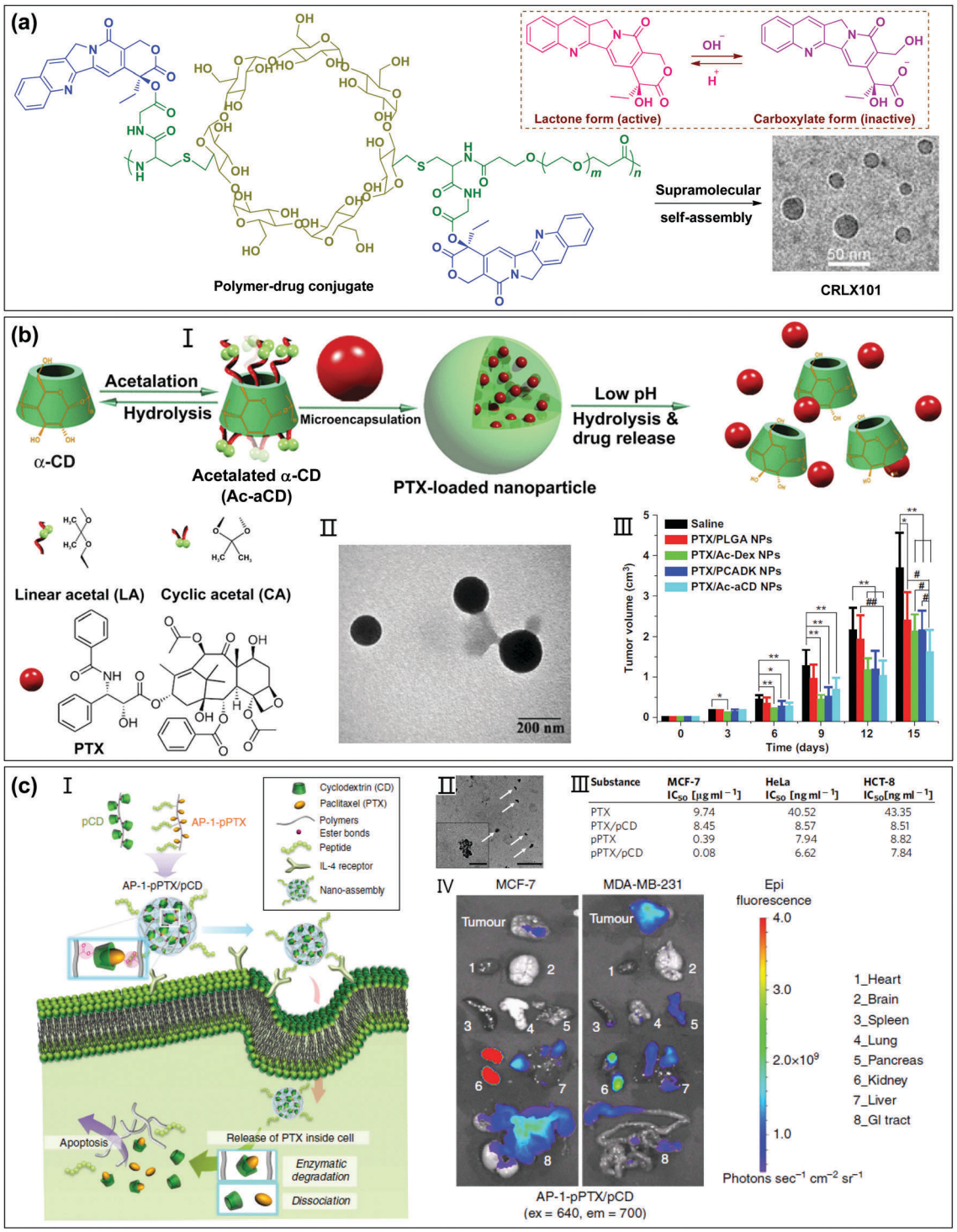


Fig. 10 (a) Structure of the polymer–drug conjugate and its self-assembled CRLX101 nanoparticles. Inset: Release mechanism of CPT (reproduced with permission of the National Academy of Sciences from ref. 151). (b) Schematic illustration of the construction of a pH-sensitive PTX nanoformulation based on acetylated α-CD (Ac-aCD) (I). TEM image of PTX/Ac-aCD30 NPs (II). *In vivo* antitumor activity of PTX-loaded nanosystems fabricated with various materials (III) (reproduced with permission of Elsevier from ref. 153). (c) Schematic representation of a nano-assembly-mediated PTX delivery vehicle formed by polymeric CD (pCD) and polymeric PTX (pPTX) through multivalent host–guest interactions (I). TEM image of the pPTX/pCD nano-assembly (II). Summarized IC_{50} values in *in vitro* cytotoxicity assays (III). *Ex vivo* images of organs retrieved from tumour-bearing mice after intravenous injection of FCR-labelled AP-1-pPTX/Pcd (IV) (reproduced with permission of Nature Publishing Group from ref. 154).

exceptionally high binding ability of CB[6] to polyamines, vesicles with functional tag-polyamine conjugates could be easily constructed. MTT assay showed that the cell viability of DOX delivered by targeting-ligand-decorated SSCB[6]VC was

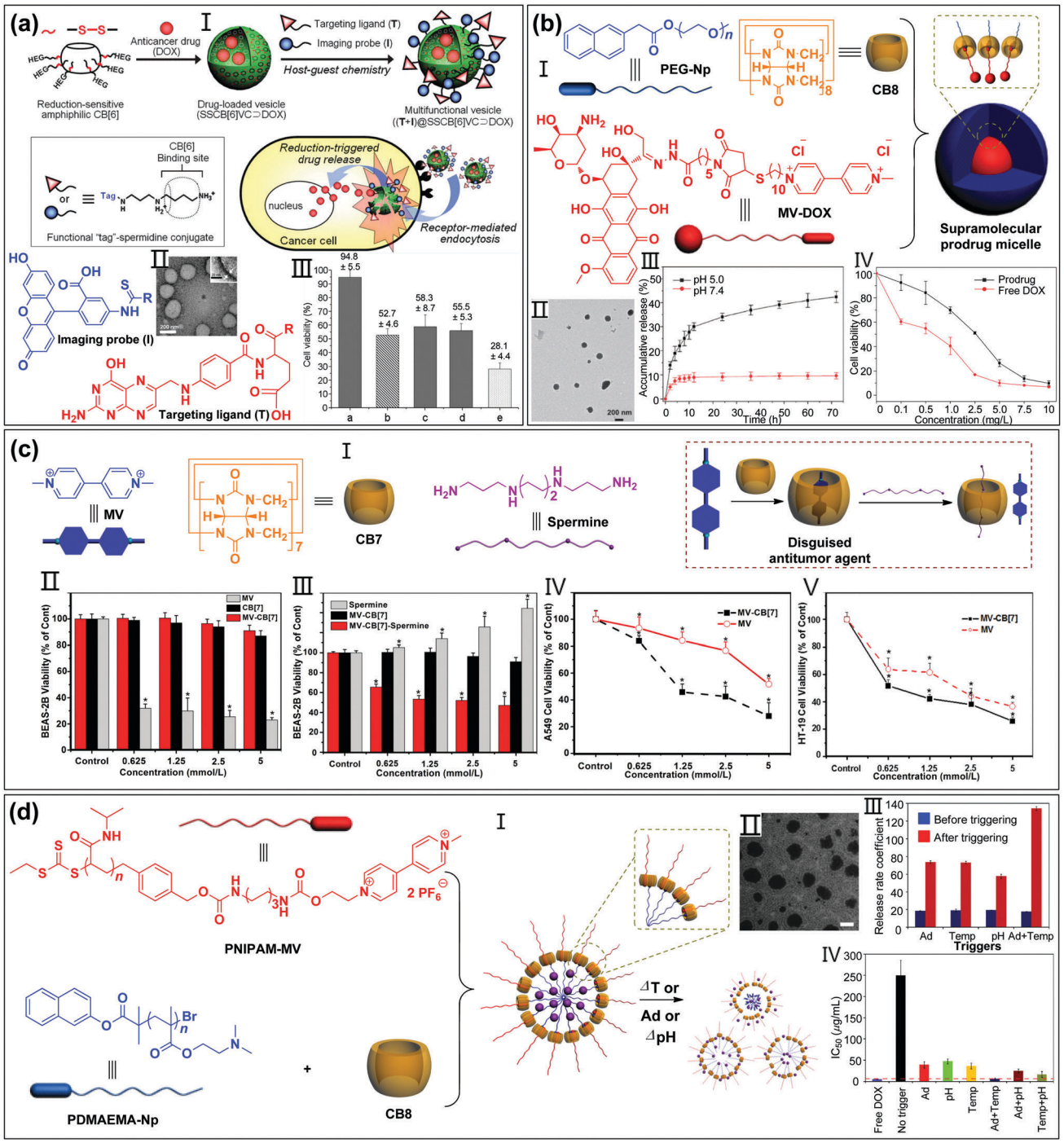


Fig. 11 (a) Reduction-sensitive, robust CB[6]-based vesicles (SSCB[6]VC) with non-covalently modifiable surfaces and their application as a multi-functional platform for targeted drug delivery. HEG = hexaethylene glycol (I). TEM images of SSCB[6]VC (II). Cell viability of (a) SSCB[6]VC, (b) free DOX, (c) SSCB[6]VC⊃DOX, (d) **T**@CB[6]VC⊃DOX and (e) **T**@SSCB[6]VC⊃DOX (III) (reproduced with permission of John Wiley & Sons, Inc. from ref. 159). (b) Schematic illustration of preparation of pH responsive supramolecular prodrug micelles (I). TEM images of the supramolecular micelles (II). *In vitro* release of DOX from the supramolecular prodrug micelles in PBS under different pH conditions (III). Cell viability of HepG2 cells incubated with various concentrations of prodrug micelles for 48 h (IV) (reproduced with permission of The Royal Society of Chemistry from ref. 160). (c) Schematic representation of supramolecular chemotherapy: controlling disguise and exposure of antitumor agents by host–guest chemistry using MV, CB[7] and spermine (I). *In vitro* BEAS-2B cytotoxicity of CB[7]⊃MV was measured by MTT after 24 h at different concentrations, compared with MV and CB[7] (II) or spermine and MV-CB[7]-spermine (III). *In vitro* A549 (IV) or HT-19 cytotoxicity (V) of CB[7]⊃MV was measured by MTT (reproduced with permission of the American Chemical Society from ref. 161). (d) Hierarchical self-assembly of the supramolecular entity and its subsequent mode of drug release after being exposed to different triggers (I). TEM micrographs of supramolecular micelles (II). Release rate coefficients of the systems after exposure to various triggers (III). IC_{50} values of the drug/micelle formulation under different stimuli (IV) (reproduced with permission of the American Chemical Society from ref. 162).

approximately 1.88-fold smaller than that of free DOX (Fig. 11a, III), which was attributable to the facile intracellular uptake of **T**@SSCB[6]VC⊃DOX through folate receptor-mediated endocytosis, followed by efficient release of DOX from the reduction-sensitive vesicle into the cytoplasm. The versatility of these CB-based vesicles encompassed a wide variety of ligands tagged onto the surfaces ranging from small molecules to antibodies, diagnostic imaging probes ranging from fluorescent dyes to magnetic particles and/or other functional moieties such as antifouling units. A wide range of drugs could be loaded inside these vesicles and specifically delivered to cancer cells.

On the basis of the 1:1:1 ternary molecular recognition between methyl viologen (MV), 2,6-dihydroxynaphthalene and CB[8], Jin, Ji and co-workers prepared pH-responsive supramolecular prodrug micelles (MV-DOX/CB[8]/PEG-Np) by using naphthalene-terminated poly(ethylene glycol) (PEG-Np) and methyl viologen functionalized doxorubicin (MV-DOX) as the building blocks for DOX delivery (Fig. 11b, I).[160] MV-DOX/CB[8]/PEG-Np self-assembled into core–shell structural micelles with an average diameter of 150 nm in water (Fig. 11b, II). Since the hydrophobic DOX unit was conjugated to the MV group through an acid-labile hydrazone bond, the formed micelles exhibited endo/lysosomal pH-sensitivity. In sharp comparison with the micelles under physiological conditions (pH 7.4), the release rate of DOX was improved effectively when the pH was decreased to 5.0 (Fig. 11b, III). MTT assay showed that the cell viability was more than 80% at a drug dosage of 0.5 mg L^{-1}, and the cell viability further decreased with a concomitant increase in the amount of drug (Fig. 11b, IV), indicating that the obtained supramolecular prodrug micelles were able to effectively inhibit cancer cell proliferation.

Sun, Zhang and co-workers provided a supramolecular strategy to tune the cytotoxicity of anticancer agents for chemotherapy by employing dynamic CB[7]-mediated host–guest interaction to control the loading and release of MV (Fig. 11c, I).[161] By encapsulating MV into the hydrophobic cavity of CB[7], the cytotoxicity of MV to normal cells can be significantly decreased (Fig. 11c, II). When the host–guest complex CB[7]⊃MV was incubated with tumor cells over-expressing spermine, the anticancer activity of MV was recovered (Fig. 11c, III). The reason was that spermine had a high affinity for CB[7], leading to the release of MV from CB[7]⊃MV. On the other hand, CB[7] could soak up spermine, which was essential for tumor cell growth, therefore further decreasing the cell viability by consuming the essential spermine. Both MV and CB[7]⊃MV exhibited considerable anticancer activity to spermine over-expressing A549 lung cancer cell and HT-19 intestinal tumor cell lines. Moreover, CB[7]⊃MV displayed even higher antitumor activity than MV (Fig. 11c, IV and V).

Scherman and co-workers constructed a supramolecular double hydrophilic block copolymer (DHBC) *via* self-assembly of pH-responsive naphthalene-terminated poly(dimethylaminoethylmethacrylate) (PDMAEMA-Np) and thermo-responsive methylviologen terminated poly(*N*-isopropylacrylamide) (PNIPAM-MV) held together by CB[8] ternary complexation (Fig. 11d, I).[162] The ternary complex formed PNIPAM core micelles with a diameter ranging from 280 to 340 nm in aqueous suspension at 37 °C (Fig. 11d, II), which could further encapsulate DOX. Triple-responsive release of DOX from the supramolecular micelles was achieved triggered by pH, temperature and the addition of a competitive guest (Fig. 11d, III). MTT assay showed that exposing the DOX-loaded micelles to different stimuli increased the corresponding anticancer efficacy (Fig. 11d, IV). This supramolecular DHBC system was able to reduce the toxicity of DOX upon incubation with HeLa cells and recover toxicity when desired *via* the use of a local and remote stimulus in a combined "burst" approach.

3.3 Supramolecular chemotherapy on the basis of supramolecular nano-vehicles formed from pillararene-based host–guest molecular recognition

P[*n*]As possess symmetrical, rigid and pillar-shaped structures compared with other macrocyclic hosts. In the past nine years, P[*n*]As have exhibited intriguing and peculiar host–guest properties. A series of cationic, anionic and neutral guest moieties have been designed and proven to be suitable for pillararene cavities of different sizes. Based on these host–guest motifs, various supramolecular assemblies with different topologies and functionalities have been successfully fabricated, serving as nano-vehicles to successfully fabricate supramolecular chemotherapeutic drugs.[163–168]

Wang and co-workers elegantly developed pH-responsive supramolecular vesicles using the host–guest inclusion complex between a water-soluble pillar[6]arene (**WP6S**) and a hydrophobic ferrocene derivative, *N*-1-decylferrocenylmethylamine (**12**), for drug delivery (Fig. 12a, I).[169] **WP6S**⊃**12** self-assembled into hollow spherical morphology with an average diameter of 130 nm (Fig. 12a, II). Hydrophilic anticancer drug mitoxantrone (MTZ) was loaded into the supramolecular vesicles with the encapsulation efficiency of 11.2% (Fig. 12a, III). Due to the pH-responsiveness of **WP6S**⊃**12**, the MTZ-loaded vesicles collapsed and released MTZ with efficiency up to 95% into the external environment at pH 4.0 within 24 h. MTT assay indicated that MTZ-loaded vesicles exhibited comparable therapeutic effect to free MTZ towards cancer cells but with remarkably reduced damage to normal cells (Fig. 12a, IV and V). Subsequently, Wang and co-workers constructed supramolecular binary vesicles based on the host–guest complexation of **WP6S** with the SAINT molecule (pyridinium amphiphile with one pyridinium group and two alkyl chains).[170] Benefiting from the intrinsic advantages of supramolecular interaction, the obtained **WP6S**⊃SAINT vesicles showed pH, temperature and Ca^{2+} responsiveness. The anticancer drug DOX could be successfully encapsulated in the hydrophobic Stern layer of the vesicles and then released efficiently in a low-pH environment or with the introduction of Ca^{2+}. By using an acid-cleavable hydrazone bond-containing DOX derivative as the guest molecule and **WP6S** as the host, Hu, Wang and co-workers constructed novel acid-responsive supramolecular prodrug nanoparticles, which showed self-catalyzed rapid release of DOX, because the host–guest complexes could catalytically speed up the cleavage of the hydrazone bond through a favored intramolecular process under acidic conditions.[171]

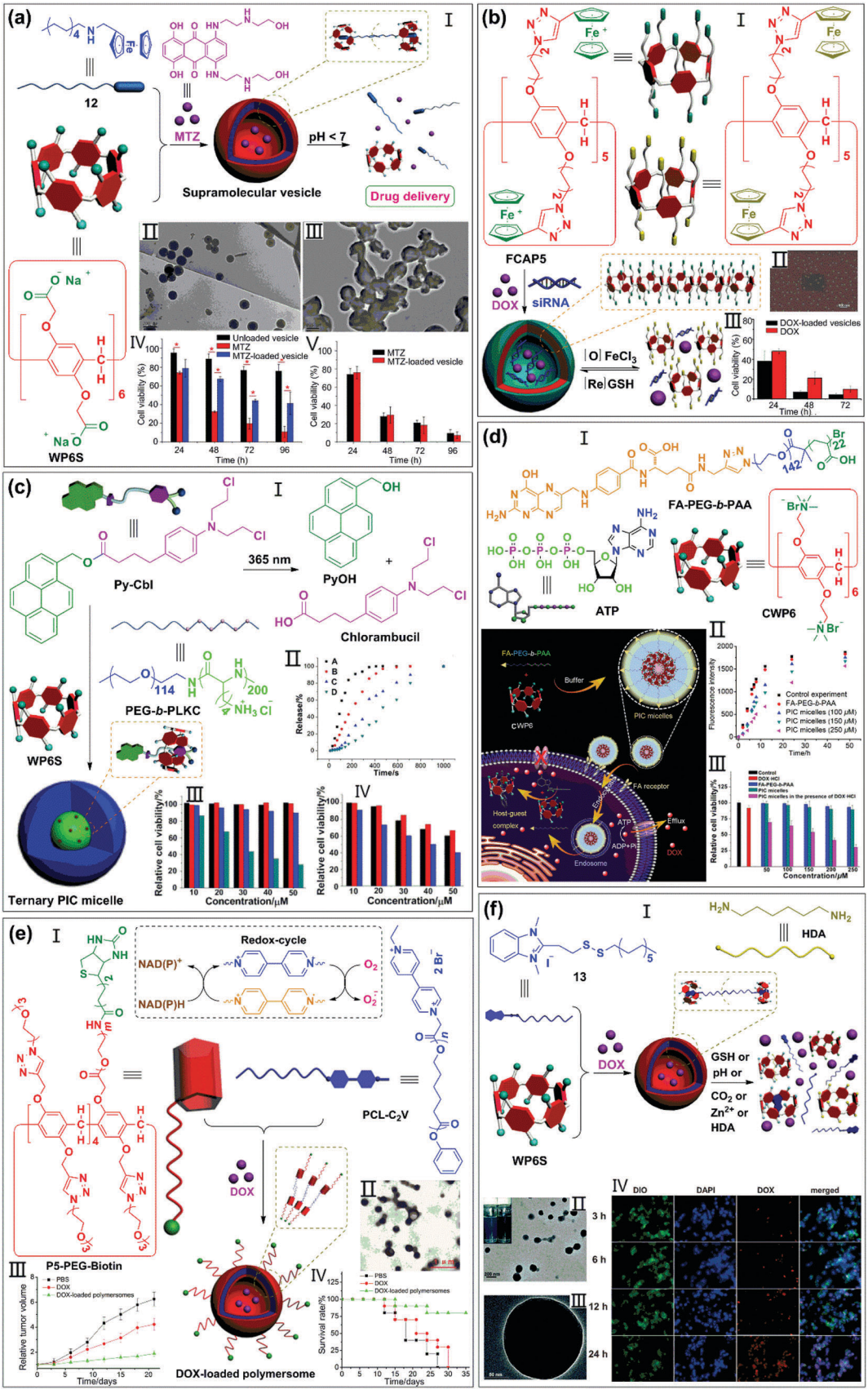


Fig. 12 (a) Schematic illustration of the formation of supramolecular vesicles and their pH-responsive drug release (I). TEM images of **WP6S⊃12** aggregates (II) and MTZ-loaded vesicles (III). Cytotoxicity of different formulations towards NIH3T3 cells (IV) and SMMC-7721 cells (V) (reproduced with permission of the American Chemical Society from ref. 169). (b) Schematic illustration of the formation of supramolecular cationic vesicles for redox-responsive DOX/siRNA co-delivery (I). SEM image of FCAP5-based vesicles (II). Anticancer activity of DOX-loaded vesicles and free DOX towards HeLa cells (III) (reproduced with permission of John Wiley & Sons, Inc. from ref. 172). (c) Schematic illustration of the combination of the host–guest complex with PEG-*b*-PLKC for the preparation of ternary PIC micelles (I). Progress of the release of chlorambucil under UV light irradiation: (A) **Py-Cbl** (8 W); (B) **WP6S⊃Py-Cbl** (8 W); (C) **Py-Cbl** (5 W); (D) **WP6S⊃Py-Cbl** (5 W) (II). Concentration-dependent (III) and irradiation-dependent (IV) cytotoxicity of **Py-Cbl** (black column), **WP6S⊃Py-Cbl** (red column), the ternary complex (blue column) and chlorambucil (cyan column) against A549 cells (reproduced with permission of John Wiley & Sons, Inc. from ref. 174). (d) Schematic illustration of the preparation of PIC micelles and possible mechanism to inhibit the efflux pump by forming a host–guest complex **CWP6⊃**ATP in the cell (I). Fluorescence intensity changes of the culture in the presence of FA-PEG-*b*-PAA or PIC micelles containing different amounts of **CWP6** (II). Cytotoxicity of DOX·HCl, FA-PEG-*b*-PAA, PIC micelles and DOX·HCl loaded PIC micelles with different concentrations of **CWP6** against MCF-7/ADR cells (III) (reproduced with permission of The Royal Society of Chemistry from ref. 175). (e) Schematic illustration of the formation of polymersomes self-assembled from the amphiphilic supramolecular copolymer **P5-PEG-Biotin⊃PCL-C_2V** and their use as reduction-responsive drug delivery vehicles (I). TEM images of the polymersomes self-assembled from **P5-PEG-Biotin⊃PCL-C_2V** (II). Tumor growth inhibition curves on the HeLa tumor model after various formulations (III). Survival rate of mice bearing HeLa tumors after different treatments (IV) (reproduced with permission of John Wiley & Sons, Inc. from ref. 176). (f) Schematic illustration of the preparation of supramolecular vesicles that are responsive to five stimuli (I). TEM image (II) and enlarged TEM image of a supramolecular vesicle (III). Cellular internalization studies of DOX-loaded supramolecular vesicles on HepG2 cells after different incubation times (IV) (reproduced with permission of John Wiley & Sons, Inc. from ref. 182).

Furthermore, Pei and co-workers constructed redox-responsive cationic vesicles consisting of ferrocenium-capped amphiphilic pillar[5]arene (**FCAP5**) for co-delivery of DOX and siRNA to cancer cells (Fig. 12b, I).[172] Due to its amphiphilicity, **FCAP5** self-assembled into spherical vesicles with an average diameter of 92 nm (Fig. 12b, II). As the GSH-responsive structural element, the ferrocenium cation could be reduced to ferrocene, resulting in the disassembly of the supramolecular cationic vesicle through an amphiphilicity-to-hydrophobicity conversion. The cytotoxicity of DOX-loaded vesicles was effectively reduced towards normal cells, whereas the DOX-loaded vesicles exhibited high anticancer activity *in vitro* than free DOX to cancer cells (Fig. 12b, III). Interestingly, when **FCAP5** was mixed with FAM-siRNA (a fluorescent labeled siRNA) at a ferrocenium cation/P ratio of 5 : 1 (defined as the molar ratio of ferrocenium cation units in the cationic vesicles to phosphate units in siRNA), the cationic vesicles self-assembled into FAM-siRNA/cationic vesicle complexes through electrostatic interactions. Enhanced therapeutic efficacy was achieved by the synergistic effect arising from the co-delivery of siRNA and DOX. Recently, Pei and co-workers developed a DNA interacting targeted DDS based on the supramolecular vesicles self-assembled from the host–guest complex between a tryptophan (Trp)-modified pillar[5]arene and galactose derivative.[173] DOX-loaded vesicles revealed an excellent pH-responsiveness and quick release of DOX under acidic environments, enabling them to achieve controlled drug release. Synergistically enhanced cytotoxicity was observed resulting from the interactions between the 10 indole rings of Trp residues on Trp-modified pillar[5]arene and DNA in cells.

In the field of controlled drug release, prodrug-based self-assembled nanostructures can act as effective drug nanocarriers, where the prodrug is composed of the anticancer drug linked with a recognition motif by a stimuli-responsive linker. Sometimes, the prodrug can form a supra-amphiphile with a water-soluble pillararene due to host–guest binding. Huang and co-workers introduced a photocontrolled ternary DDS developed from **WP6S**, a photodegradable anticancer prodrug (**Py-Cbl**) containing the anticancer drug chlorambucil and fluorophore pyrene, and a hydrophilic diblock copolymer methoxy-poly(ethylene glycol)$_{114}$-*block*-poly(L-lysine hydrochloride)$_{200}$ (PEG-*b*-PLKC) (Fig. 12c, I).[174] The anionic host–guest complex between **WP6S** and **Py-Cbl** acted as an anionic supramolecular cross-linker to prepare stable ternary polyion complex (PIC) micelles (average diameter of 127 nm) with a positively charged polylysine block of PEG-*b*-PLKC through electrostatic interactions. The biocompatibility and membrane permeability of the ternary PIC micelles were enhanced by PEGylation of the host–guest inclusion complex. Due to the formation of a stable host–guest inclusion complex between **WP6S** and **Py-Cbl**, the photodegradation rate of the drug was reduced (Fig. 12c, II). MTT experiments demonstrated that the toxicity was decreased significantly by introducing a photo-responsive fluorophore into the drug to form the prodrug, effectively reducing side effects to healthy tissue (Fig. 12c, III). Under UV irradiation, **Py-Cbl** was cleaved to release the chlorambucil drug, thereby causing cytotoxicity to the cancer cells (Fig. 12c, IV). The release process was accompanied by significant changes in fluorescence, thus allowing the real-time visualization of the therapeutic response and providing useful information for dose adjustment, prognosis and toxicity.

MDR remains a significant impediment to the success of cancer chemotherapy. Huang and co-workers employed the size selective host–guest complexation between cationic water-soluble pillar[6]arene (**CWP6**) modified by trimethylammonium groups on both sides and ATP to potentially inhibit the efflux pump of multidrug resistant cancer cells, resulting in the enhancement of the efficacy of cancer chemotherapy (Fig. 12d, I).[175] PEGylation by FA-PEG-*b*-PAA contributed to the formation of PIC micelles with excellent targeting ability, preferentially delivering **CWP6** to folate receptor (FR) over-expressing cancer cells. The core of the PIC micelles had **CWP6** molecules along with anionic carboxylate segments of the diblock copolymer held through electrostatic interactions, which could be employed to reduce the cytotoxicity of the cationic **CWP6**. It was also observed that **CWP6** selectively bound with ATP to form a stable 1 : 1 inclusion complex **CWP6⊃**ATP rather than other ribonucleotides, attributing to the cavity size of **CWP6**, the charge and length of ATP and the excellent binding affinity between **CWP6** and ATP. Accompanied by the

enhancement of the concentration of **CWP6**, the efflux rate and the total efflux amount of calcein from cells were reduced efficiently caused by the inhibition of ATP hydrolysis (Fig. 12d, II). The specific delivery of the FA-modified ternary PIC micelles loaded with DOX to the KB cells was aided by receptor-mediated endocytosis. It was noteworthy that the anticancer efficacy of DOX was markedly enhanced by blocking the efflux pump (Fig. 12d, III). This supramolecular method provided an extremely distinct strategy to potentially overcome MDR of cancer cells.

Polymersomes fabricated from supramolecular block copolymers based on host–guest interactions exhibited enormous advantages as DDSs in cancer therapy, because the structures of DDSs can be controlled based on the host–guest interactions and the drug release can be triggered by various stimuli at active sites benefiting from the rich environment-responsiveness of host–guest interactions. Huang and co-workers prepared a pillar[5]arene-based amphiphilic supramolecular diblock copolymer (**P5-PEG-Biotin** $\supset$ **PCL-C_2V**) by using a ''block-copolymer-free'' strategy, which was further utilized as a smart DDS (Fig. 12e, I).[176] Based on the new recognition motif between a water-soluble pillar[5]arene and a viologen salt, **P5-PEG-Biotin** $\supset$ **PCL-C_2V** was fabricated, with PEG functionalized with a triglycol monomethyl ether-modified pillar[5]arene host unit and a biotin targeting group (**P5-PEG-Biotin**) as the hydrophilic part and poly(caprolactone) bearing a viologen terminator (**PCL-C_2V**) segment as the hydrophobic section, which self-assembled into polymersomes with a diameter of $\sim$150 nm in water (Fig. 12e, II). The biotin groups on the surface of the DOX-loaded polymersomes acted as targeting ligands to specifically deliver DOX to cancerous HeLa cells overexpressing biotin receptors. After internalization by the cells, the host–guest interactions were destroyed by the reduction of the viologen group into its cationic radical state by the intracellular reductase NAD(P)H, resulting in the release of the loaded DOX concomitantly with disassembly of the polymersomes. The anticancer efficacy of DOX was greatly maintained through this supramolecular formulation. *In vivo* experiments revealed that the DOX-loaded supramolecular polymersomes prolonged the circulation time in the bloodstream, promoted the antitumor efficacy and reduced the systemic toxicity of the nanomedicine through a flexible and modular supramolecular strategy (Fig. 12e, III and IV).

By employing the same molecular recognition, Chen, Huang and co-workers recently constructed an amphiphilic supramolecular brush copolymer (**P5-PEG-Biotin** $\supset$ **PTPE**),[177] which self-assembled into highly emissive SNPs by taking advantage of the aggregation-induced emission (AIE) effect.[178,179] The hydrophobic core of the SNPs was utilized to encapsulate the anticancer drug DOX, affording a self-imaging DDS. The fluorescence arising from both TPE and DOX was quenched caused by the energy transfer relay (ETR) effect, mediated by Förster resonance energy transfer (FRET) and the aggregation-caused quenching (ACQ) effect. The ''silenced'' fluorescence ''woke up'' after the loaded drug DOX escaped from the SNPs, which was used to monitor the drug release during the delivery process. *In vivo* investigations showed that the DOX-loaded SNPs promoted the antitumor ability with reduced systemic toxicity by taking advantage of the EPR effect and active targeting capability. Besides, Huang and co-workers prepared a multi-responsive amphiphilic supramolecular diblock copolymer based on pillar[10]arene/paraquat 1 : 2 cooperative complexation,[180] which self-assembled into micelles in water for the rate-tunable controlled release of DOX.[181] By heating or adding a competitive host or guest, the release rate of DOX could be finely tuned. This study showed that connecting sensitive components *via* reversible non-covalent bonds was a good and simple way to produce nanocarriers with diverse and tunable release kinetics.

Very recently, Du and co-workers constructed novel supramolecular vesicles from **WP6S** and disulfide-linked benzimidazolium amphiphiles, which underwent controlled drug release in response to five triggers including glutathione (GSH), pH, CO_2, Zn^{2+} ions and hexanediamine (HDA) (Fig. 12f, I).[182] DOX was further loaded within the supramolecular vesicles with a loading efficiency of DOX of 17.4%. The supramolecular vesicles were disassembled and the encapsulated DOX was released at acidic pH values or in the presence of GSH. The cytotoxicity analyses indicated that **WP6S** and **13** were only slightly cytotoxic. DOX was released from the supramolecular vesicles and entered the cell nuclei to induce cell apoptosis (Fig. 12f, IV). The smart pillararene-based supramolecular vesicles possessing five types of stimuli-responsiveness to the microenvironments of tumors and other diseases meet the diverse requirements of controlled drug release.

3.4 Supramolecular chemotherapy on the basis of supramolecular nano-vehicles formed from other types of host–guest molecular recognition

Through aromatic donor–acceptor interactions or multiple non-covalent interactions, supramolecular assemblies with a well-defined structure and tailor-made functionality can be produced.[183–187]

Liu and co-workers constructed supramolecular binary vesicles based on the host–guest complexation of *p*-sulfonatocalix[4]arene (SC[4]A) and an asymmetric viologen (MVC_{12}) (Fig. 13a, I).[188] Benefiting from the intrinsic advantages of supramolecular chemistry, the obtained vesicles exhibited excellent sensitivity to multiple external stimuli, including temperature, the addition of a cyclodextrin and redox reactions. Any of these stimuli could act as an effective switch that triggered the efficient release of the entrapped DOX from the vesicle interior. *In vitro* experiments indicated that the loading of DOX did not affect its therapeutic effect to cancer cells, whereas this supramolecular encapsulation reduced the damage to normal cells (Fig. 13a, III and IV). Later on, they developed ''drug chaperones'' by directly coassembling amphiphilic *p*-sulfonatocalix[4]arene with anticancer drugs (irinotecan·HCl and mitoxantrone·HCl) *via* electrostatic and hydrophobic interactions.[189] The resulting nanoparticles possessed high loading efficiency and protected drug molecules from alkalization. After being decorated with targeting ligands, the ternary nanoparticles showed enhanced anticancer activities compared to free drugs.

Papot and co-workers designed an enzyme-sensitive [2]-rotaxane programmed for the intracellular delivery of PTX within tumor cells (Fig. 13b, I).[190] The functionality of rotaxane **14** relied on

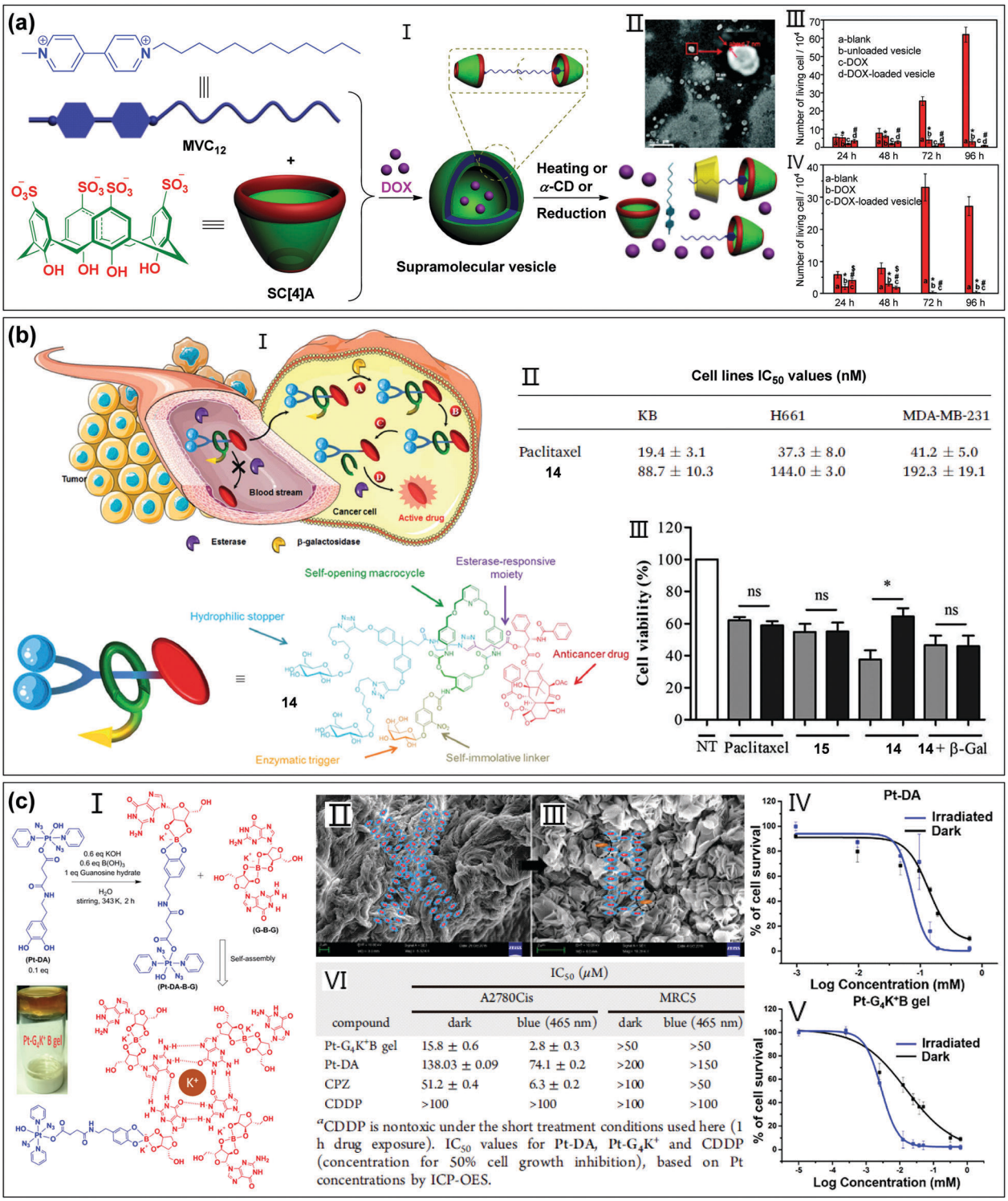


Fig. 13 (a) Schematic illustration of the construction of a supramolecular binary vesicle based on the host–guest complexation of SC[4]A with MVC_{12} and its multistimuli-responsiveness (I). TEM image of SC[4]A⊃MVC_{12} aggregation (II). Number of living NIH3T3 cells (III) or HepG-2 cells (IV) in a blank group and after treatment at different times (reproduced with permission of the American Chemical Society from ref. 188). (b) Structure of rotaxane **14** and the principle of intracellular drug delivery with a functional interlocked system (I). IC_{50} values of paclitaxel and rotaxane **14** on KB, H661 and MDA-MB-231 cell lines after two days of treatment (II). Viability of KB tumor cells treated for 48 h with the indicated compounds. White bar: untreated KB cells (NT). Light grey bar: non-transfected KB cells. Dark grey bar: siRNA-transfected KB cells. Rotaxane **14** and thread **15** were tested at 100 nM. Paclitaxel was tested at 20 nM (III) (reproduced with permission of The Royal Society of Chemistry from ref. 190). (c) Schematic representation of the self-assembly of **Pt-DA** functionalized G_4K^+ borate hydrogels (I). SEM images of the G_4K^+ borate hydrogel (II) and **Pt-G_4K^+B** hydrogel (III). Growth curves of A2780Cis cells treated for 1 h with **Pt-DA** (IV) and **Pt-G_4K^+B** (V) hydrogels, followed by 1 h irradiation with blue LEDs. IC_{50} values of **Pt-DA** and **Pt-G_4K^+** borate hydrogels against cisplatin-resistant A2780Cis human ovarian cancer cells and normal MRC-5 human fibroblast cells, in comparison with chlorpromazine (CPZ) and cisplatin (VI) (reproduced with permission of the American Chemical Society from ref. 191).

the association of several distinct units, including an enzymatic trigger, a self-immolative linker, a self-opening macrocycle, a hydrophilic stopper and an esterase-sensitive thread linked to the C2′-OH position of PTX. The macrocycle played the role of a temporary molecular shield protecting the ester bond from hydrolysis by plasmatic esterases, thereby avoiding the release of the active drug in the bloodstream. Once inside cancer cells, activation of the galactoside trigger by β-galactosidase (Fig. 13b, I, step A) would initiate a sequence of chemical reactions leading ultimately to the decomposition of the interlocked architecture through the controlled opening of the protective ring (Fig. 13b, I, steps B and C). Unmasked in this way, the ester bond of the free thread then became accessible to intracellular esterases, allowing the release of PTX within the cells (Fig. 13b, I, step D). Compared to free PTX, rotaxane **14** had a lower cytotoxicity towards KB, H661 and MDA-MB-231 cell lines as a result of its higher hydrophilicity, which reduced its passive penetration through the cell membrane (Fig. 13b, II). Furthermore, *in vitro* biological evaluations revealed that this biocompatible functional system exhibited a noticeable level of selectivity for cancer cells overexpressing β-galactosidase (Fig. 13b, III).

Sadler and co-workers utilized biocompatible G-quadruplex G_4K^+ hydrogels to deliver a photoactivatable dopamine-conjugated platinum(IV) complex (**Pt-DA**) to cancer cells (Fig. 13c, I).[191] This prodrug was incorporated into G_4K^+ borate hydrogels by using borate ester linkages (**Pt-G_4K^+B** hydrogel). Microscopy investigations revealed the transformation of extended fibers into discrete flakes after modification of **Pt-DA** (Fig. 13c, II and III). **Pt-DA** showed photocytotoxicity against cisplatin-resistant A2780Cis human ovarian cancer cells (IC_{50} 74 μM, blue light) with a photocytotoxic index <2, whereas **Pt-G_4K^+B** hydrogels exhibited more potent photocytotoxicity (IC_{50} 3 μM, blue light) with a photocytotoxic index >5 (Fig. 12c, IV and V). Most notably, the chemical modified **Pt-G_4K^+B** hydrogel dramatically increased the selective phototoxicity between normal and cancer cells (>18-fold) (Fig. 13c, VI).

4. Supramolecular chemotherapy based on supramolecular organic–inorganic hybrid materials

Supramolecular organic–inorganic hybrid materials are an emerging type of hybrid nanomaterials. They are prepared by anchoring organic molecules and supramolecules onto inorganic scaffolds. They have found biological applications such as human healthcare based on controlled delivery of diagnostic, therapeutic and pharmaceutical agents.[192–194] The combination of nanomaterials as solid supports and supramolecular concepts has led to the development of hybrid materials with improved functionalities. These ''hetero-supramolecular'' ideas provide a means of bridging the gap between supramolecular chemistry, materials sciences and nanotechnology. This approach allows the fine-tuning of the properties of nanomaterials and offers new perspectives for the application of supramolecular concepts.[195,196]

4.1 Carbon material-based supramolecular chemotherapy

Carbon-based nanomaterials such as fullerenes, carbon nanotubes, graphene, graphene oxide, carbon nanofibers, carbon dots, nanodiamonds and carbon nanothreads have received considerable attention as promising materials for supramolecular chemotherapeutic agents *via* π–π stacking and hydrophobic interactions with anticancer drugs.[197–205] These materials exhibit many outstanding intrinsic physical and chemical properties that make them potentially desirable for biomedical applications in the treatment of cancer.[206–208]

Liu and co-workers constructed a tumor-targeted delivery system for CPT based on the inclusion complexation of hyaluronated adamantane (HA-ADA) with β-CD functionalized graphene oxide (GO-CD).[209] The ternary supramolecular nanomedicine (CPT@GO-CD–HA-ADA) exhibited a higher curative effect and a lower cytotoxicity than free CPT. The β-CD⊃ADA inclusion complex prevented the GO skeletons from intermolecular aggregation and the resultant uniform and small-sized GO nanosheets promoted the targeted receptor-mediated internalization of the biocompatible supramolecular complex by cells. Another DDS formed from rGO-C_6H_4-COOH (reduced graphene oxide covalently modified with *p*-aminobenzoic acid) and β-CD for the loading and targeted delivery of DOX was contributed by Hao and co-workers.[210] The introduction of β-CD not only accommodated water insoluble anticancer drugs but also reduced the cytotoxicity of the DDS to normal cells. This DDS displayed an enhanced dispersity in water and improved biocompatibility benefiting from the formation of β-CD⊃DOX. Conjugation of rGO-PEI-CD-Biotin and DOX effectively hindered the HepG2 cancer cells in the G2 phase and prevented the HepG2 cancer cells from entering the mitosis period (M phase).

4.2 Gold material-based supramolecular chemotherapy

Gold-based nanostructures, including gold nanoparticles, gold nanorods, gold nanoshells, gold nanocrystals and gold nanocages, that display intriguing physical and/or chemical properties, have been actively explored as new nano-sized agents for cancer therapy.[211–216] These nanostructures are particularly captivating because they are inert, nontoxic, biocompatible and easy to prepare and functionalize by attaching bioactive ligands such as drugs and proteins.[217–221]

Rotello and co-workers reported that the cytotoxicity of therapeutic gold nanoparticles could be mediated by CB[7] encapsulation (Fig. 14a, I).[222] The cationic gold nanoparticles functionalized with terminal diaminohexane units (AuNP-NH_2) strongly interacted with cell membranes and subcellular compartments, resulting in membrane disruption and cytotoxicity. However, the complexation of AuNP-NH_2 with CB[7] reduced the ability of the gold nanoparticles to disrupt endosomal membranes, lowering their cytotoxicity (Fig. 14a, II). More interestingly, the host–guest complex on the gold nanoparticles could be intracellularly disassembled by adding a competitive guest molecule 1-adamantylamine (ADA) with a very high affinity for CB[7]. Intracellular displacement of CB[7] from the

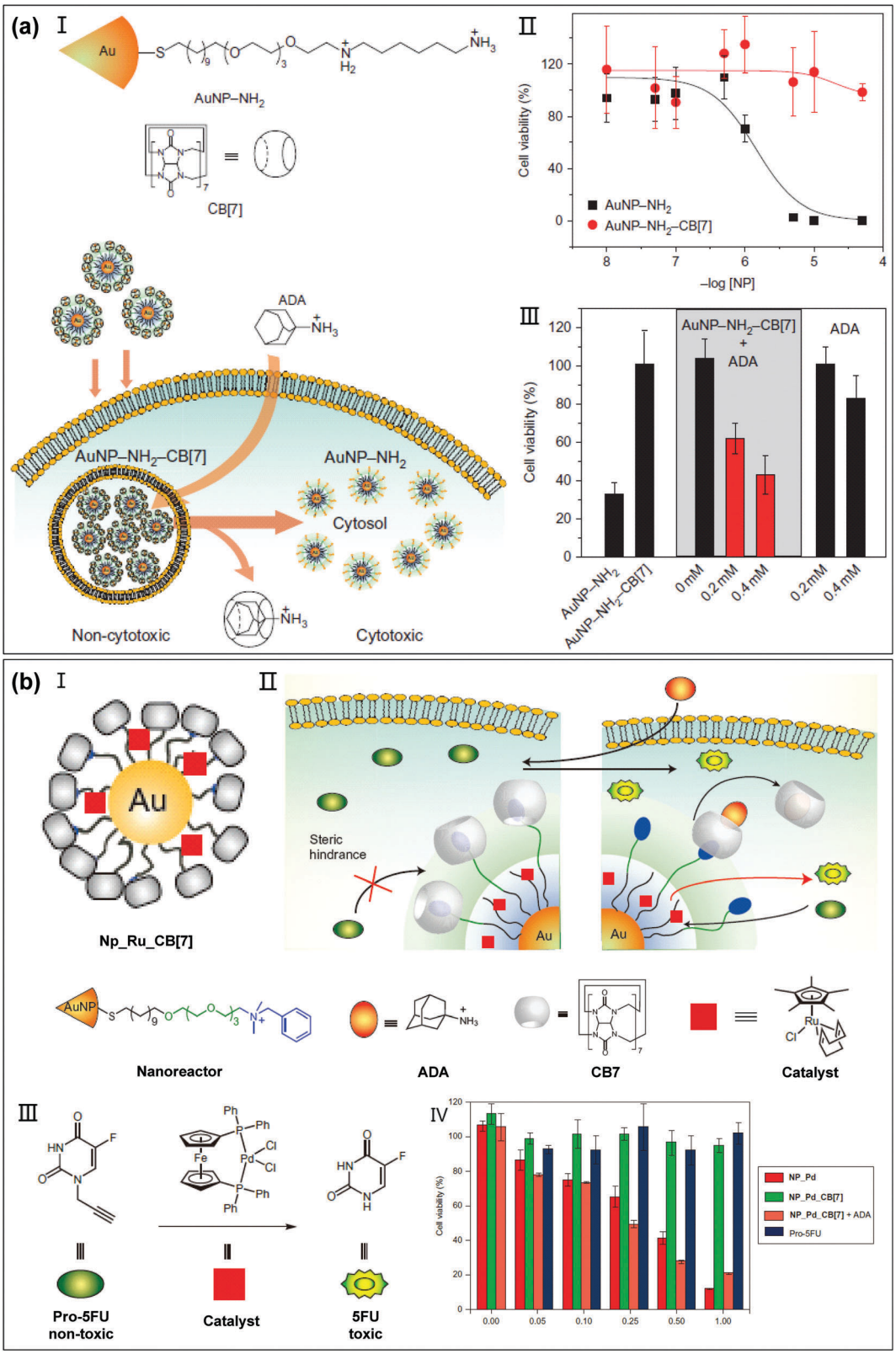


Fig. 14 (a) Schematic representation of the structure of a diaminohexane-terminated gold nanoparticle (AuNP-NH_2) and CB[7], and the activation of AuNP-NH_2-CB[7] cytotoxicity by dethreading of CB[7] from the nanoparticle surface by ADA (I). Cytotoxicity of AuNP-NH_2 and AuNP-NH_2-CB[7] measured by Alamar blue assay after 24 h of incubation in MCF-7 (II). Triggering cytotoxicity using ADA (III) (reproduced with permission of Nature Publishing Group from ref. 222). (b) Schematic structure of NP_Ru_CB[7] (I). Scheme of prodrug activation in cells (II). Structures of pro-5FU, 5FU and the palladium catalyst used for prodrug activation (III). Cell viability of HeLa cells incubated with various concentrations of NP_Pd, NP_Pd_CB[7], NP_Pd_CB[7] + ADA and pro-5FU for 24 h (IV) (reproduced with permission of Nature Publishing Group from ref. 223).

gold nanoparticles resulted in endosomal escape of AuNP-NH_2, activating the cytotoxicity of AuNP-NH_2 and inducing cell death (Fig. 14a, III). This result suggested a powerful strategy for triggering therapeutic systems especially for the regulation of cytotoxicity by using host–guest chemistry.

Very recently, Rotello and co-workers explored the benefit of high affinity CB[7]–ADA pairs for the supramolecular regulation of bioorthogonal catalysis in cells (Fig. 14b, I).[223] They developed a protein-sized bioorthogonal nanozyme through the encapsulation of hydrophobic transition metal catalysts into the monolayer of water-soluble gold nanoparticles. The activity of the catalyst was reversibly controlled by using CB[7] as the 'gate-keeper' onto the monolayer surface which provided a biomimetic control mechanism that mimicked the allosteric regulation of natural enzymes (Fig. 14b, II). 5-Fluorouracil (5FU) is a chemotherapeutic drug used in cancer treatment, including treatment of breast, stomach, pancreatic and skin cancers. The propargyl-modified 5FU (pro-5FU) was introduced to evaluate the catalytic ability of NP_Pd_CB[7] (Fig. 14b, III) because only unmodified 5FU showed intracellular toxicity after being activated. Co-incubation of HeLa cells with ADA-treated NP_Pd_CB[7] showed increasing cytoxicity resulting from the conversion of the prodrug into active 5FU, while NP_Pd_CB[7] did not show toxicity at any investigated prodrug concentration due to the blockage of catalysis (Fig. 14b, IV). This gated platform integrating biomimetic and bioorthogonal design elements performs totally abiotic chemistry that can be controlled intracellularly through a very simple host–guest feature.

Sun, Che and co-workers reported a dual-functionalized supramolecular polymer self-assembled from a cyclometalated gold(III) complex containing a hydrogen-bonding motif and its application in anticancer treatment.[224] The organogold(III) supramolecular polymer showed distinctive physical features including concentration-dependent specific viscosity and formation of nanofibrillar networks. It displayed sustained cytotoxicity and selective cytotoxicity toward cancerous cells. In addition, this organogold(III) supramolecular polymer was used to encapsulate other cytotoxic agents like gold(III) porphyrin complex [Au^{III}(TPP)]Cl (H_2TPP = *meso*-tetraphenylporphyrin) to achieve sustained-release behavior. Taken together, these results suggested that the organogold(III) supramolecular polymer exhibited potential application in sustained delivery therapy with improved therapeutic efficiency and safety by reducing the frequency of drug administration and the dose of drug required.

4.3 Mesoporous silica-based supramolecular chemotherapy

Stimuli-responsive silica nanoparticles with porous channels have great potential for drug delivery applications due to their high stability and encapsulation capacity for loading guest molecules in the channel and unique responsiveness to diverse external stimuli.[225–229] The excellent properties of mesoporous silica nanoparticles, such as good biocompatibility, tunable nanoparticle sizes, uniform mesopores, porous interior amenable to drug loading, large surface areas and easy surface functionalization, make them highly suitable as DDSs.[230–243]

Zink, Nel and co-workers reported a mesoporous silica nanoparticle (MSNP) delivery system capable of DOX delivery based on the function of a β-CD nanovalve that was responsive to the endosomal acidification conditions (Fig. 15a, I).[244] This nanovalve consisted of an aromatic amine containing stalk that was attached to the opening of pores. β-CD was then added as a cap that encircled the stalk. A TEM image indicated that the capped MSNP was composed of ~100 nm primary nanoparticles (Fig. 15a, II). The non-covalent interaction blocked the release of DOX from the MSNPs. Protonation of the aromatic amines triggered the disassociation of the host–guest complexes, thus resulting in the release of the encapsulated DOX (Fig. 15a, III). This study provided a platform for effective and rapid DOX release by optimizing the surface functionalization of MSNPs.

Zhao and co-workers developed multifunctional MSNPs for cancer-targeted drug delivery (Fig. 15b, I).[245] The nanoparticle surface was functionalized with amino-β-CD rings bridged by cleavable disulfide bonds, blocking drugs inside the mesopores of the nanoparticles. Poly(ethylene glycol) polymers, functionalized with an adamantane unit at one end and a folate unit at the other end, were immobilized onto the nanoparticle surface through strong β-CD/adamantane host–guest complexation. The non-cytotoxic nanoparticles containing the folate targeting units were efficiently trapped by folate-receptor-rich HeLa cancer cells through receptor-mediated endocytosis and released loaded DOX into the cells triggered by acidic endosomal pH. After the nanoparticles escaped from the endosome and entered the cytoplasm of cancer cells, the high concentration of GSH in the cytoplasm removed the β-CD capping rings by cleaving the pre-installed disulfide bonds, further promoting the release of DOX from the drug carriers. Calculated IC_{50} values for the inhibition of cell growth by DOX-MSNPs-CD-PEG-FA and free DOX revealed that cancer cells were 21-fold more sensitive to DOX-MSNPs-CDPEG-FA as compared with normal cells, while both types of cells were equally sensitive to free DOX (Fig. 15b, II). Moreover, the cytotoxicity of DOX-MSNPs-CD-PEG-FA to HEK293 normal cells can be significantly enhanced by treating with glutathione monoester (GSH-OEt), a compound which could be efficiently internalized into cells and hydrolyzed to generate GSH (Fig. 15b, III). The high efficacy of multifunctional nanoparticles was attributed to the cooperative effects of folate-mediated targeting and stimuli-triggered drug release. In addition, the introduction of the β-CD$(NH_2)_7$ ring as the mesopore capping agent on MSNPs provided a novel platform for the incorporation of targeting ligands onto the nanocarrier system.

More recently, Cai, Zhao and co-workers functionalized α-CD-based [2]rotaxanes onto hollow MSNPs, where the folic acid unit served as both the stopper of [2]rotaxane and a targeting agent toward tumor cells.[246] The embedded disulfide bond could be cleaved by intracellular reducing agent GSH, leading to redox-controlled DOX release for cancer therapy *in vitro* and *in vivo*. Subsequently, Tan, Zhao and co-workers developed biocompatible, uniform and redispersible multifunctional MSNPs for cancer-targeted drug delivery *in vivo* by optimizing the size and surface decoration.[247] The therapeutic efficacy of DOX-loaded multifunctional MSNPs with a diameter of 48 nm was superior to

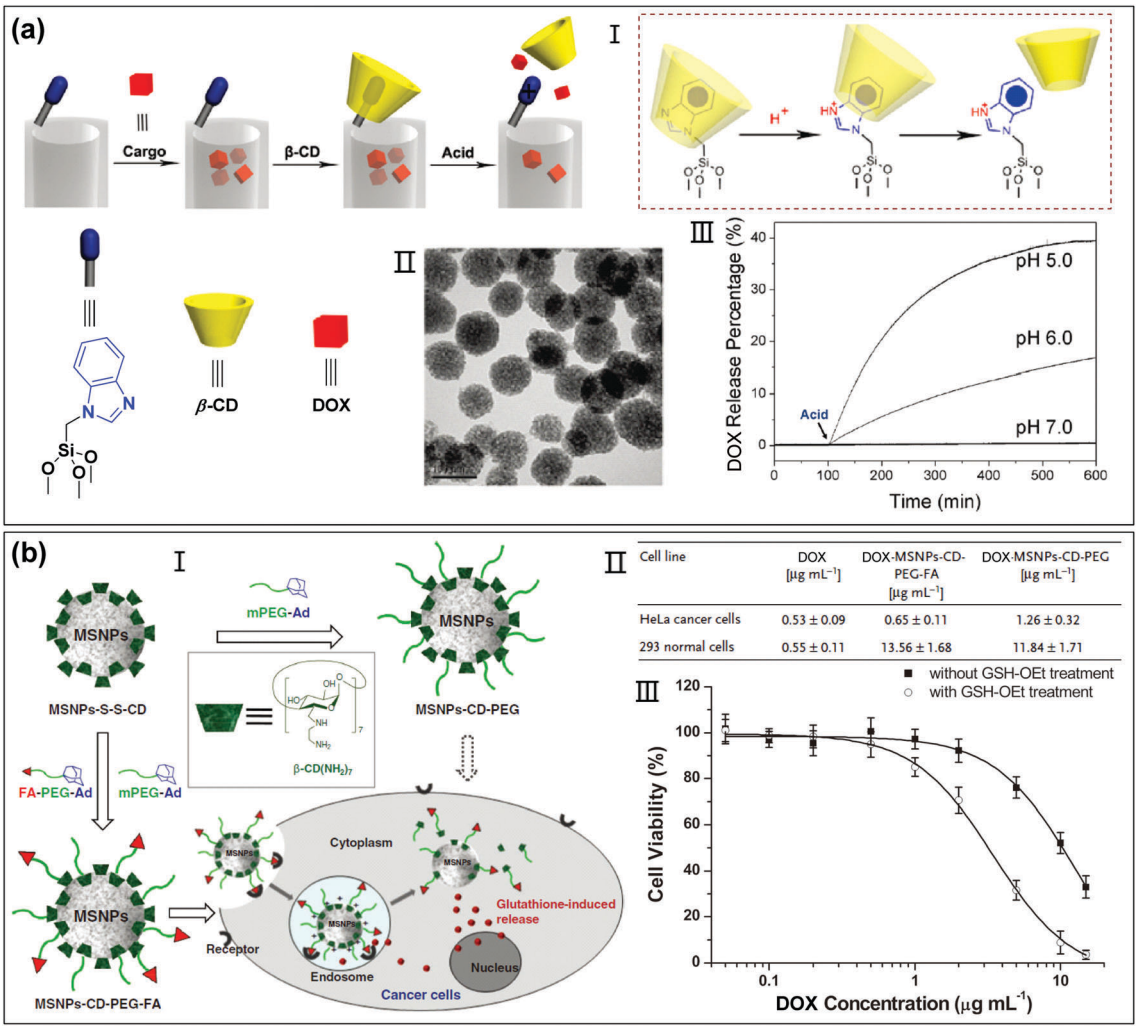


Fig. 15 (a) Design and operation of the pH responsive MSNP nanovalve (I). TEM image of a capped MSNP (II). Release profiles of DOX from the ammonium-modified MSNP (III) (reproduced with permission of the American Chemical Society from ref. 244). (b) Schematic illustration of multi-functional MSNPs-CD-PEG-FA for targeted and controlled drug delivery (I). IC_{50} values of free DOX, DOX-MSNPs-CD-PEG-FA and DOX-MSNPs-CD-PEG after 72 h of incubation with cells (II). Viability of 293 cells incubated with DOX-MSNPs-CD-PEG-FA at different DOX doses for 72 h (III) (reproduced with permission of John Wiley & Sons, Inc. from ref. 245).

those of free DOX and non-targeted nanoparticles. Moreover, no obvious sign of toxicity from the drug carriers was observed, because most of the multifunctional MSNPs could be excreted in the urine and feces of the animal.

Zhang and co-workers fabricated a type of cellular-uptake-shielding multifunctional envelope-type mesoporous silica nanoparticle (MEMSNP) for specific delivery of DOX to cancer cells.[248] β-CD was anchored on the surface of MSNPs *via* disulfide linking for GSH-triggered intracellular DOX release. Then a peptide sequence containing an Arg-Gly-Asp (RGD) motif and a matrix metalloproteinase (MMP) substrate peptide Pro-Leu-Gly-Val-Arg (PLGVR) was introduced onto the surface of the nanoparticles *via* host–guest interaction. To protect the targeting ligand and prevent the nanoparticles from being uptaken by normal cells, the nanoparticles were further decorated with poly(aspartic acid) (PASP) to obtain MEMSNPs. *In vitro* study demonstrated that the MEMSNPs were shielded against normal cells. After being internalized by tumor cells, the targeting properties could be switched on by removing the PASP protection layer *via* hydrolyzation of PLGVR at the MMP-rich tumor cells, which enabled the easy uptake of the drug-loaded nanoparticles by tumor cells and subsequent GSH-induced DOX release intracellularly. This "programmed packing" manner enabled an easy formulation of the tumor-triggered targeting drug delivery. Compared with traditional functionalizations, the host–guest interactions here greatly simplify the time-consuming synthesis.

Gao, Yang and co-workers reported biocompatible layer-by-layer (LbL) coated MSNs (LbL-MSNs) that were designed and crafted to release encapsulated DOX by changing the pH.[249] The LbL coating process comprised bis-aminated poly(glycerol methacrylate)s (BA-PGOHMAs) and CB[7], where CB[7] served as a molecular bridge holding two different bis-aminated polymeric layers together by means of host–guest interactions.

Although MSNPs possess several advantageous features in drug delivery studies, the structural stability of silica makes it problematic for *in vivo* medical applications due to its difficulty in biodegradation, which may cause unexpected long-term immunotoxicity.[250] Tang, Huang and co-workers developed a decomposable nanocarrier by immobilizing **WP5A** (the water-soluble pillar[5]arene analogous to **WP6A**) onto Mg^{2+}-incorporated hollow mesoporous nanoparticles (HMNPs) for cancer therapy *in vitro* and *in vivo* with an enhanced tumor therapeutic effect.[251] The host–guest complexation between **WP5A** and HMNPs enabled the pH-sensitive storage and release of DOX from the nano-vector. **WP5A**@HMNPs decomposed into small water-soluble fragments, which enabled nanoparticles to be excreted from the body after the treatment. The excellent biocompatibility, decomposability and efficient pH-responsive drug release of **WP5A**@HMNPs opened up an alternative host–guest complexation-based strategy for clinical medical applications.

4.4 Magnetic iron oxide-based supramolecular chemotherapy

Magnetic nanoparticles are promising supramolecular chemotherapeutic drug carriers because they can deliver anticancer drugs more selectively to the target site under the guidance of an external magnetic field and hence abate the lesions in tumor tissues precisely.[252–255] Superparamagnetic iron oxide nanoparticles are attractive drug carriers by virtue of their biocompatibility, biodegradability, aqueous dispersibility and magnetisability. Moreover, these inorganic materials are excellent magnetic resonance imaging (MRI) contrast agents, which can be fully utilized in imaging-guided theranostics.[256,257]

Cheon, Tseng and co-workers utilized a supramolecular system based on the host–guest interaction between β-CD and Ad with magnetic nanoparticles to prepare size-controllable supramolecular magnetic nanoparticles (SMNPs) (Fig. 16, I).[258] Anticancer drug DOX was loaded to produce DOX-encapsulated supramolecular magnetic nanoparticles (DOX⊂SMNPs). On-demand magnetothermally responsive DOX release was realized by quickly generating thermal energy when applying an external alternative magnetic field (AMF). Here 6 nm Ad-MNP functioned as a built-in transformer in the whole systems, which can convert the energy from an AMF into local heat, as a stimulus to speed up the release of encapsulated DOX. After applying an AMF for 2 min, approximately 50% of DOX was released from the disassembled SMNP structures. DOX⊂SMNPs also showed superior inhibition of tumor growth even at very low concentrations of the drug (2.8 μg kg^{-1} DOX) compared to normal protocols (Fig. 16, II), significantly decreasing the side effects. This result indicated that an acute level of drug concentration could be delivered to a tumor with spatiotemporal control thus significantly reducing the drug dosage.

The magnetic materials can be exploited to induce a therapeutic response through hyperthermic effects. Cheon, Zink and co-workers constructed a magnetically activated release system by encapsulating DOX and zinc-doped iron oxide nanocrystals within mesoporous silica frameworks and capping the pores with a cyclic CB[6] nanovalve.[259] Under an oscillating magnetic field, the nanocrystals generated local internal heating, causing the nanovalves to disassemble and allowing the encapsulated DOX to be released. The controlled release provided 7-times higher cytotoxicity than that without hyperthermic release *in vitro*. This research opened the door to develop a noninvasive and externally controlled DDS with cancer-killing properties.

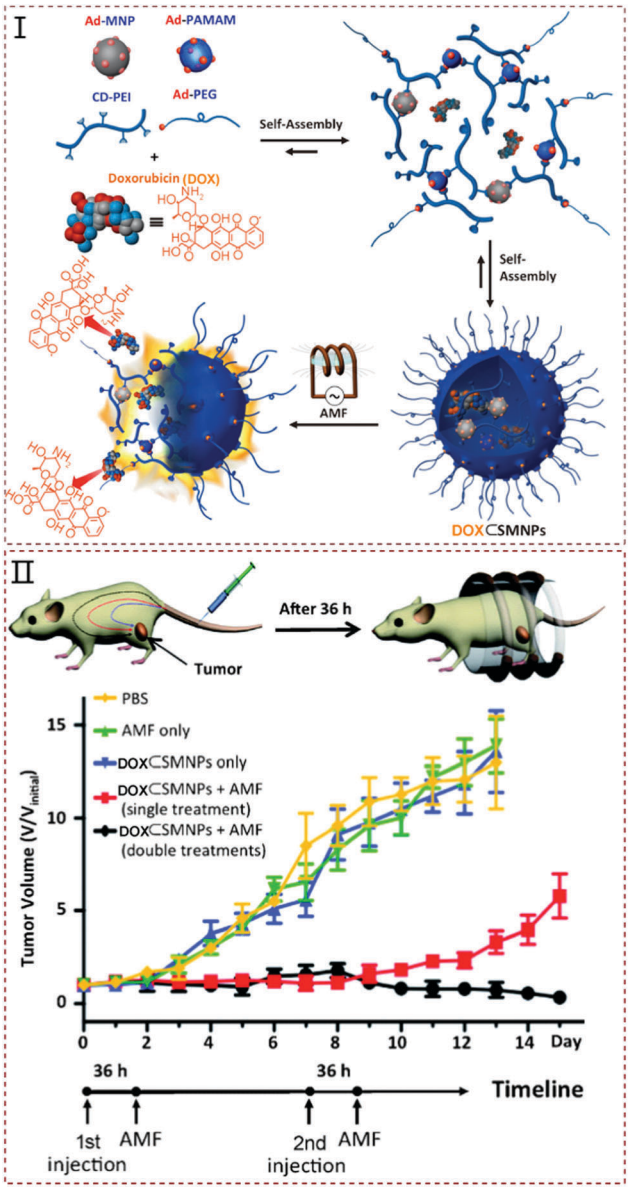


Fig. 16 Molecular design, self-assembly and function of magnetothermally responsive DOX-encapsulated supramolecular magnetic nanoparticles (DOX⊂SMNPs) (I). Treatment scheme of DOX⊂SMNPs in mice and the results of the tumor volume change over the course of the treatment (15 days) in DLD-1 xenografted mice (II) (reproduced with permission of John Wiley & Sons, Inc. from ref. 258).

Cai and co-workers constructed a redox-responsive controlled release system employing disulfide bonds as coupling linkers to immobilize β-CD grafting polyethylenimine (PEI/β-CD) molecules onto magnetic nanoparticles for intracellular CPT delivery.[260] The resulting DDS could respond to the reducing milieu of the cytoplasm by endosomal escape. Meanwhile, the conjugation of

PEI/β-CD molecules to MNPs improved the endocytosis efficiency. Moreover, the system could deliver PEI/β-CD@CAMP complexes within cells to induce cell apoptosis *in situ*.

5. Supramolecular chemotherapy based on metal-coordination

Platinum and ruthenium complexes constitute a promising class of second-generation transition metal compounds for anticancer therapy with a long history.[261–266] The strong and highly directional nature of metal–ligand interactions results in the construction of stable and rigid supramolecular coordination complexes *via* a process called coordination-driven self-assembly.[267,268] From the wide range of metal ions and ligands that are compatible with this strategy, a large library of building blocks with selective guest encapsulation have emerged which aim at improving the efficacy of cancer therapy.

5.1 Metallacage-based supramolecular chemotherapy

Metallacages are three-dimensional supramolecular coordination complexes for encapsulating various guest molecules as drug delivery nanosystems. By modification of the ligand and linking the metal center, the properties of the complexes can be altered to obtain desired biological characteristics.[269–273]

Briken, Isaacs and co-workers decorated the external surface of Fujita-type $Pd_{12}\mathbf{L}_{24}$ metal–organic polyhedrons (MOPs)[274,275] with **MV** ligands, explored their non-covalent functionalization with CB[*n*], and demonstrated their ability to deliver DOX to cancer cells (Fig. 17, I).[276] MOP **18** was studded with 24 **MV** units, which enabled it to undergo well-defined host–guest interactions with CB[7] and CB[8]. Advantageously, MOP **19** could be loaded with up to 24 molecules of DOX prodrug **17** by the formation of CB[8] promoted hetero-ternary charge transfer complexes. The release of DOX from **21** occurred by cleavage of the acid sensitive acylhydrazone linkages. Flow cytometry experiments showed that the intracellular drug concentration was 2-fold higher for **21** compared to free prodrug **17** (Fig. 17, II). MTS assays demonstrated that MOP **21** was taken up better by HeLa cells than free **17**, which resulted in a 10-fold decrease in the IC_{50} value (Fig. 17, III). Importantly, the cytotoxicity of MOP **21** was comparable to that of free DOX, which showed that the nanoscale architecture of **21** imparted improved uptake properties but did not diminish the inherent activity of the drug.

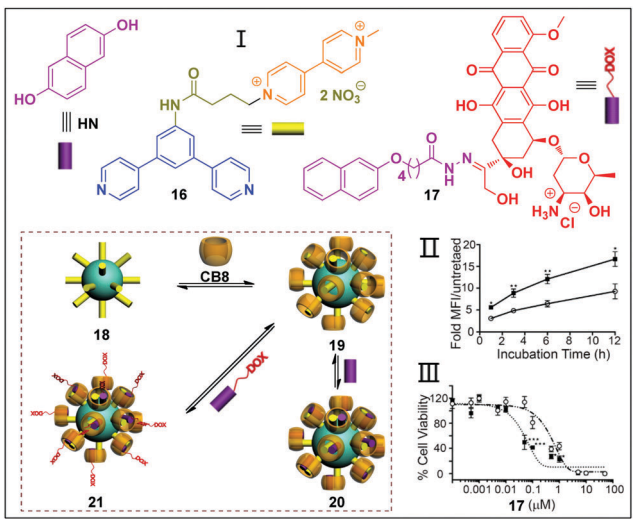


Fig. 17 Sequential self-assembly of the MV units of metal–organic polyhedron (MOP) **18** as the first guest with CB[8] to yield MOP **19** followed by hetero-ternary complex formation with HN or **17** to yield MOP **20** and MOP **21**, respectively (I). Plot of normalized mean fluorescence intensity (MFI) *versus* incubation time derived from flow cytometry experiments for HeLa cells treated with **17** (1 μM, ○) or **21** ([**17**] = 1 μM, ■) for 1, 3, 6, or 12 h (II). The results of a MTS assay for HeLa cells treated with **17** (○) or **21** (■) (III) (reproduced with permission of the American Chemical Society from ref. 276).

Crowley and co-workers showed that discrete dipalladium(II) molecular cages of the formula $[Pd_2L_4](X)_4$ could be quantitatively self-assembled from a simple tripyridyl ligand (2,6-bis(pyridin-3-ylethynyl)pyridine) and $[Pd(CH_3CN)_4](X)_2$ (X = BF_4^- or SbF_6^-).[277] The central cavities of the $[Pd_2L_4](X)_4$ cages were linked with four hydrogen bond accepting pyridine units which enabled the encapsulation of two cisplatin drug candidates through hydrogen bonds between the cage and the amine ligands of the cisplatin guests. Additionally, they have demonstrated that the cage⊃cisplatin could release the cisplatin drug upon disassembly of the complex due to the addition of competing ligands. The DDS based on host–guest chemistry could circumvent the side effects and drug resistance associated with cisplatin and other anticancer therapeutic agents.

Therrien and co-workers reported the "Trojan horse" strategy,[278] in which a relatively hydrophobic complex encapsulated within a hydrophobic pocket of a metal-containing host functioned in a synergic fashion by accelerated release inside cancer cells. Recently, a well-defined supramolecular delivery system for cisplatin based on the use of Pt(IV) prodrugs and a self-assembled hexanuclear Pt(II) cage was developed by Lippard and co-workers.[279] Relying on host–guest interactions between adamantyl units tethered to the Pt(IV) molecules and the cage, four prodrugs could be encapsulated within one cage. Upon formation of such a supramolecular system, the cytotoxicity of the prodrug was improved because of the high cellular uptake of the cage.

5.2 Metallacycle-based supramolecular chemotherapy

Two-dimensional metallacycles can work as anticancer agents capable of recognizing DNA or enzymes/proteins with target binding motifs.[280,281] Some complexes have been designed to show multimodal binding with DNA, allowing both intercalation and groove binding.

Yam and co-workers explored a series of multiaddressable alkynylplatinum(II) terpyridine molecular rectangles to exhibit reversible capture and release of anticancer therapeutic guests under different pH conditions (Fig. 18).[282] The reversible host–guest interactions were found to be perturbed by metal–metal, π–π and electrostatic interactions. This study led to the development of a multiaddressable model system to illustrate the capability of reversible guest capture and release processes for therapeutic delivery.

5.3 Metal–organic framework-based supramolecular chemotherapy

Metal–organic frameworks (MOFs) are a class of hybrid porous materials, which result from the assembly of inorganic clusters and easily tunable organic linkers (carboxylates, imidazolates or phosphonates). The superior properties of MOFs, such as well-defined pore aperture, tailorable composition and structure, tunable size, versatile functionality, high agent loading and improved biocompatibility, make them promising candidates for encapsulation of several antitumor and retroviral drugs against cancer.[283–288]

MOFs can act as metallo-hosts to selectively encapsulate different drugs for cancer therapy by altering the metal and/or the organic linker, where the pores serve as supramolecular hosts and drugs act as guests. Horcajada, Gref and co-workers reported the use of non-toxic porous iron(III)-based MOFs with engineered cores and surfaces for efficient controlled delivery and release of several antitumor and retroviral drugs (*i.e.*, cidofovir, busulfan, azidothymidine triphosphate or doxorubicin) against cancer and AIDS (Fig. 19a, I).[289] The nanoparticles based on MOFs were characterized in terms of biocompatibility, degradability and imaging properties (Fig. 19a, II and III). A progressive release of the three active molecules (AZT-TP, CDV and DOX) was observed using MIL-100 nanoparticles (Fig. 19a, IV), with no 'burst effect'. The comparison between the kinetics of drug delivery and the degradation profiles suggested that the delivery process was governed mainly by diffusion from the pores and/or drug–matrix interactions. These results opened new perspectives to use nano-MOFs for improved cancer treatment.

Lin and co-workers constructed nanoscale metal–organic frameworks (NMOFs) for the co-delivery of cisplatin and pooled small interfering RNAs (siRNAs) to enhance therapeutic efficacy by silencing MDR genes and resensitizing resistant ovarian cancer cells to cisplatin treatment (Fig. 19b, I).[290] UiO NMOFs with hexagonal-plate morphologies were loaded with a cisplatin prodrug and pooled MDR gene-silencing siRNAs *via* encapsulation and surface coordination, respectively (Fig. 19b, II). Compared to the naked siRNA solution, cellular uptake of siRNA/UiO-Cis was significantly enhanced (Fig. 19b, III), indicating that the NMOF facilitated the siRNA internalization *via* endocytosis pathways. NMOFs protected siRNAs from nuclease degradation, enhanced siRNA cellular uptake and promoted siRNA escape from endosomes to silence MDR genes in cisplatin-resistant ovarian cancer cells. The cisplatin-resistant ovarian cancer cells could be resensitized after being transfected with siRNA/UiO-Cis, and the synergistic effects of siRNA and cisplatin led to an order of magnitude enhancement in chemotherapeutic efficacy *in vitro* (Fig. 19b, IV). This represents a simple approach to the co-delivery of chemotherapeutics and other nucleic acid drugs such as siRNA, microRNA and plasmid DNA by NMOFs.

Deng, Zhang and co-workers developed a multifunctional MOF-based tumor targeting DDS for cancer therapy.[291] The fabrication of this MOF-based DDS was carried out by a one-pot post-synthetic method starting from the nanoscale MOF MIL-101.[292] After DOX loading, the azide modified MOF MIL-101-N_3 (Fe) was covered with a layer of a β-CD derivative. A targeted peptide functionalized polymer was tethered to the surface of the MOF *via* the host–guest interaction between the surface decorated β-CD and the adamantane group at the end of the polymer. Due to the pH responsive benzoic imine bond and the GSH-responsive disulfide bonds, the DDS exhibited enhanced cellular uptake and promoted drug release. *In vitro* results indicated that the cytotoxicity of loaded DOX to normal cells was significantly reduced because of surface modification. Meanwhile *in vivo* experiments proved that DOX loaded into the DDS exhibited effective cancer cell inhibition with minimal side effects.

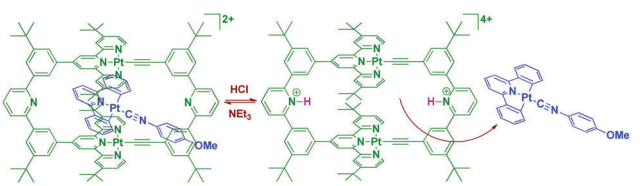


Fig. 18 Schematic diagram representing the reversible host–guest association between an alkynylplatinum(II) terpyridine molecular rectangle and an anticancer therapeutic guest.

6. Combination of supramolecular chemotherapy and other treatments for cancer therapy

In order to improve the anticancer efficacy and reduce side effects of chemotherapy, other therapeutic modalities are introduced to realize additive or synergistic effects, including gene therapy,[293–300] radiotherapy,[301,302] photothermal therapy (PTT),[303,304] photodynamic therapy (PDT)[305–308] and immunotherapy.[309–312] In this part, we will discuss the combination of supramolecular chemotherapy and other therapeutic modalities to achieve higher treatment efficiency by "collecting" the merits of each treatment.

Therrien and co-workers prepared water-soluble metallacages to deliver hydrophobic porphyrin molecules to cancer cells (Fig. 20a, I).[313] The cage⊃porphin systems displayed no phototoxic effect outside of cells. After internalization, both cage⊃porphin systems showed photodynamic effects due to the intracellular release of porphin from the cage (Fig. 20a, II). This ability defines the water-soluble metallacages as very safe and powerful tools for new photodynamic strategies in photodynamic treatment. Recently, Jin, Ji and co-workers reported GSH activatable photosensitizer-conjugated pseudopolyrotaxane nanocarriers for enhanced photodynamic therapeutic performance with reduced side effects by taking advantage of the host–guest interactions between α-CD and PEG.[314] The pseudopolyrotaxane nanocarrier significantly enhanced Chlorin e6 (Ce6) accumulation in tumors and prolonged its tumor retention time.

Noble-metal nanostructures with unique photophysical properties have been considered as prime candidate agents for the photothermal treatment of cancer.[315,316] Wang, Chiou, Tseng and co-workers developed a supramolecular self-assembly approach for the preparation of size-controlled Au supramolecular nanoparticles (Au-SNPs) based on multivalent β-CD/adamantane

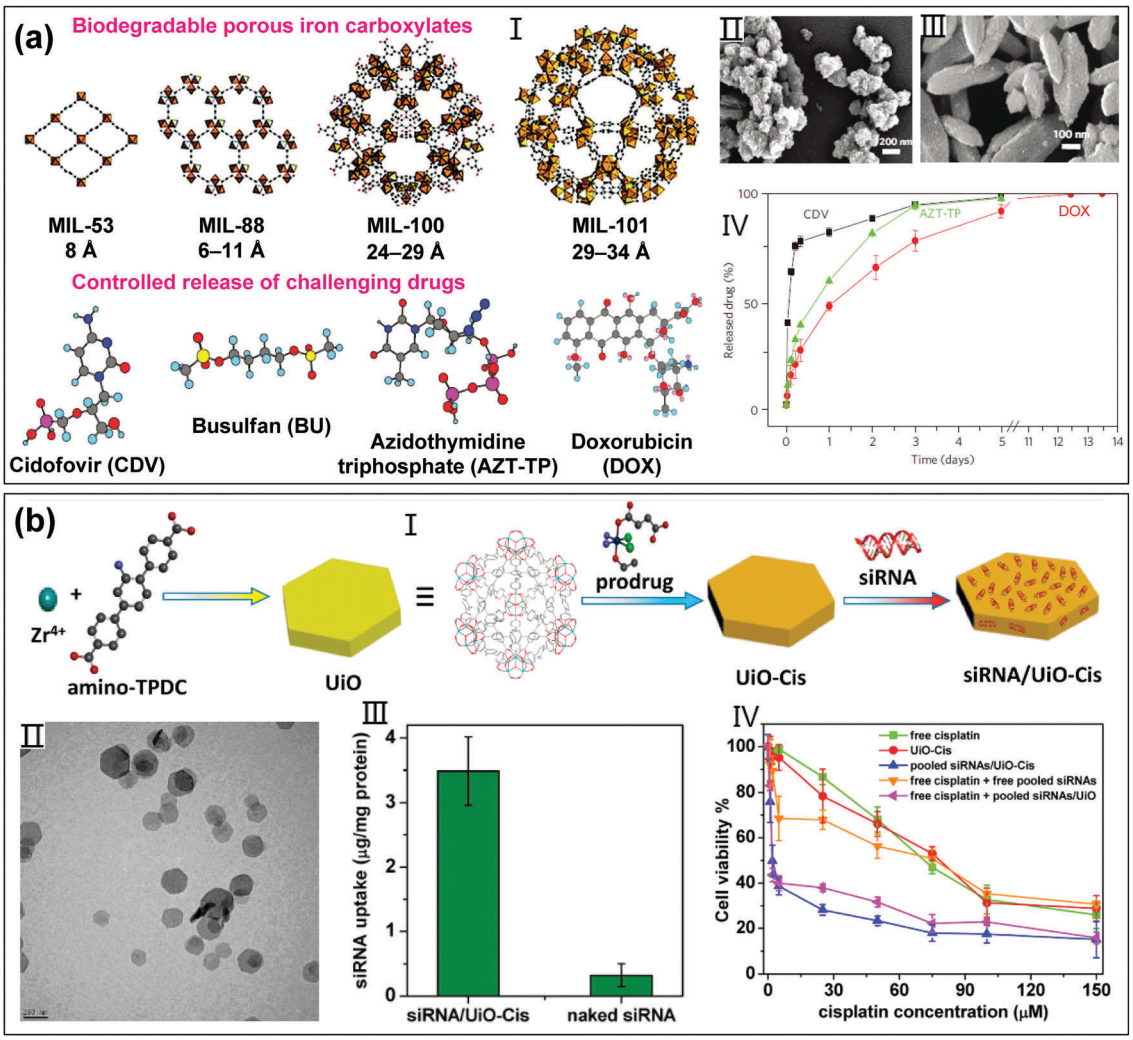


Fig. 19 (a) MOFs and drug structures used in the study of ref. 289 (I). SEM images of MIL-100 (II) and MIL-88A nanoparticles (III). CDV (black), DOX (red) and AZT-TP (green) delivery under simulated physiological conditions (PBS, 37 °C) from MIL-100 nanoparticles (IV) (reproduced with permission of Nature Publishing Group from ref. 289). (b) Schematic presentation of siRNA/UiO-Cis synthesis and drug loading (I). TEM image of siRNA/UiO-Cis (II). Cellular uptake and endosomal escape of siRNA/UiO-Cis in SKOV-3 cells (III). The results of MTS assay for SKOV-3 cells incubated with free cisplatin, UiO-Cis, pooled siRNAs/UiO-Cis, free cisplatin plus free pooled siRNAs and free cisplatin plus pooled siRNAs/UiO at different concentrations for 72 h (IV) (reproduced with permission of the American Chemical Society from ref. 290).

host–guest molecular recognition motifs for use as a new type of photothermal agent.[317] The resulting Au-SNPs exhibited significantly enhanced photothermal effects and were used to demonstrate the targeted photothermal treatment of a subpopulation of cancer cells after the incorporation of tumor-specific ligands. This supramolecular assembly approach can be used to assemble other "small" inorganic nanoparticles for broader application in materials science and biomedicine.

Xu, Tang and co-workers developed PEI-CD/Ad-DOX/pDNA SNPs to co-deliver DOX and therapeutic gene pTRAIL for synergistic treatment of tumors (Fig. 20b, I).[318] Such delivery systems possessed the good ability of *in vivo* retention of chemotherapeutic drugs, achieved good therapeutic effects in the inhibition of tumor growth and significantly prolonged the survival time of tumor-bearing mice (Fig. 20b, II). With good therapeutic effects, the anticancer drug DOX and therapeutic gene pTRAIL-loaded host–guest supramolecular co-delivery system offered new opportunities for clinical cancer therapy. Very recently, Tang, Ping, Chu and co-workers prepared a lanthanide-integrated supramolecular polymeric nanoassembly that simultaneously delivered chemotherapeutic drugs and siRNA for multidrug resistant cancer therapy.[319] Both *in vitro* and *in vivo* studies demonstrated that the nanotherapeutic system exhibited higher antitumor efficacy than a delivery system containing either the anticancer drug or therapeutic gene alone. This study revealed a simple and universal strategy to transform polymer-based nanoassemblies into advanced organic–inorganic nanotherapeutics suitable for multidrug resistant cancer therapy.

Zhao, Xu and co-workers synthesized disulfide-bridged and DOX-embedded degradable silica nanoparticles (DS-DOX) with unique self-destruction features by a one-pot method for

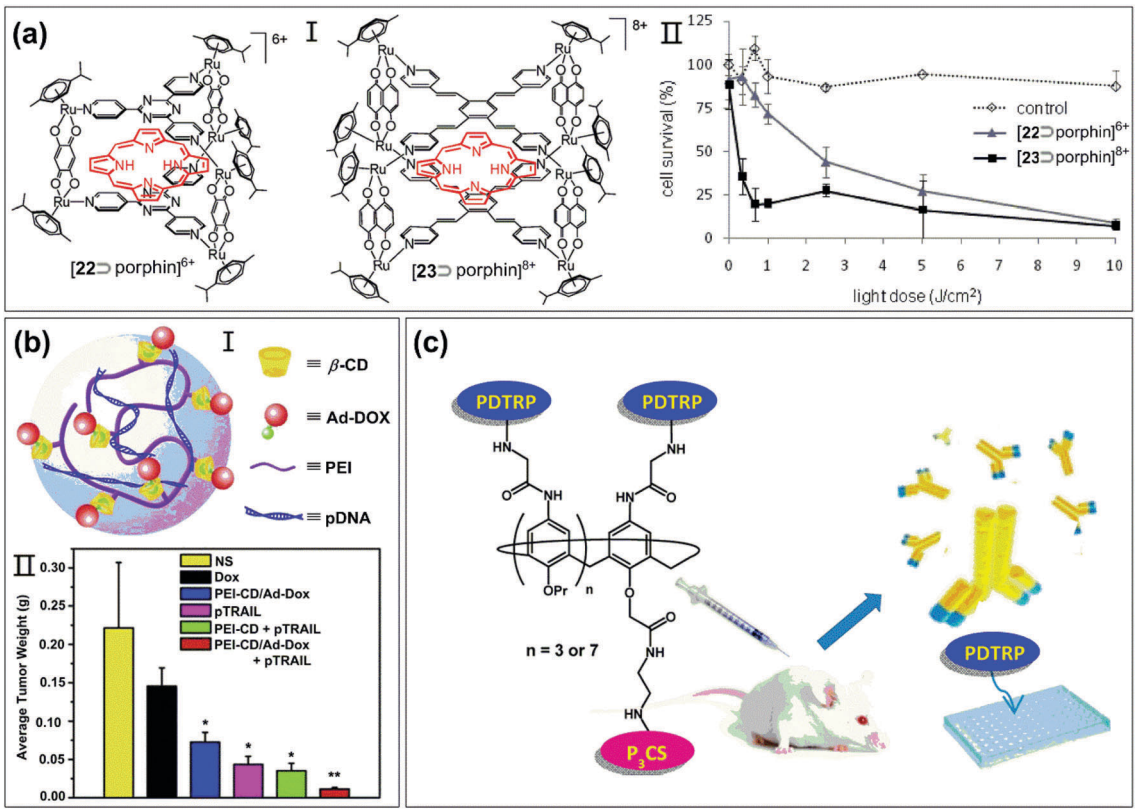


Fig. 20 (a) Molecular structures of [**22**⊃porphin]$^{6+}$ and [**23**⊃porphin]$^{8+}$ (I). Photodynamic activity of cage⊃porphin systems in HeLa cancer cells (II) (reproduced with permission of the American Chemical Society from ref. 313). (b) Schematic illustration of SNPs based on PEI-CD/Ad-DOX/pDNA for anticancer drug and gene co-delivery (I). Antitumoral therapeutic effects of SNPs with pTRAIL in tumor tissues showing weight changes after different treatments (II) (reproduced with permission of Elsevier from ref. 318). (c) Schematic illustration of the self-adjuvant multicomponent vaccine based on calixarene platforms (reproduced with permission of the American Chemical Society from ref. 321).

gene/drug co-delivery.[320] The surface of DS-DOX nanoparticles was functionalized with the host–guest assembly of adamantine and CD-PGEA (a hydroxyl-rich gene carrier compromising one β-CD core and two ethanolamine-functionalized poly(glycidyl methacrylate) arms) to achieve DS-DOX-PGEA. The redox-responsive self-destruction behavior of DS-DOX caused DS-DOX-PGEA to release DOX at the target region, while the low-toxicity hydroxyl-rich CD-PGEA brushes could deliver the antitumor gene for combined gene/chemotherapy.

Geraci, Spadaro and co-workers constructed anticancer self-adjuvant vaccine candidates based on a calix[4,8]arene platform exposing a MUC1 PDTRP immunodominant peptide sequence (Fig. 20c).[321] The arrangement of multiple PDTRP epitopes on a calixarene platform resulted in an increase of the immunological response with respect to the monovalent epitope due to the multivalency effect.[322] This work suggested the potential use of the calixarene platform as a convenient carrier for building promising immunotherapeutic anticancer agents.

7. Summary and outlook

As described above, various types of supramolecular chemotherapy, capable of encapsulating drugs, incorporating stimuli-responsive components and introducing other therapeutic modalities, have been extensively developed in cancer treatment, so as to improve target specificity and treatment efficacy and reduce the side effects that usually occur in conventional chemotherapy. By taking advantage of host–guest chemistry, some limitations impeding traditional chemotherapy for clinical applications can be eliminated effectively. Although supramolecular chemotherapy has been widely developed in recent years and achieved some charming progress, there are still many challenges that researchers are facing. Chemists, material scientists, biologists, engineers and medical doctors need to collaborate to realize its final practical applications. For example, some studies need to be exploited in future:

(i) Intelligent supramolecular therapeutic agents should be developed, of which the binding affinities can be adjusted according to tumor microenvironments. For traditional nanomedicines, premature burst release of loaded drugs during the blood circulation is a serious issue caused by large dilution volume, which results in the reduction of drug efficacy and occurrence of severe side effects towards normal tissues. Perfect supramolecular nanomedicines are extremely stable during the delivery process, while they totally collapse in cancer cells triggered by a specific stimulus, resulting in the burst release of the loaded drugs to kill the cancer cells. Due to the dynamic

nature of non-covalent interactions, it seems reasonable to fabricate smart supramolecular nanomedicines containing adjustable linkages that are responsive to slight differences between normal cells and cancer cells. The toxicity of nanoparticle carriers is always a major concern when they are used in real patients. Reducing the dosage of nanocarriers and enhancing their biodegradability *in vivo* are the most promising solutions.

(ii) The selectivity of supramolecular therapeutic agents to cancer cells needs to be improved in order to reduce the side effects caused by supramolecular chemotherapy. Targeting ligands, such as antibodies, aptamers and peptides, can be employed to modify the building blocks to endow the resultant nanomedicines with excellent selectivity. Additionally, two or more kinds of non-covalent interactions can be integrated into one system, which are responsive to different tumor-specific stimuli. For example, according to the imbalance of pH value and reactive oxygen species (ROS) levels in tumor sites, pH- and redox-responsive recognition can be introduced simultaneously to prepare tumor selective supramolecular DDSs, where the ''molecular gates'' can only be opened by these two ''keys'' together.

(iii) Diagnostic/imaging functions should be integrated into supramolecular nanomedicines. The diagnostic/imaging role of theranostic supramolecular agents reports the presence and location of the tumor, its status and its response to a specific treatment, which is important for precision therapy. Various imaging methods can be chosen, including fluorescence imaging, X-ray computed tomography (CT), positron emission tomography (PET)/single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), ultrasound imaging (US) and photoacoustic imaging (PA). The imaging probes can act as the hydrophobic or hydrophilic part of supramolecular theranostic platforms, rarely affecting the self-assembly and delivery of nanomedicines.

(iv) Synergistic combinations of multiple therapeutic modalities will show charming prospects in cancer therapy. Malignant tumors, especially hypoxic solid tumors, are extremely difficult to eradicate using a single treatment due to its intrinsic drawbacks. Several kinds of treatments should be simultaneously utilized to produce additive therapeutic effects by ''collecting'' the merits of each treatment. Gene therapy, immunotherapy, PDT, PTT, magnetic hyperthermia (MHT), radiotherapy and ultrasound therapy can be used to enhance the antitumor performance of supramolecular chemotherapy. Supramolecular hybrid materials combining multiple functions need to be developed for integrating multiple theranostic modalities within these sophisticated platforms, where supramolecular chemistry acts as the bridge between the organic and inorganic materials.

Cancer research is growing so rapidly and also broadening and diversifying. The future of supramolecular chemotherapy definitely demands more collaborative efforts at the interfaces of interdisciplinary subjects including cancer biology, materials engineering, chemistry, pharmacology, radiology and oncology. With all the innovations in these different research fields, effective supramolecular chemotherapeutic strategies will be continuously developed, which will further inspire more efforts toward personalized cancer diagnosis and therapy in future healthcare. In view of the significant research efforts being dedicated to this field, it could be expected that humanity will greatly benefit from supramolecular nanomedicines in the near future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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