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Hydrogen-Bonds Mediated Nanomedicine: Design, Synthesis and Applications

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Abstract

Among the various challenges in medicine, diagnosis, complete cure and healing of cancers remain difficult given the heterogeneity and complexity of such disease. Differing from conventional platforms with often unsatisfactory theranostic capabilities, the contribution of supramolecular interactions, such as hydrogen-bonds (H-bonds), to cancer nanotheranostics opens new perspectives for the design of biomedical materials, exhibiting remarkable properties and easier processability. Thanks to their dynamic characteristics, a feature generally observed for non-covalent interactions, H-bonding (macro)molecules can be used as supramolecular motifs for yielding drug- and diagnostic carriers that possess attractive features, arising from the combination of assembled nanoplatforms and the responsiveness of H-bonds. Thus H-bonded nanomedicine provides a rich toolbox that useful to fulfill biomedical needs with unique advantages in early-stage diagnosis and therapy, demonstrating the promising potential in clinical translations and applications. We here summarize the design and synthetic routes towards H-bonded nanomedicines, capitalizes on the growing understanding of the structure-function relationship for efficient cancer treatment. It also ambitions to propose guidance for designing new H-bonded intelligent theranostic agents, to inspire more successful explorations of cancer nanotheranostics and finally to promote potential clinical translations.

Introduction

Cancer has become one of the world's most pressing health threats, and continues to impose a severe socio-economic burden on society.¹ Over the past several decades, there have been significant advances in discovery and understanding of cancer biology, yet the survival trend and outcomes of many cancer patients have hardly been changed.^{2,3} In fact, basic and clinical researches are essential to fight with cancer, novel discoveries are indeed moving from bench to bedside at a remarkable rate.⁴ Among them, well-designed nano-formulations incorporating diagnostic and therapeutic capabilities have achieved outstanding breakthroughs over the past years.⁴⁻⁷ Nanomedicine's strategy is featured by improved clinical performances and reduced adverse side effects, thus shows promising potential in biomedical applications. There are some commercial nanomedicine products such as Abraxane® (paclitaxel bound to albumin nanoparticles) which have demonstrated a positive risk-benefit balance and so have been approved by U.S. Food and Drug Administration (FDA), which shows considerable formulations and aspects at different phases in clinical trial. Other prominent examples, especially via liposomal-formulations, such as the formulation of doxorubicin, daunomycin, vincristine or irinotecan have also been reported highlighting both, the improved performance as well as challenges of novel drug-formulations.³

Along with remarkable progress in cancer nanomedicine, scientists have also gradually realized that several obstacles are indeed lied ahead regarding their clinical translations.⁸⁻¹⁶ Foremost, the tumor heterogeneity and complexity require a precise selection of patients to identify those most likely benefitting from the given nanotheranostics.¹⁷⁻²⁰ The specificity and detection limit of nanomedicine needs to be further adapted, also in early-stage of diagnosis.²¹⁻²⁴ Therapeutic outcomes should also be improved by optimizing both pharmacodynamic and pharmacokinetic behaviors of nano-formulations by designing effective fabrication strategies and adjusting nanocarriers properties. In addition, side effects, such as acute toxicity and long-term immunotoxicity are usually the main cause of failure for nanomedicines at the stage of clinical

trials, therefore pushing scientists to develop novel biomaterials (e.g., polymers,²⁵ liposomes,²⁶ semiconductors,²⁷ and peptide²⁸) with appropriate physico-chemical properties to avoid those fatal limits.^{20,29}

Supramolecular chemistry - defined as “chemistry beyond the molecule”³⁰ - enables the formation of ordered yet dynamic assemblies on the basis of non-covalent molecular recognition moieties interacting through hydrogen bonds, metal coordination, host-guest ligation, π - π stacking, or van der Waals interactions,^{31,32} metal coordination, host-guest interactions, π - π interactions, and van der Waals interactions.^{33,34} These moieties can be designed to fabricate diverse supramolecular (bio)materials,³⁵⁻³⁸ featuring unique properties originating from the dynamic, stimuli-responsive and reversible characters of their constituents. By using specific and dynamic non-covalent interactions, engineered approaches to smart nanomedicine and drug delivery can be realized.³⁹ Clear advantages of this strategy are the molecular-level control of composition, an improved approach for incorporating and targeting drugs, and new methodologies to fabricate delivery vehicles that respond to a range of physiologic indicators.⁴⁰ The use of supramolecular moieties can further give rise to nanomedicine for specific encapsulation and controlled release of therapeutics. Moreover, the modularity of supramolecular interactions can facilitate the combination of several drugs within one delivery system in a programmable manner, avoiding time-consuming and tedious synthesis. In the context of clinical translation, features of supramolecular design may contribute additional advantages, specifically in endowing quantitative drug loading, the design of discrete delivery system, as well as a priori knowledge of carrier degradation and/or clearance mechanisms.³⁶

There are diverse supramolecular interactions, such as H-bonds, metal coordination, host-guest interactions, π - π interactions, and van der Waals interactions, truly enable the rapid growing applications in supramolecular nanomedicine. The nature of the involved **non-covalent** interaction must be carefully evaluated and chosen, depending on the modality of selectivity,

directionality and sensitivity which are sought. H-bonds are the fundamental interactions of various relevant functions in biological system, as they can be strong enough to hold biological (macro)molecules together, also can be weak enough to be broken in organisms and cells if necessary.⁴¹ H-bonds are the vital element of major biomacromolecules in life (such as DNA, RNA, proteins, aptamers and nucleosides).⁴² Furthermore, H-bonds in proteins contribute the arrangement of different types of folding and the specificity of protein-ligand interactions in molecular-scale recognition.⁴³ In addition to protein-ligand interactions, H-bonds are also involved in diverse intermolecular interactions, such as protein-nucleic acid, protein-liposome and protein-protein, complexes.⁴⁴ Thus as a well-known example, H-bonds between heterocomplementary nucleotides facilitate the linking of two strands of a DNA helix, in which the heteocomplementary base pairs of cytosine and guanine (or thymine and adenine) are connected by H-bonds.⁴⁵ Because of the often significant weakness of single H-bonds, the existence of numerous H-bonds in biological macromolecules endows the remarkable stability in aqueous environments by cooperativity effects. Moreover, H-bonds bridge the biological and synthetic sciences, implementing dynamic functions into assembled molecules and artificial materials, not achieved via the purely covalent bonds. Thus, benefitting from the reversible and dynamic nature of H-bonds, an additional element of responsivity is incorporated into nanomedicine, leading to novel functional biomaterials such as those with stimuli-dependent-properties and modular fashion, may even enable the biomimetic recapitulating of native biological signaling and/or structural cues.⁴⁶ Yet, despite the expansion of various strategies to design H-bonded biomaterials, the investigation of nanomedicine within such platform opposing the ordering effects via H-bonding forces is a newly emerging and extremely promising field.⁴⁷⁻⁴⁹

Considering their outstanding potential in clinical research and translation, H-bonded nanomedicines have attracted the growing attention from synthetic chemists, materials scientists, biologists and physicians.⁵⁰ Several outstanding reviews have been reported in the

field of supramolecular nanotheranostics.^{36,37,50-53} But still there has been no specific and systematic review so far to highlight the importance of H-bonded nanotheranostics in cancer treatment in detail. In view of the unique advantages of H-bonded nanotheranostics in cancer diagnosis and therapy, we here present a comprehensive review on the current state-of-the-art for designing novel H-bonded nanomedicines for precise diagnosis and targeted therapeutic drugs delivery.

We will focus here on the facts of engineered drug delivery systems designed through diverse H-bonding moieties, discuss molecular-scale organization in the design of these H-bonded nanomedicine, including (I) H-bonds driven assembly of small-molecule drugs, (II) H-bonds driven assembly of small-molecule drugs with polymeric carrier, and (III) H-bonds driven assembly of polymeric carriers encapsulating small-molecule drugs (**Figure 1, Table 1**). We will highlight the promises that may be achieved from the design, and the opportunities of clinical use of such technologies, with a specific highlight on their use in the emerging fields such as smart therapeutics and precision medicine. Additionally, it is our intention to convey the broad prospects and excitement in using H-bonding design within drug delivery as these strategies can facilitate molecularly defined medicines, promoted therapeutic performance, and customized treatment options.

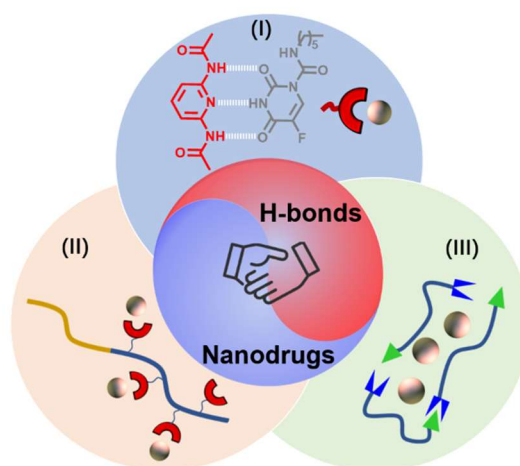


Figure 1: Nanomedicines designed through H-bonding interactions, including (I) assembly of small-molecule drugs, (II) assembly of small-molecule drugs with polymeric carrier, and (III) assembly of polymeric carriers encapsulating small-molecule drugs.

Table 1: The progress of literatures in drug delivery systems designed through diverse H-bonding moieties, including molecular-scale organization such as (I) assembly of small-molecule drugs, (II) assembly of small molecule drugs with polymeric carrier, and (III) assembly of polymeric carriers encapsulating small-molecule drugs.

Molecular-scale organization	Involved H-bonding moieties	Figure	Ref.
(I) Assembly of small-molecule drugs	Clofarabine/Raltitrexed (CA/RT)	Figure 3	80
	Pemetrexed/Cytidine (Pem/Cyt)	Figure 4,5	66,81
	Methotrexate/5-Fluorouracil (MTX/5-FU)	Figure 6	82
	Uridine/Deoxyadenosine (U/A)	Figure 7	83
(II) Assembly of small molecule drugs with polymeric carrier	Urea/Doxorubicin (U/DOX)	Figure 8	84
	Thiourea/ Doxorubicin (TU/DOX)	Figure 9	67
	Hydroxyl/carbonyl (-OH/-C=O)	Figure 10	85
	Electronegative atoms (O, N, F)/Hydroxyl (-OH)	Figure 11	86
	Cyanuric acid/Methotrexate (CA/MTX)	Figure 12	87
	Thymine/Methotrexate (Thy/MTX)	Figure 13	88
(III) Assembly of polymeric carriers encapsulating small-molecule drugs	2,6-diaminopyridine/Carmofur (DAP/HCFU)	Figure 14	76
	Adenine/Uracil (A/U)	Figure 15,19,22	89-91
	Carboxylic acid/Oxygen atom (PAA/PEO- <i>b</i> -PCL)	Figure 16	92
	Adenine/Thymine (A/T)	Figure 17,18	64,93
	Uracil/2,6-diaminopyridine (U/DAP)	Figure 20	68
	Adenine/Adenine (A/A)	Figure 21	94
	-NH-, -OH/-C=O	Figure 23	95
Cytosine/Guanine (GEM/ACV)	Figure 24	96	

Principles of assembly in H-bonded nanomedicine

In H-bonded system, the strength of H-bonds can be adjusted through chemical design (Figure 2), where the number of H-bonds,³¹ solvation, along with the secondary electrostatic interactions between adjacent H-bonds⁵⁴ have a vital effect on the stability of H-bonding arrays. Two H-bonding moieties bearing donor groups (D) acceptor sites (A) can interact specifically and selectively, which is described via a thermodynamic association constant (K_a). In nonpolar

solvents, such specific H-bonding interaction is generally dominant, in turn allowing a selective A/B interaction in the sense of a “key-lock” bridge models. Both, moderately polar solvents and dipolar repulsion⁵⁵ can diminish the strength of H-bonds significantly, as then enthalpic benefits of forming selective A/B H-bonding interaction offset competitive H-bonding with those from the surrounding solvent, including water, which is abundant in biological environments. Therefore, many small molecules with quite associative H-bonds in nonpolar organic solvents do not form appreciably strong H-bonds in water. Accordingly, a majority of H-bonds directed platforms, which are extensive, typically use noncompetitive nonpolar organic solvents.⁵⁶ On the other hand, the first example where the assembly is promoted by H-bonding moieties directly in water, is demonstrated by Bouteiller, Colombani et. al,⁵⁷ reporting rod-like H-bonding assemblies in water via a penta-urea sticker decorated with poly(ethylene oxide) (PEO) side chains, without alkyl chains or alkylene spacers to protect the H-bonds from the competitive water molecules.

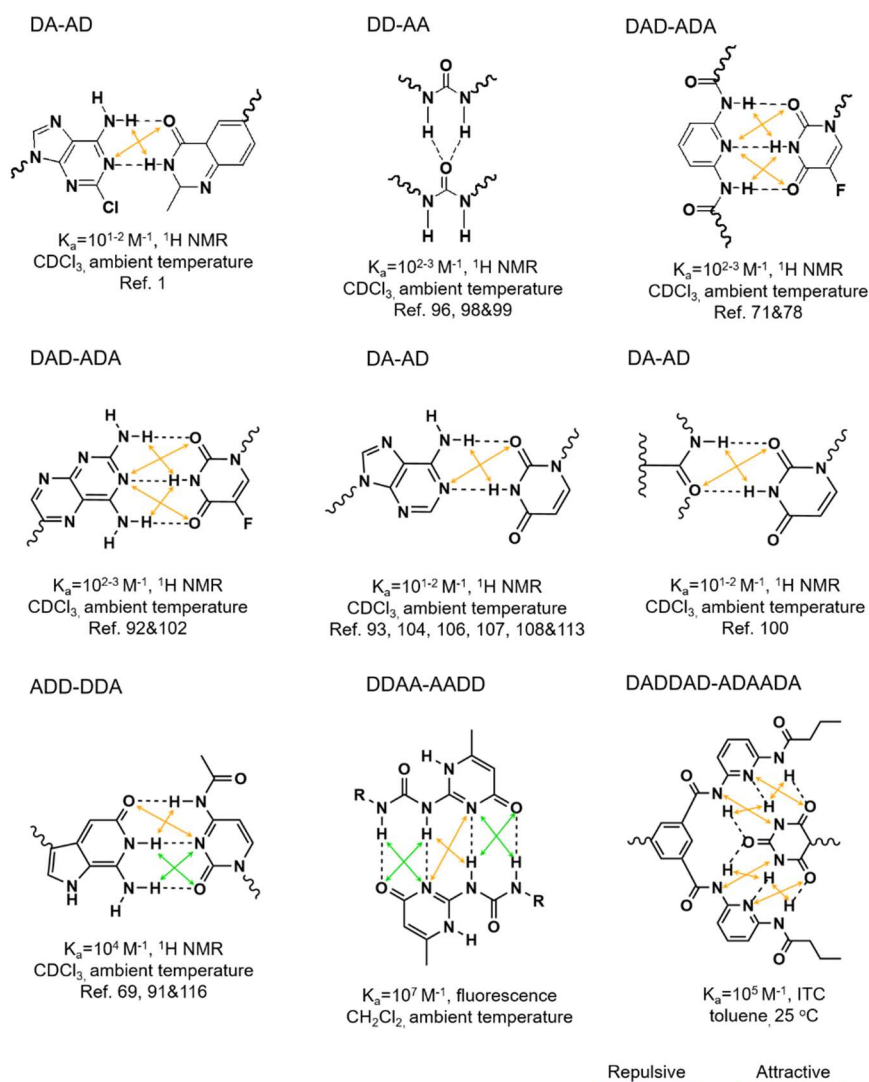


Figure 2: Examples of H-bonding arrays varying the number of H-bonds and their selective association in solvent. Arrows indicate secondary electrostatic interactions (yellow: repulsive; green: attractive). This figure has been reproduced from ref.³¹ with permission from American Chemical Society, copyright 2016.

In contrast, several man-made H-bonded systems have judiciously exploited robust H-bond moieties,⁵⁸ with additional collective interactions (e.g. aromatic stacking,⁵⁹ and/or the hydrophobic interaction⁶⁰) to afford the energetic costs of breaking H-bonds formed with water molecules, in turn achieving self-assembly in aqueous media. The conjunction of H-bonds with hydrophobic interactions, endowing the interface of a monolayer and thus shielding H-bonds from water, can furnish a suitable environment for H-bonding formation. The recognition sites

involving H-bonds in biological systems are indeed shielded from the competing water molecules within the hydrophobic microenvironments, such as those existed in the cell membranes, protein pockets,⁶¹ or aromatic stacks within DNA helix⁶² or G-quartets.⁶³

The principle of assembly in H-bonded nanomedicine thus relies on the use of two types of interactions, H-bonds and hydrophobic interactions, that function together, where H-bonds directed recognition occurred within the shielding hydrophobic microenvironment in aqueous solution. The specific pairwise recognition and stimuli responsive features of H-bonding systems are putting the predominant properties into H-bonded nanomedicine, namely, their reversible linking and reorganization, in turn generating responsivity and adaptivity to the external stimuli. H-bonds interactions⁶⁴⁻⁶⁶ can stabilize nanodrug in physiological media through non-covalently cross-linking, also enhance the drug loading capacity thanks to the molecular recognition and association. Moreover, stimuli-responsive drug release⁴⁰ can be steadily realized by triggering the H-bonding dissociation, generally induced by the parameters such as temperature,⁶⁷ pH,⁶⁸ or radiation.⁶⁶ **Thermal responsiveness of H-bonds is an important characteristic to afford intelligent delivery and responsive release. Combined with photothermal agent, rapid drug release, then aggregation of drugs in nucleus could be realized upon (near-infrared) laser irradiation, which is due to the destabilization of H-bonds induced by the photothermal effect. It is also highly anticipated that thermal responsive H-bonded nanomedicine, featured by intelligent and efficient anticancer bioactivity, will bring a new horizon of advanced cancer nanomedicine.** Especially in the use of thermally triggered gels, where superparamagnetic nanoparticles generate sufficient thermal energy to rupture the H-bonds to release an embedded drug are prominent components in the development of site-specific release systems.⁶⁹ Therefore, H-bonded nanomedicine, featured by their enhanced stability, can lead to promoted circulation times and superior transport performance, with the ability to trigger drug release in the tumor microenvironment, thus become gaining momentum in the area of cancer therapy, can reveal in-depth innovation in nanomedicine strategies. **It is**

noteworthy that the preparation H-bonded complexes is also a crucial step in the field of nanomedicine, which can affect the properties of the H-bonded complexes (e.g., size, geometry, surface features, elasticity, porosity), also influence the biological process and ultimately the therapeutic outcomes. Currently, the fabrication methods of H-bonded complexes preparation are mostly involving nanoprecipitation^{39,70-73} and ultrasonic emulsification.⁷⁴⁻⁷⁶

In addition, the development of efficient anti-bacterial and anti-inflammatory materials with novel mechanism of action is of great interest in view of research and clinical demand. H-bonded nanomedicine with integrated multi-functions, especially fast thermally reversible formation–dissociation processes,⁷⁷⁻⁷⁹ also hold great promising potential in other diseases such as inflammatory diseases.

H-bonds driven assembly of small-molecule drugs

Model systems, where one small drug assembles with another one in a singular ordering process to afford supramolecular nanomedicine. Thanks to the specifically interacting H-bonds collectively with hydrophobic interactions, such carrier-free supramolecular nanomedicine featured by amphiphilic nanoparticles with H-bonding linkage in water can be realized. Compared to conventional free drugs, such supramolecular systems exhibit longer blood retention half-life, so to facilitate accumulation of drugs into the tumor tissues, and to promote tumor cellular uptake.^{29,97} Most importantly, H-bonded nanomedicine can exhibit nanoscale characteristics, featured with drug-self-delivery system for tumor therapy, in which the antitumor drugs can self-deliver without the need for nanocarriers.⁹⁸ After tumor cellular internalization, H-bonds interactions between hydrophilic and hydrophobic drugs are prone to responsively break to release the drug, in a controlled and localized manner and with reduced adverse effects, thus achieving enhanced anticancer activity *in vitro* and *in vivo*.⁹⁹ In addition, this straightforward self-assembly does not require any sophisticated synthetic pathways, consequently avoiding undesirable changes in drug structure and property, thus endowing a feasible method for mass production of nanomedicine.¹⁰⁰⁻¹⁰³

Gefitinib (GEF) and tripeptide tyroservatide (YSV) which are both clinically approved chemotherapeutic molecules against non-small-cell lung cancer, have been employed to construct drug-self-delivery systems through molecular recognition, driven by supramolecular interactions including H-bonds and π - π stacking. The assembled GEF-YSV nanomedicine not only solves the poor aqueous solubility issues of GEF, which hinders the circulation to approach its effective blood drug concentration, but also gathers the divergent drug function mechanisms of both GEF and YSV. Thus it demonstrates a remarkable therapeutic efficiency towards non-small-cell lung cancer.¹⁰⁴

Benefiting from H-bonds driven molecular recognition, a hydrophobic antitumor drug clofarabine (purine nucleoside analogue, CA) and a hydrophilic antitumor drug raltitrexed (quinazoline-based folate analogue, RT), are self-assembled into supramolecular nanomedicine (**Figure 3**),⁸⁰ where CA acts as direct inhibitor of ribonucleotide reductase and reducer of DNA polymerase, while RT exerts its cytotoxic activity via the specific inhibition of thymidylate synthase. Such H-bonded nanomedicine generated from CA and RT molecular recognition, can self-organize in aqueous solution into highly stable spherical nanoparticles. Moreover, H-bonded nanomedicine build through rational combination of CA and RT illustrates the ability to decrease the side effects of free CA or RT drugs which could have induced a synergistic cytotoxicity thanks to their different mechanisms of action. In this way, the antitumor efficiency is considerably enhanced, as evidenced by in vitro and in vivo studies.⁸⁰

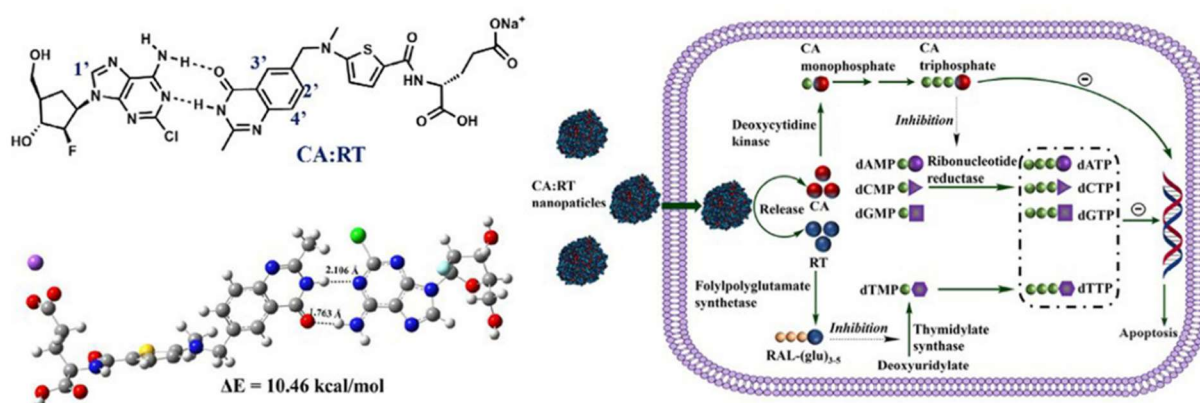


Figure 3: H-bonding driven CA/RT assemblies and anticancer mechanism of CA/RT nanomedicine. This figure has been reproduced from ref. ⁸⁰ with permission from American Chemical Society, copyright 2018.

Pemetrexed (Pem), a novel pyrrolo[2,3-d] pyrimidine-based antifolate analog and also a first-line chemotherapeutic molecule, is self-assembled with synthesized cytosine-containing diselenides (Cyt-SeSe-Cyt) via H-bonding interactions, yielding diselenide-pemetrexed (Pem/Se) assemblies. This system can act as tumor chemotherapy, radiotherapy and immunotherapy (**Figure 4**).⁶⁶ Specifically, γ -radiations not only cleave H-bonding interactions between Pem and Cyt, resulting in the controlled release of pemetrexed for chemotherapy, but also oxidize diselenide to seleninic acid, which suppresses the expression of human leukocyte antigen E in tumor cells, in turn activating the immune response of NK cells. In this way, radiotherapy was combined with tumor chemotherapy and immunotherapy, constituting a novel strategy for cancer treatment. Additionally, Pem in the form of H-bonded nanomedicine owns the suited stability and tumor-targeting efficiency, therefore further improves anti-tumor efficiency with reduced side effect.

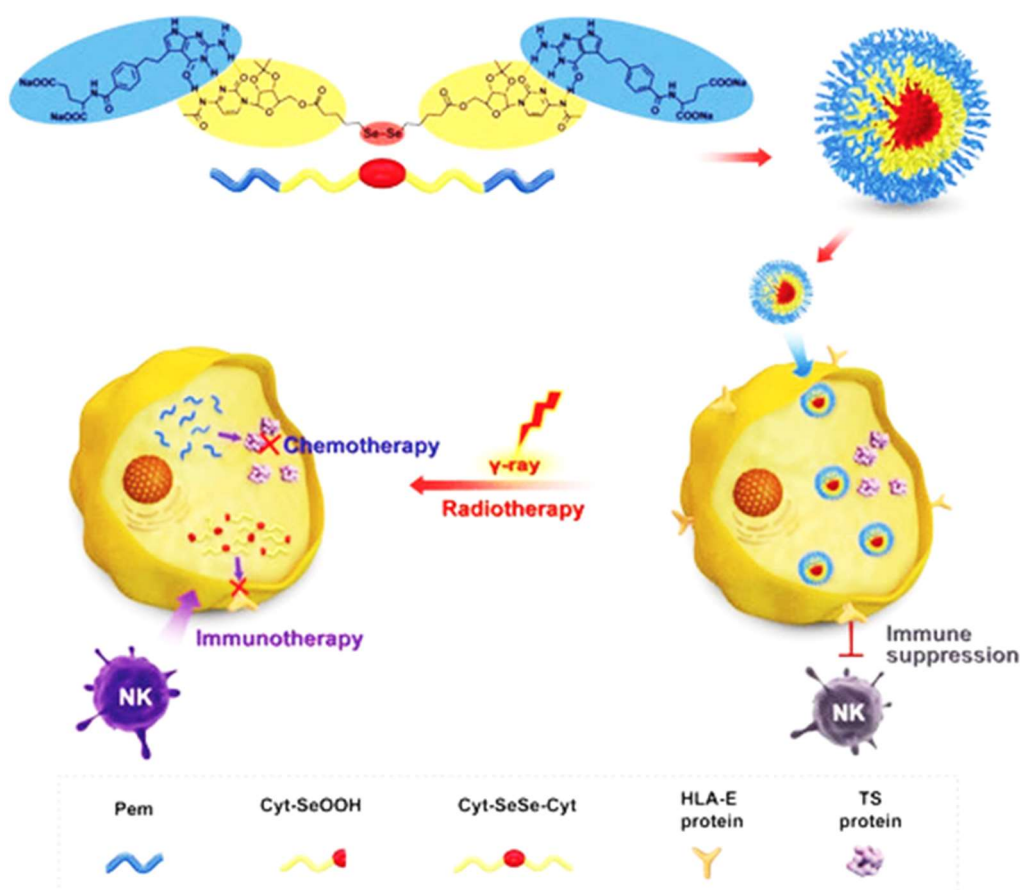


Figure 4: H-bonding driven Pem/Cyt assemblies for combined cancer immunotherapy with radiotherapy and chemotherapy. This figure has been reproduced from ref.⁶⁶ with permission from John Wiley & Sons, Inc., copyright 2020.

Very recently a **similar supramolecular nanomedicine** was reported for delivery of Pem and β -seleno ester into tumor tissues to achieve a synergistic chemotherapy and immunotherapy (**Figure 5**), using the same H-bonding interactions between Pem and Cyt.⁸¹ Cyt linked with β -seleno ester was associated with Pem via triple H-bonds to form nanoparticles **via nanoprecipitation**. These nanoparticles show higher transmembrane efficiency than free Pem and tend to localize in tumor sites. Considering the aberrant reactive oxygen species (ROS) level in tumor cells and the oxidation responsiveness of β -seleno ester, β -seleno ester is converted to seleninic acid in situ, subsequently transfers to tumor cell surface to suppress human leukocyte antigen E, thus resulting in the activation of NK cells. In addition, seleninic acid efficiently depletes intracellular glutathione (GSH), causing the rapid accumulation of ROS, thus further restraining tumor growth when associated with Pem-mediated chemotherapy.

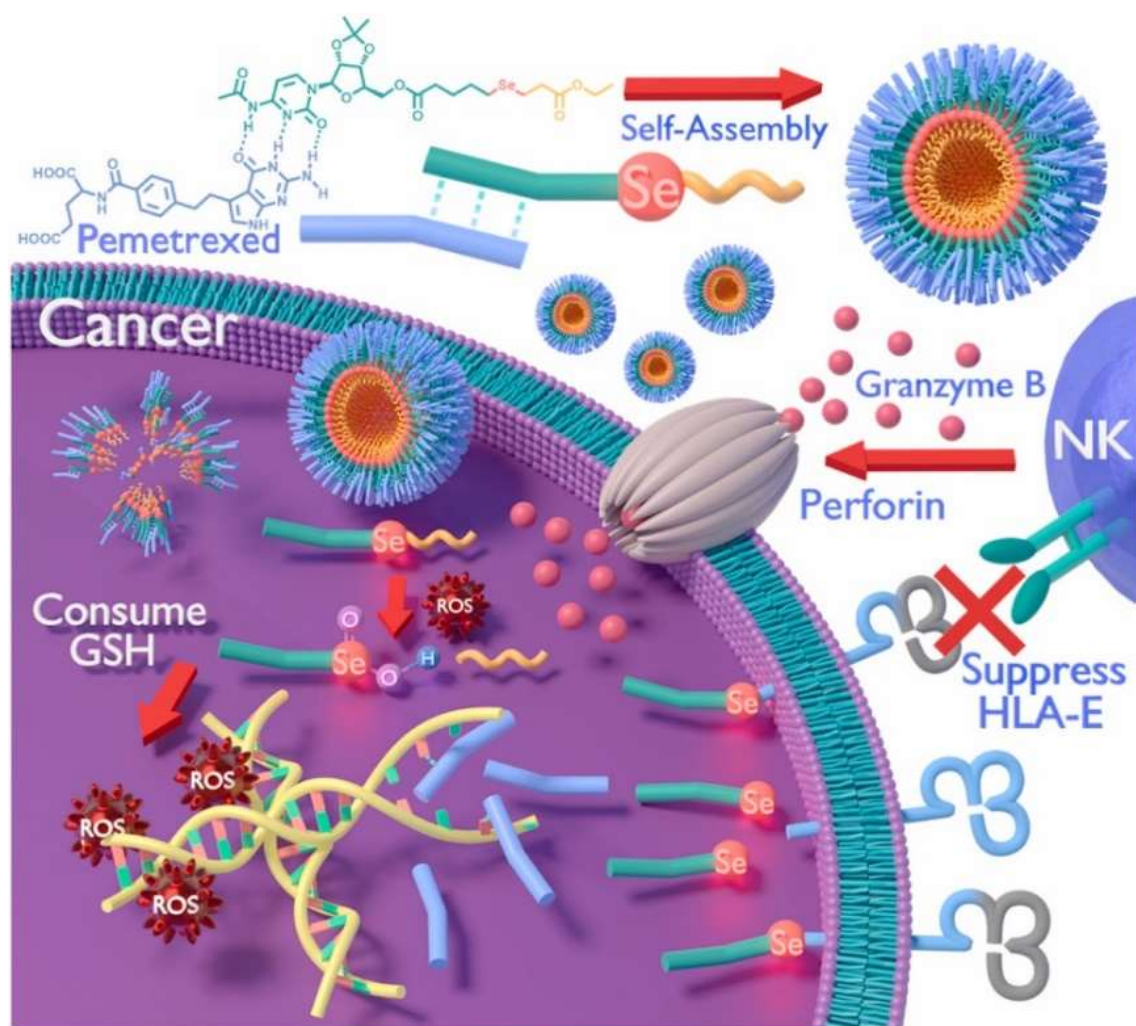


Figure 5: H-bonded nanodrug particles formed from Pem and Cyt linked with β -seleno ester, and mechanism underlying H-bonded nanomedicine synergistic chemotherapy and immunotherapy. This figure has been reproduced from ref.⁸¹ with permission from Elsevier, copyright 2022.

Inspired by Watson-Crick G.C base pairing, FDA-approved the chemotherapeutic molecule methotrexate (MTX, a folate analogue and an inhibitor of dihydrofolate reductase) and 5-fluorouracil (5-FU, a pyrimidine analogue and an inhibitor of DNA/RNA synthetase), sequentially aggregated into MTX/5-FU nanoparticles via a H-bonding directed assembly (**Figure 6a**).⁸² Within such MTX/5-FU nanoparticles, both MTX and 5-FU demonstrate different but complementary action sites and antitumor mechanisms, therefore the combination of MTX with 5-FU into carrier-free nanomedicine can significantly enhance the antitumor synergetic efficiency with reduced side effects if compared to conventional strategy involving

free drugs. Sequentially, a weak acidity-responsive polyethylene glycol (PEG) is localized onto the MTX/5-FU nanoparticles surface, to temporarily shield the self-targeting function of MTX and thus to increase the time during which it circulates into blood. Once PEG involved MTX/5-FU nanoparticles reach the weakly acidic tumor microenvironment (TME), the PEG corona is cleaved from MTX/5-FU nanoparticles surface, re-exposing MTX thus recovering its self-recognition ability and notably elevate the tumor cells uptake. Furthermore, de-PEGylated MTX/5-FU nanoparticles react to the stronger acidity of lysosome, triggering H-bonds dissociation and core disassembly and finally leading to the burst release of both MTX and 5-FU for chemotherapy.⁸² Further in vitro and in vivo studies confirmed that the H-bonded nanomedicine indeed exhibited preferable accumulation at tumor sites along with extraordinarily synergistic chemotherapeutic effects (**Figure 6b**).

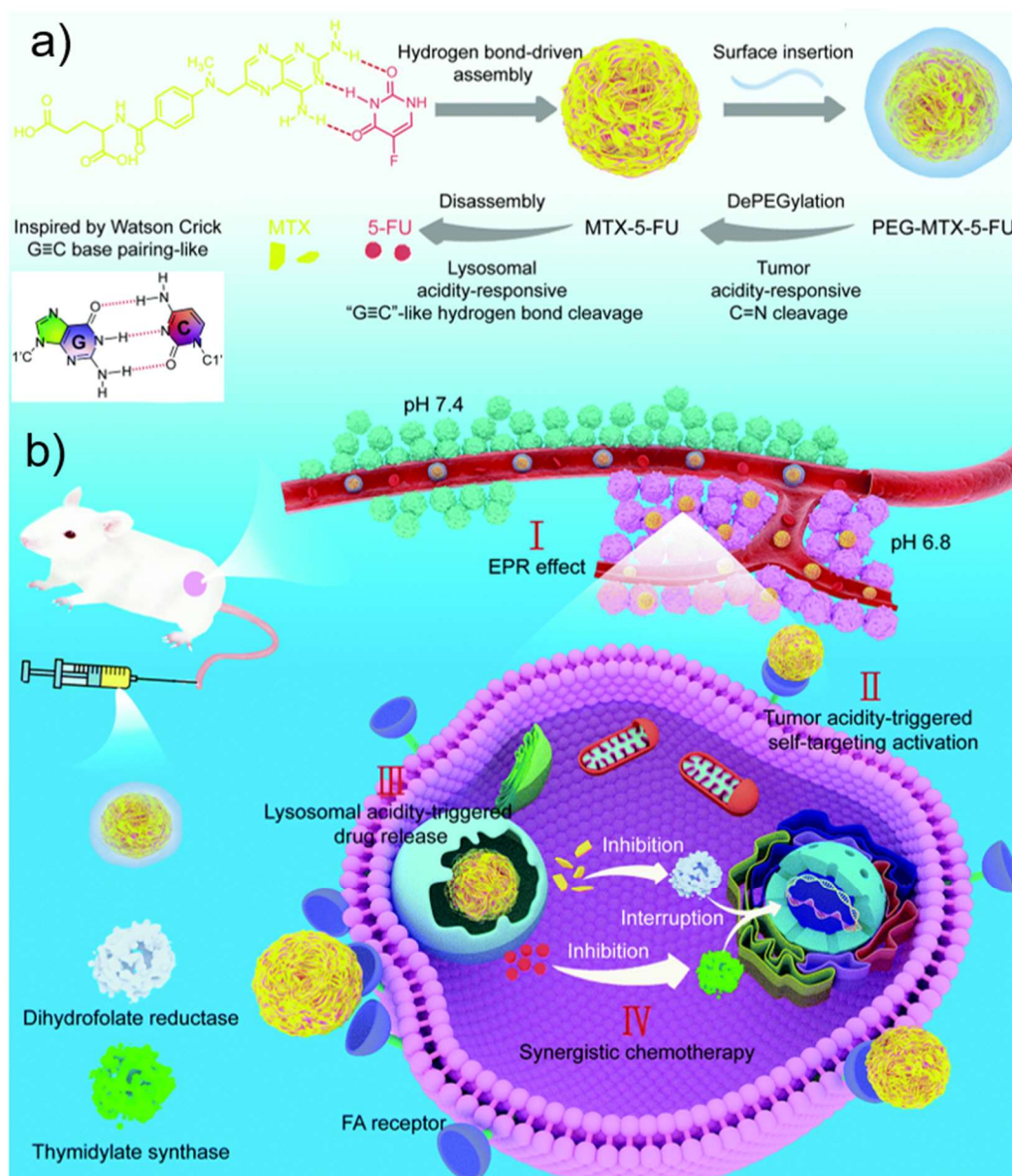


Figure 6: (a) Fabrication of PEG-MTX/5-FU nanoparticles via Watson-Crick G-C-like H-bonds-driven supramolecular self-assembly followed by dynamic PEGylation. (b) Illustration of tumor acidity-triggered self-targeting activation and lysosomal acidity triggered drug release of PEG-MTX/5-FU nanoparticles. This figure has been reproduced from ref.⁸² with permission from Royal Society of Chemistry, copyright 2020.

Another similar strategy relies on self-assembled phospholipids-liposomes. Hydrophilic head and hydrophobic tails of phospholipids are linked together via hydrogen-bonded heterocomplementary uridine (U) and adenosine (A, **Figure 7**).⁸³ These upgraded phospholipids self-assemble into liposome-like bilayer nanostructures in aqueous media,

exhibiting a fast stimuli-responsive ability ascribed to H-bonding interaction. In vitro and in vivo studies indeed show that H-bonded liposomes from nucleoside phospholipids could effectively transport therapeutic agents such as doxorubicin (DOX) into tumor tissues. They rapidly enter the tumor cells, and lead to a controllable release of DOX in response to the intracellular acidic media, therefore yielding a higher antitumor activity when compared to conventional liposomes.⁸³

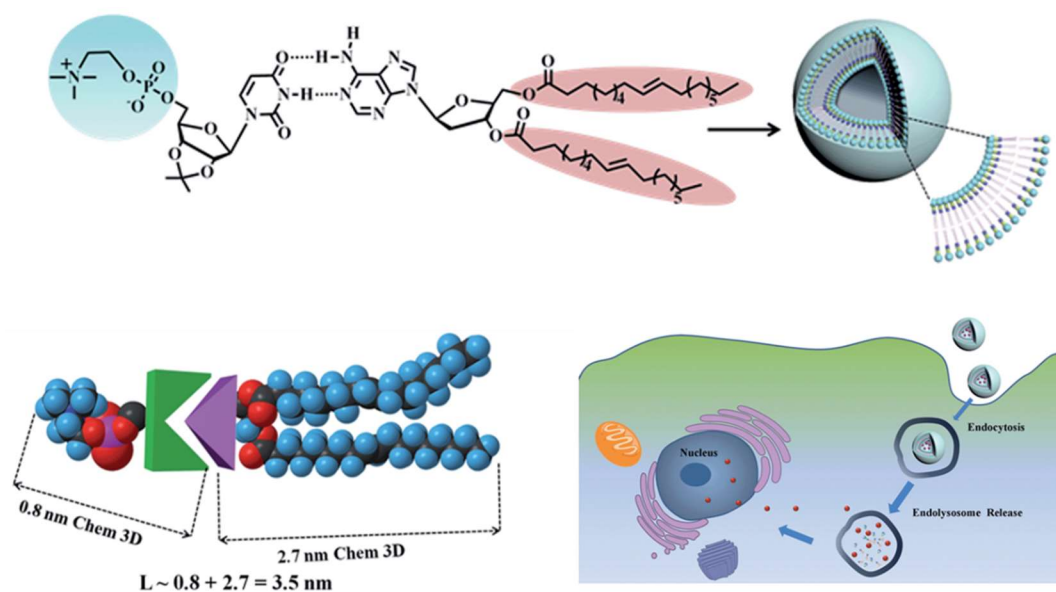


Figure 7: H-bonded liposome assembled from hydrophilic and hydrophobic phospholipids to afford bilayer structures in aqueous solution, and schematic representation for cellular uptake of H-bonded liposomes along with controlled intracellular DOX release. **This figure has been reproduced from ref.⁸³ with permission from Royal Society of Chemistry, copyright 2015.**

H-bonds driven assembly of small-molecule drugs with polymeric carrier

Driven by H-bonding forces, urea moieties are known to associate to carboxylate derivatives that are present in several antitumor drugs, such as DOX and paclitaxel (PTX), and their isosteres (e.g. sulfonates, phosphonates, and phosphates).^{105,106} This property can be exploited to fight with cancer cells. Therefore, urea-functional block copolymers, poly(ethylene glycol)-*b*-poly(ethyl-*co*-urea carbonate), with differing urea contents and polymer molar mass, were synthesized (**Figure 8a**) to act as an efficient carrier of these drugs via multiple H-bonding.⁸⁴ The incorporation of urea moieties significantly lower the critical micelle concentration (CMC)

of these block copolymers, promoted the kinetic stability of micelles enhance DOX loading contents (**Figure 8b**) and facilitated the generation of drug-loaded micelles with desirable size along with a narrow size distribution.¹⁰⁷ Importantly, the DOX-loaded micelles indeed exert effective cytotoxic effect against HepG2 cells, a model cancer cell line, highlighting the importance of the control of H-bonding interactions in stabilizing nanostructures and enhancing antitumor efficiency for nanomedicine.

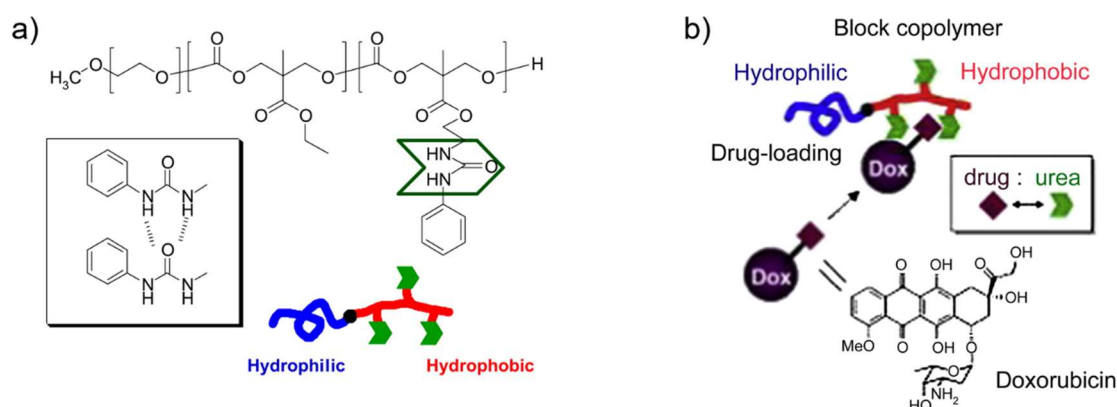


Figure 8: (a) Schematic representation of urea-functional poly(ethylene glycol)-*b*-poly(ethyl-co-urea carbonate) with H-bonding interaction, (b) drug loading mediated via H-bonding interaction between urea and DOX. This figure has been reproduced from ref.⁸⁴ with permission from Elsevier, copyright 2010.

As another system, amphiphilic diblock copolymers poly(ethylene glycol)-*b*-poly(L-lysine) (mPEG-*b*-PLL), bearing different H-bonding moieties (urethane, urea, and thiourea groups) were synthesized to test their capacities for the co-delivery of antitumor drugs (e.g., DOX) together with photothermal agents (e.g., indocyanine green, ICG) (**Figure 9**).⁶⁷ The resulting supramolecular polymeric micelles displayed enhanced micelle stabilities due to H-bonds between urea moieties in the polymers. Moreover, H-bonds between urea/thiourea and DOX endow the carriers with enhanced drug loading efficiency, decreased micelles size, as well as slower drug release profiles. When exposed to near-infrared laser irradiation, destabilization of H-bonds through photothermal effect triggers fast and controlled DOX releases from H-bonded

micelles, which dramatically promotes the aggregation of the drugs in the nuclei, thus resulting in the enhanced anticancer activity.⁶⁷

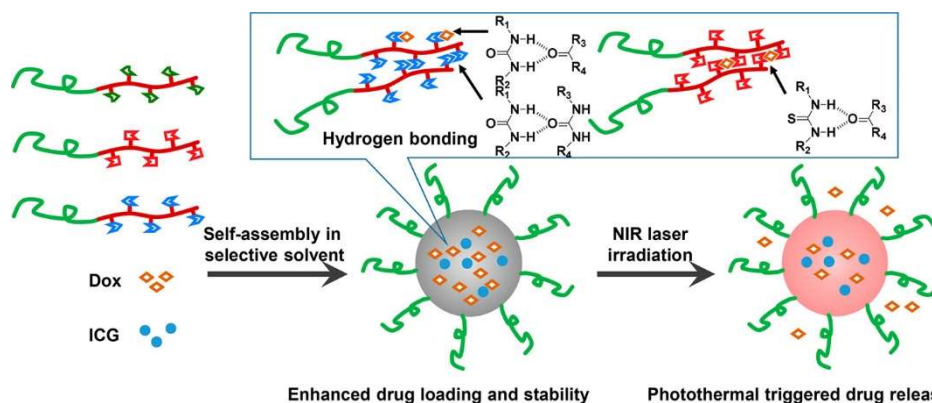


Figure 9: DOX-loading and NIR-triggered drug release from H-bonding-enhanced micelles. This figure has been reproduced from ref.⁶⁷ with permission from American Chemical Society, copyright 2018.

Another strategy relies on a biodegradable ABA type triblock copolymer (mPEG-*b*-HRSCP-*b*-mPEG), bearing alternated hydroxyl and disulfide groups on the main chain. The incorporated hydroxyl groups can not only regulate the hydrophilicity of mPEG-*b*-HRSCP-*b*-mPEG, but also form H-bonds with DOX, therefore enhancing DOX loading efficiency and solubility and finally allowing a controlled release of DOX due to the disruption of pH-sensitive H-bonds of polymeric micelles (**Figure 10**).⁸⁵

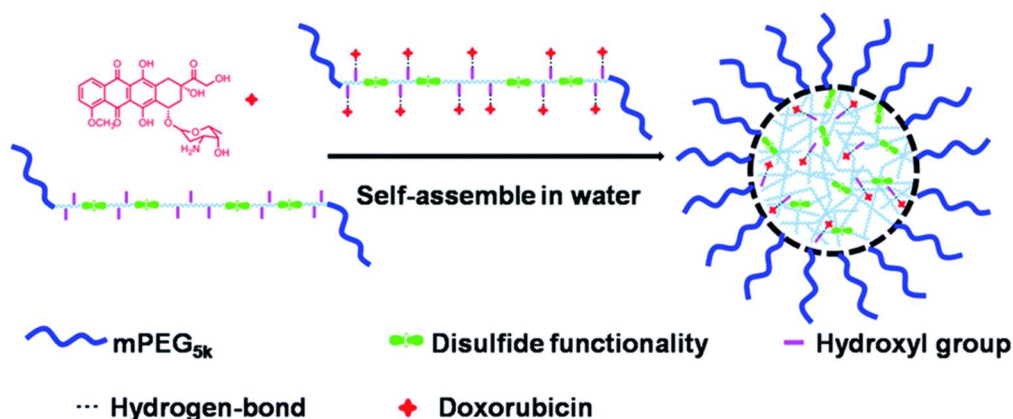


Figure 10: H-bonds mediated DOX-loading into mPEG-HRSCP-mPEG to afford the H-bonded micelles. This figure has been reproduced from ref.⁸⁵ with permission from Royal Society of Chemistry, copyright 2014.

An alternate therapeutic route can also be based on hollow microcapsules made of poly(L-glutamic acid) (PLGA) and chitosan (CS) which are built through layer-by-layer (LbL) assembly using melamine formaldehyde (MF) microparticles as sacrificial template (**Figure 11a**). 5-FU was chosen to investigate the drug loading and release properties of the obtained PLGA/CS microcapsules, showing high 5-FU loading capacity, ascribed to spontaneous deposition of 5-FU induced by H-bonding between 5-FU and PLGA/CS microcapsules (**Figure 11b**).⁸⁶ Moreover, the release rate of 5-FU after loading in PLGA/CS microcapsules drastically slows down, and shows sustained release behavior. In vitro cytotoxicity evaluation by the MTT assay revealed good cell viability over the entire concentration range of PLGA/CS microcapsules.

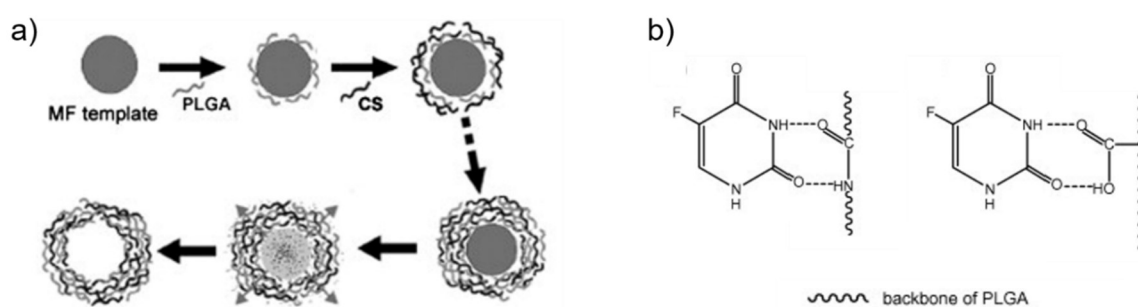


Figure 11: (a) Preparation of hollow PLGA/CS microcapsules, and (b) scheme of the most stable structures of the hydrogen-bonded complexes between 5-FU and PLGA. **This figure has been reproduced from ref.⁸⁶ with permission from Elsevier, copyright 2011.**

A tumor-targeting amphiphilic peptide with cyanuric acid conjugated to the hydrophobic tail A tumor-targeting amphiphilic peptide, CA-C11-GGGRGDS, with a terminal cyanuric acid (CA) moieties has also been reported (**Figure 12a**). Thanks to heterocomplementary H-bonding interactions between CA and MTX, CA-C11-GGGRGDS exhibits a satisfying ability to upload and release anti-tumor drug of MTX. The complementary H-bonding interactions between MTX and terminal CA moieties (**Figure 12b**)⁸⁷ result in an increase in the overall hydrophobicity of the assembled system, leading to the formation of MTX-loaded nanorods at low MTX concentration, and nanofibers at high MTX concentration. As the MTX release, the

hydrophilic-hydrophobic balance is changed, inducing the recovery of micelles from nanorods or nanofibers and so reflecting a reversible supramolecular morphology transition from spherical micelles to nanofibers.

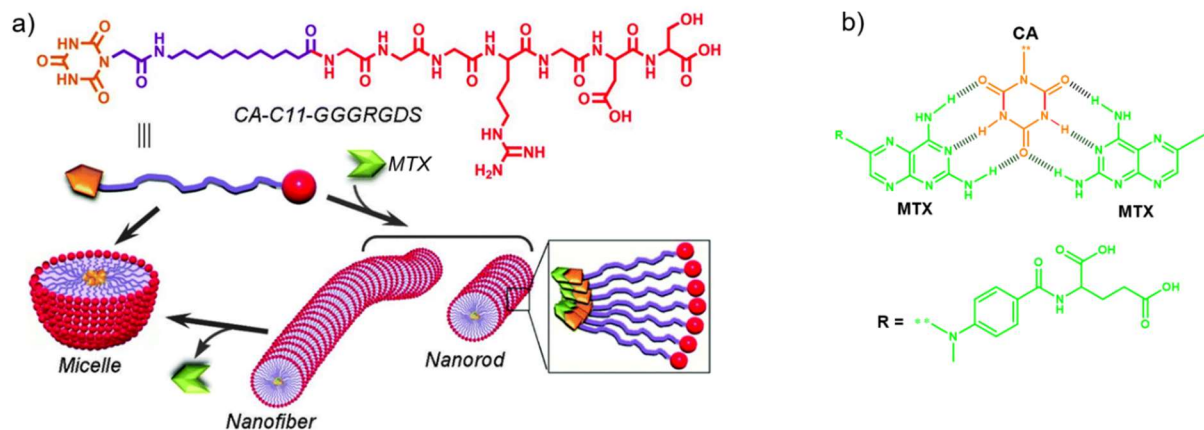


Figure 12: Molecular structure of the amphiphilic peptide CA-C11-GGGRGDS and its self-assembly with MTX (a), and scheme of multiple H-bonding interactions between CA and MTX (b). This figure has been reproduced from ref.⁸⁷ with permission from Royal Society of Chemistry, copyright 2015.

Another system relies on a thymine-functionalized six-membered cyclic carbonate monomer (TAC) which can be synthesized via Michael-addition reaction between thymine and acryloyl carbonate (AC). The corresponding thymine-functionalized amphiphilic mPEG-*b*-PTAC diblock copolymer is then generated by ring-opening polymerization using mPEG as macroinitiator. Due to multiple H-bonding interactions between exposed thymine moieties of hydrophobic PTAC segments and MTX molecules, mPEG-*b*-PTAC was proven as a powerful controlled drug delivery system with high drug uploading capacity and entrapment efficiency. Moreover, MTX-loaded mPEG-*b*-PTAC indeed demonstrates a sustained drug release behavior and also a pH-sensitive MTX-release profile to tumor cells (**Figure 13**).⁸⁸ MTT assays also showed lower toxicity of amphiphilic mPEG-*b*-PTAC diblock copolymer but higher potent cytotoxic activity of MTX-loaded micelles against HeLa cells.

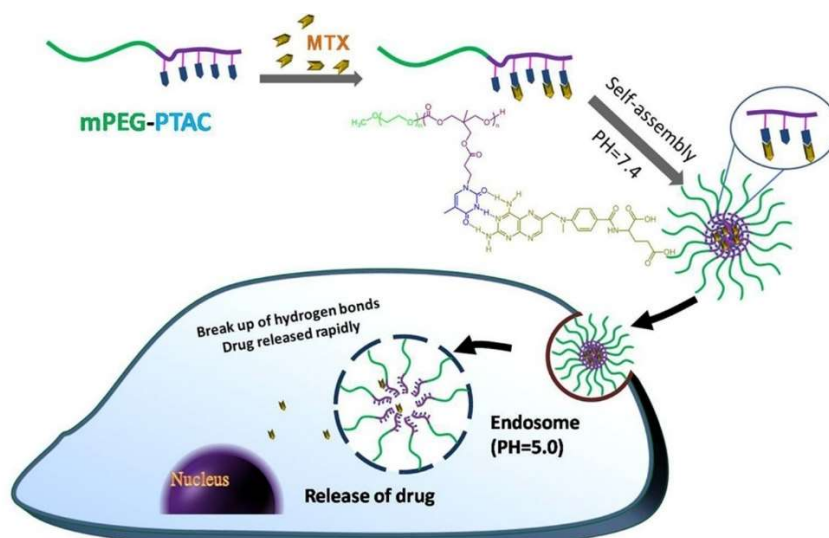


Figure 13: Thymine-functionalized amphiphilic biodegradable mPEG-*b*-PDTC diblock copolymers for enhanced loading contents and controlled release of MTX. This figure has been reproduced from ref.⁸⁸ with permission from Royal Society of Chemistry, copyright 2015.

Very recently, we used an amphiphilic ABA triblock copolymer POEGEA-*b*-P(DAPA-*co*-TFEA)-*b*-POEGEA, with hydrophilic and biocompatible POEGEA block (poly(oligo (ethylene glycol) ethyl acrylate)) as exterior corona, and hydrophobic P(DAPA-*co*-TFEA) block (poly(diaminopyridine acrylamide-*co*-2,2,2-trifluoroethyl acrylate)), which displays multiple H-bonding 2,6-diaminopyridine (DAP) moiety, as interior core (**Figure 14**).^{76,108} The presence of DAP moiety within the hydrophobic core enhances the loading content of carmofur (1-hexylcarbamoyl-5-fluorouracil, HCFU, an approved hydrophobic antitumor agent) thanks to the establishment of selective DAP/HCFU triple H-bonding interactions. Concomitant incorporation of IR780, a photothermal agent, promoted the development of a combined chemo-photothermal therapy (CT/PTT) drug delivery platform, where HCFU is released in a controlled manner, owing to the dissociation of DAP/HCFU H-bonding interactions under temperature stimulus.

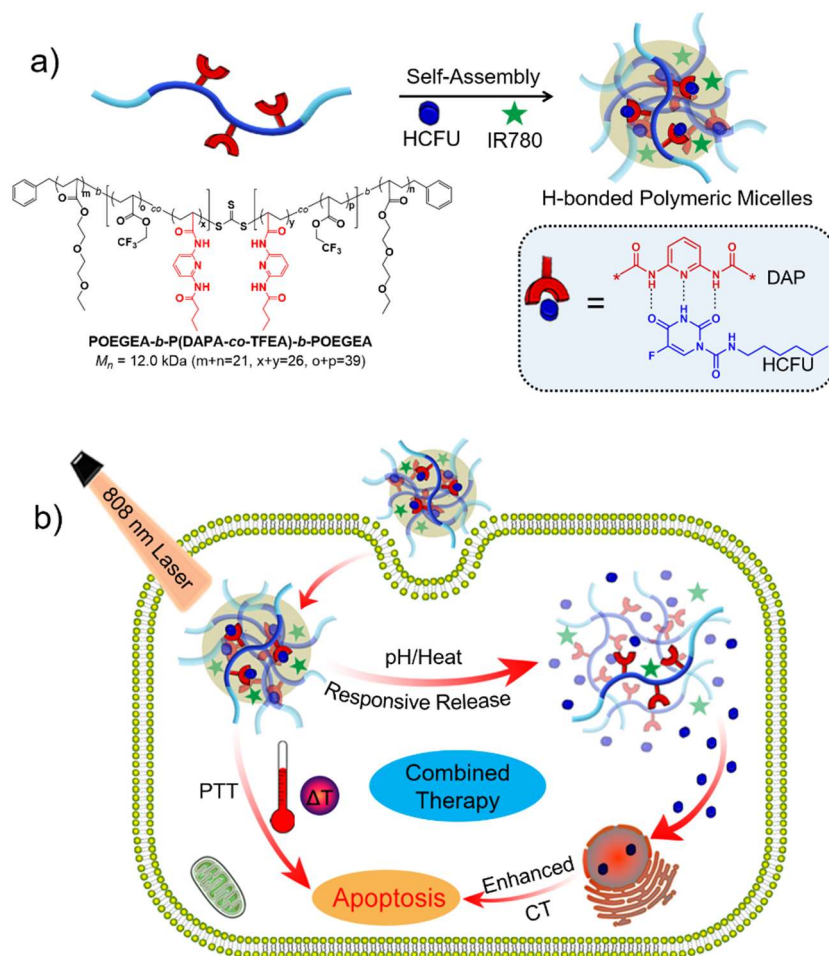


Figure 14: HCFU/IR780 co-loading and assembly to yield H-bonded nanomedicine (a), scheme of pH/thermal-triggered HCFU release and combined CT/PTT (b). This figure has been reproduced from ref.⁷⁶ with permission from Royal Society of Chemistry, copyright 2022.

H-bonds driven assembly of polymeric carrier encapsulating small-molecule drugs

Adenine-terminated poly(ϵ -caprolactone) (PCL-A) and uracil-terminated poly(ethylene glycol) (PEG-U) were used to fabricate H-bonded nanocarriers driven by adenine/uracil association, which show stimuli-responsive abilities and can encapsulate and then deliver DOX in a controlled manner (**Figure 15**).⁸⁹ H-bonded micelles assembled from PCL-A/U-PEG are sufficiently stable in water, but prone to disassemble rapidly in acidic condition due to pH sensitivity of H-bonding interactions. The low cytotoxicity of H-bonded micelles was confirmed by MTT assay against NIH/3T3 normal cells. In vitro DOX release profiles from H-bonded nanomedicine is notably faster in mild acidic medium (pH =5.0) than in physiological

environment (pH 7.4). Moreover, MTT assay against HeLa cancer cells revealed that DOX-loaded micelles demonstrate high antitumor efficiency.

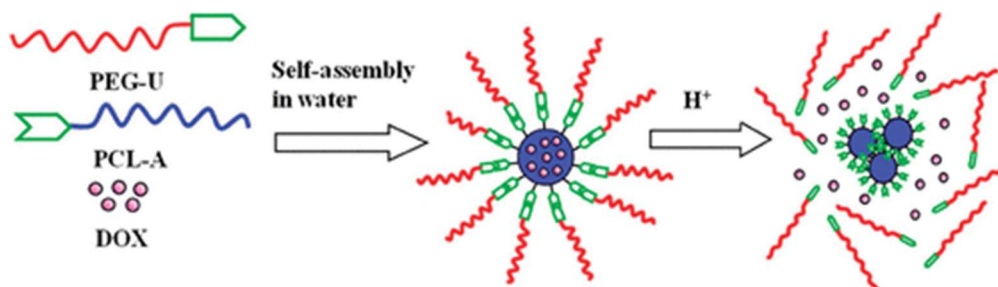


Figure 15: Micellization of self-assembled PEG-U and PCL-A for encapsulation and pH-driven controlled delivery of DOX. This figure has been reproduced from ref.⁸⁹ with permission from American Chemical Society, copyright 2011.

Another reported system relies on amphiphilic block copolymer micelles which constitute nanocarriers of triclosan, a hydrophobic active antibacterial drug (**Figure 16**).⁹² A film is constructed by layer by layer deposition onto a hydrophobic surface of poly(acrylic acid) (PAA) as H-bonds donor and biodegradable poly(ethylene oxide)-block-poly(ϵ -caprolactone) (PEO-*b*-PCL) micelles as H-bonds acceptor. The resulting film can be peeled off the hydrophobic surface since it weakly adheres to it. Considering the sensitive nature of H-bonds used to build these multilayers, the film is steadily de-constructed to release the micelles when exposed to physiological conditions. *In vitro* Kirby-Bauer assays against *Staphylococcus aureus* revealed that triclosan-loaded micelles layer-by-layer film indeed can deliver significant amounts of active drugs, to efficiently inhibit the growth of bacteria. Such noncovalent system provides with a straightforward route to upload active small, unchanged therapeutics for biological and biomedical coatings.



Figure 16: H-bonding layer-by-layer assembly of block copolymer micelles for triclosan delivery vehicles from surfaces. This figure has been reproduced from ref.⁹² with permission from American Chemical Society, copyright 2008.

A double pH-responsive H-bonded polymeric micelle was developed, which was based on complementary multiple H-bonds of α,ω -thymine terminated PEG (T-PEG-T) and adenine-terminated acetalated dextran (AcDEX-A), allowed the construction of H-bonded amphiphilic triblock copolymer AcDEX-A:T-PEG-T:A-AcDEX, which was further assembled into H-bonded polymeric micelles in water (**Figure 17**).⁹³ It allows the construction of H-bonded amphiphilic triblock copolymer AcDEX-A:T-PEG-T:A-AcDEX, which is further assembled into H-bonded polymeric micelles in water. These micelles are stable at pH 7.4, but disruptive at pH 5.0 due to the double pH-sensitivity of H-bonds within the copolymer backbones along with the hydrolysis of acetalated dextran. Cytotoxicity evaluation revealed the good biocompatibility of these micelles, and DOX was encapsulated into H-bonded polymeric micelles as a model drug. The *in vitro* drug release profile shows that DOX release rate at pH 5.0 can be adjusted by tuning the hydroxyl coverage of Ac-DEX. Meanwhile, DOX-loaded H-bonded polymeric micelles can be efficiently internalized into tumor cells and demonstrate a similar inhibition of proliferation of Hela cells as free DOX.⁹³

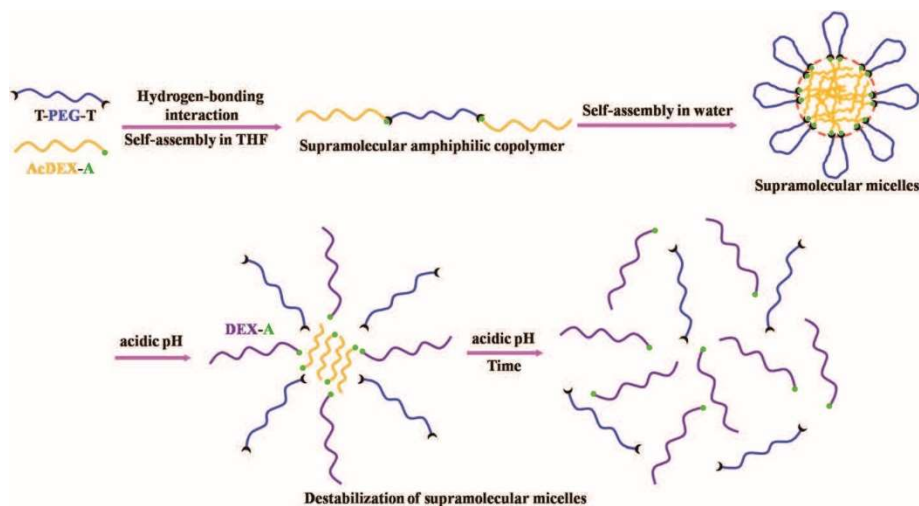


Figure 17: Formation and destabilization of H-bonded polymeric micelles AcDEX-A:T-PEG-T:A-AcDEX from complementary multiple H-bonds of α,ω -thymine terminated PEG (T-PEG-T) and adenine-terminated acetalated dextran (AcDEX-A). This figure has been reproduced from ref.⁹³ with permission from Royal Society of Chemistry, copyright 2015.

In the same way, adenine or thymine side-chain conjugated amphiphilic biodegradable copolymers methoxyl poly(ethylene glycol)-*b*-poly(L-lactide-*co*-2-methyl-2-allyloxycarbonylpropylene carbonate) (mPEG-*b*-P(LA-*co*-MAC)) were exploited as nanocarriers to encapsulate DOX (**Figure 18**).⁶⁴ The incorporation of adenine/thymine H-bonding pair into the hydrophobic segment of the amphiphilic (mPEG-*b*-P(LA-*co*-MAC)) copolymers facilitates the core-crosslinking of micelles showing a lowered CMC, ascribed to H-bonding interaction between adenine and thymine in aqueous solution. The in vitro drug release profile shows that the incorporation of adenine/thymine pair significantly inhibit DOX release at pH 7.4, due to the compact H-bonding crosslinking structure of micelles. In contrast, much faster release rate is determined at pH 5.0, because of the dissociation of adenine/thymine H-bonds. Meanwhile, the DOX-loaded H-bonding core-crosslinked micelles can be efficiently internalized into tumor cells and exhibits similar antitumor efficiency against MDA-MB-231 cells if compared with free DOX.⁶⁴

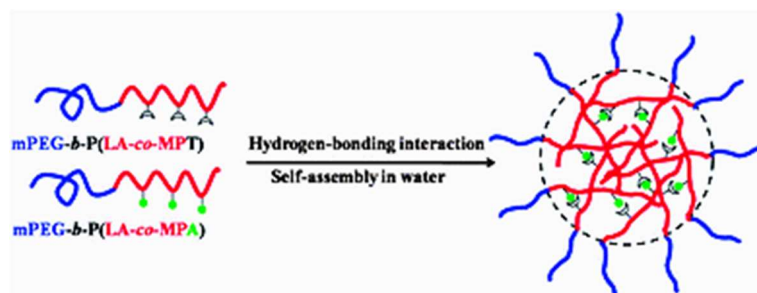


Figure 18: Schematic representation showing the preparation of core-crosslinked micelles based on the complementary adenine/thymine H-bonding interactions. This figure has been reproduced from ref.⁶⁴ with permission from Royal Society of Chemistry, copyright 2012.

Similarly, an uracil-side-chain functionalized PCL (U-PCL) and adenine-ends-capped PEG (BA-PEG) showed high affinity and specific association in solution owing to uracil/adenine induced H-bonding cross-links. H-bonded micelles produced by U-PCL/BA-PEG assembly can be readily tuned to provide the desired CMC, particle size, and stability. Upon DOX encapsulating in such H-bonded micelles, *in vitro* drug release studies revealed remarkable stability of H-bonded nanomedicine in physiological conditions. Importantly, when pH values of the aqueous solution were reduced from 7.4 to 5.0, H-bonded micelles can be rapidly triggered to achieve the controlled release of encapsulated DOX (**Figure 19**).⁹⁰

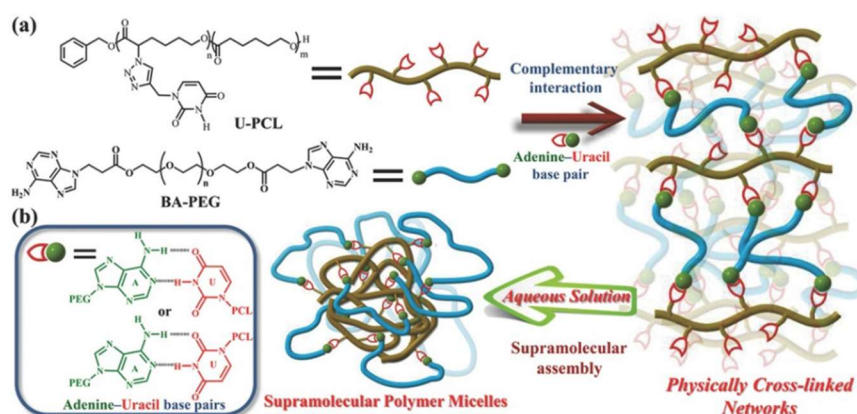


Figure 19: H-bonded micelles formed by U-PCL/BA-PEG assembly (a), and association structure of uracil-adenine pair. This figure has been reproduced from ref.⁹⁰ with permission from John Wiley & Sons, Inc., copyright 2016.

Also, well-defined, highly size-uniform single-chain polymeric nanoparticles, generated from poly[oligo(ethylene glycol) methyl methacrylate] (POEGMA) containing uracil-

diamidopyridine (U-DPy) H-bonding side-groups (POEGMA-U-DPy), were employed as carriers to encapsulate the hydrophilic 5-FU towards H-bonded nanomedicine (**Figure 20**).⁶⁸ Such H-bonded single-chain polymeric nanoparticles exhibits high 5-FU-loading capacity (19.6%), drug-entrapment stability and satisfies thermo/pH-responsive 5-FU release conditions.

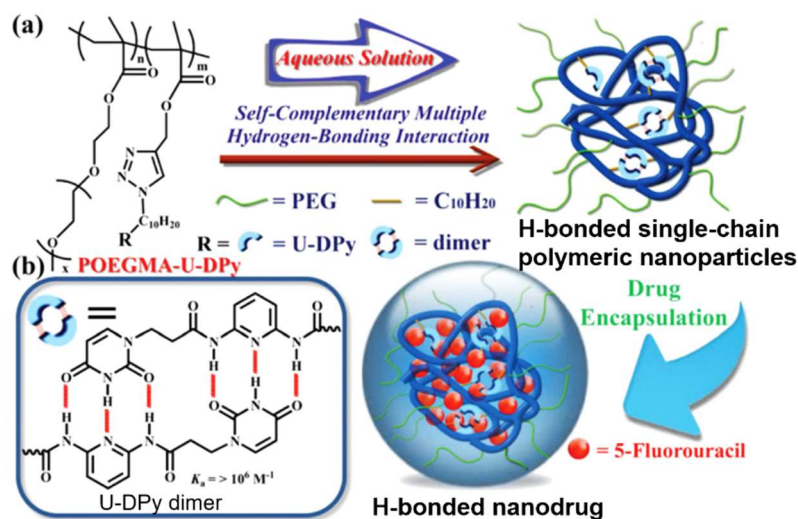


Figure 20: H-bonded single-chain polymeric nanoparticles and drug-encapsulation (a), association structure of U-DPy dimer (b). This figure has been reproduced from ref.⁶⁸ with permission from Royal Society of Chemistry, copyright 2016.

Consequently, the same group utilized cytosine (Cy) moiety to design a water-soluble linear H-bonding polymer by incorporating Cy into both ends of low-molar-mass polypropylene glyco (Cy-PPG-Cy), which exhibited high micellar stability and DOX-encapsulating capacity (24.8%), tunable phase transition temperature, and a rapid DOX release profile ascribed to the presence of Cy-induced highly efficient dynamic structures.¹⁰⁹ U-DPy-ends-capped PEG (U-DPy-PEG-DPy-U) was also synthesized, U-DPy directed assembly in aqueous media generated well-defined, uniformly sized spherical micelles. In addition, thanks to the presence of U-DPy associated dimers within H-bonded micellar interior, the resulting H-bonded micelles exhibit remarkable DOX-encapsulating ability and structural stability in serum-containing environments.¹¹⁰ On the other hand, adenine-ends-capped PPG (A-PPG-A) was developed⁹⁴ to encapsulate magnolol (**Figure 21**), a hydroxylated biphenyl natural compound isolated

from *Magnolia officinalis* and considered as a promising therapeutic agent for clinic research.¹¹¹

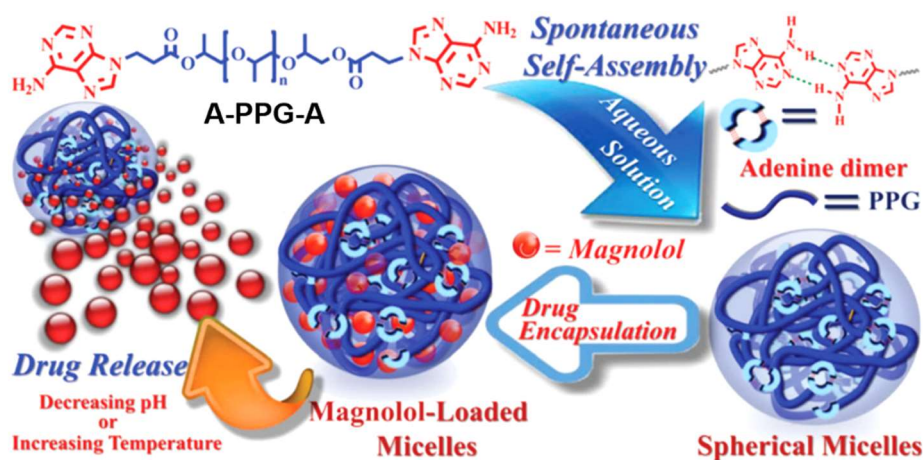


Figure 21: Self-assembly of A-PPG-A micelles, magnolol encapsulating and pH/thermal responsive drug release. This figure has been reproduced from ref.⁹⁴ with permission from Royal Society of Chemistry, copyright 2020.

The DNA-derived H-bonding moiety uracil, is also a photoactive nitrogenous base that can undergo a $[2\pi + 2\pi]$ cycloaddition reaction to form the cyclobutane uracil photodimers upon exposure to (UV) light (**Figure 22**).⁹¹ A photosensitive H-bonded nanocarrier containing uracil moieties was studied to improve the efficiency of cancer chemotherapy. Uracil or adenine end-capped PPG polymers (U-PPG-U, or A-PPG-A) were blended together to generate stable spherical micelles in aqueous solution before and after photoirradiation. The resulting H-bonded micelles exhibited photo-induced tunable phase-transition behavior, outstanding biocompatibility, controlled spherical morphology, and can be tuned in size. Importantly, flow cytometry studies revealed that DOX-encapsulating irradiated micelles enhanced the rate and extent of the tumor cellular uptake and rapidly induced the cell death compared with the nonirradiated ones. In addition, DOX and pro-photosensitizer 5-aminolevulinic acid (5-ALA) were encapsulated within A-PPG-A assembled micelles, achieving effective drug delivery integrated with photo-chemotherapy. The resulting DOX/5-ALA- encapsulated micelles exhibit high drug-entrapment stability in serum-rich media and light/pH-responsiveness in aqueous

solution. Short duration (1-2 min) laser irradiation with visible light triggers the dissociation of DOX/5-ALA complexes within H-bonded micelles, which disrupts the micellular stability and leads to fast release of encapsulated drugs from the micelles.¹¹²

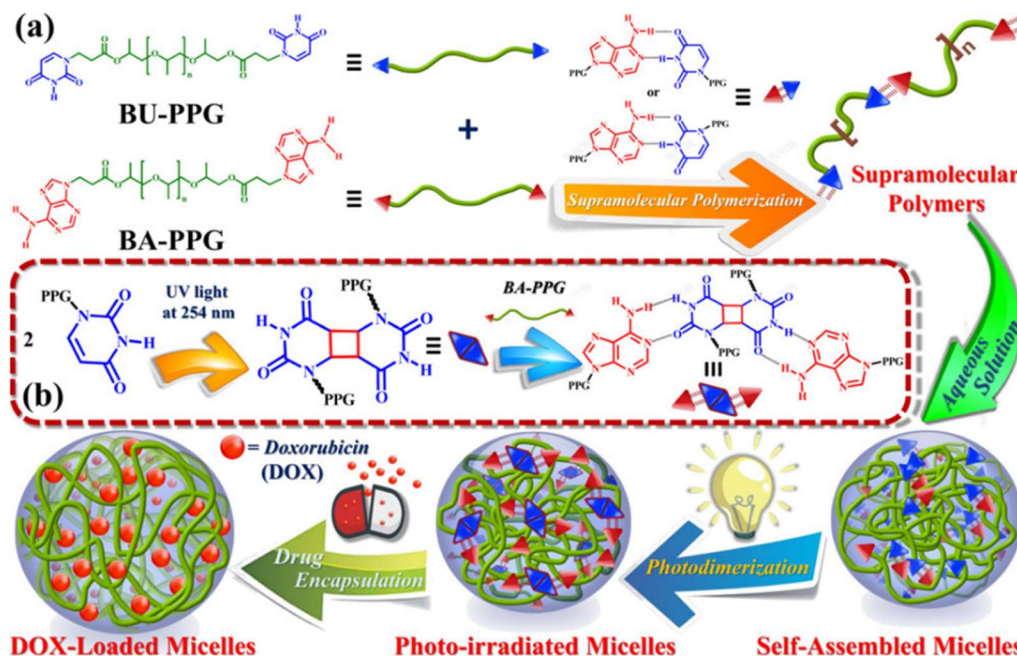


Figure 22: H-bonded micelle formation and DOX-encapsulating/release by photosensitive U-PPG-U/A-PPG-A in aqueous solutions (a), structural representation of photo-reacted U-PPG-U, and H-bonding interactions between adenine and uracil photodimers moieties. This figure has been reproduced from ref.⁹¹ with permission from American Chemical Society, copyright 2010.

To solve biostability and organ distribution issues in polymer-coated liposomes, tumor-extracellular matrix pH-induced targeting polymer-liposome complexes (ECM-targeting liposome) were built, from methoxy-poly(ethylene glycol)-*b*-poly(N-2-hydroxypropyl methacrylamide-*co*-histidine)-cholesterol (PEG-*b*-P(HPMA-*co*-His)-Chol) polymer-based stealth liposome, a functional biotin2-PEG cross-linker and encapsulated DOX. Linear PEG-*b*-P(HPMA-*co*-His)-Chol was incorporated into liposomes by inserting cholesterol into the lipid bilayer (dipalmitoylphosphatidylcholine (DPPC)), which was then cross-linked by biotin2-PEG to prepare ECM-targeting liposomes (Figure 23).⁹⁵ Specifically, biotin2-PEG locates at the

interface layer in liposomes since H-bonds are formed between biotin and histidine/PHPMA. In this way, direct adsorption of proteins on the lipid bilayer of liposomes is prevented and liposome structure during circulation is stabilized. Simultaneously, owing to the low pH in the tumor extracellular matrix, the imidazole ring of histidine in linear polymers is protonated, and so releases partial biotin2-PEG from the interface layer of liposomes. The exposed biotin2-PEG can increase the tumor cell uptake of ECM-targeting liposomes from the interaction between biotin and cell membrane and can further improve the tumor accumulation. This liposome system with a functional cross-linker enables reducing proteins interaction, minimizing drug leakage, and increasing specific tumor targeting.⁹⁵

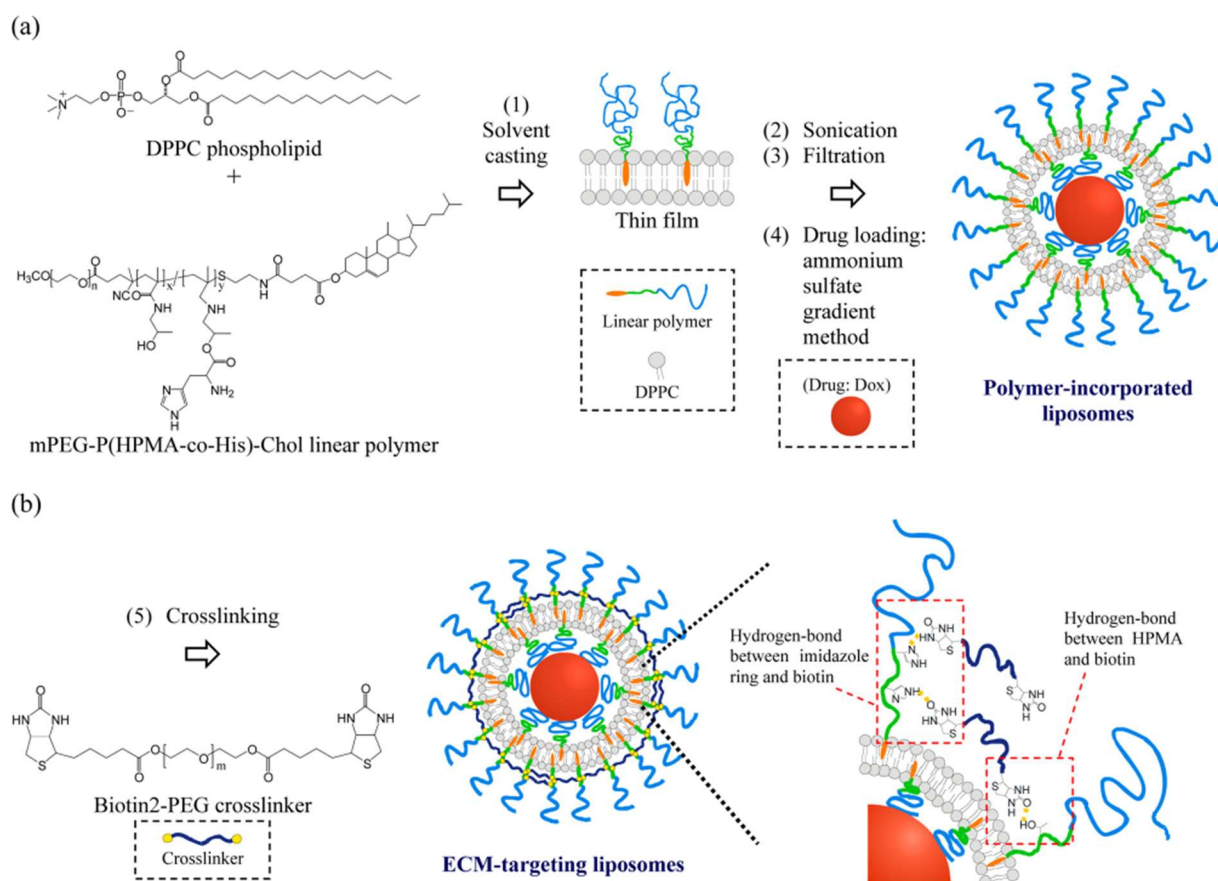


Figure 23: Polymer-incorporated liposomes were fabricated by DPPC and PEG-*b*-P(HPMA-*co*-His)-Chol, followed by encapsulating of DOX into liposomal vesicle (a), ECM-targeting liposomes were formed by directly adding a biotin2-PEG into a polymer-incorporated liposome solution (b). This figure has been reproduced from ref.⁹⁵ with permission from American Chemical Society, copyright 2013.

Intratumoral up-regulated ROS have also been extensively studied as exclusive stimulus to activate drug release for targeted therapies. However, insufficient endogenous ROS level and tumor heterogeneity severely restrict the clinical translation of ROS-responsive drug delivery systems. Therefore, a tailored ROS-activatable self-amplifying nano-prodrug which is H-bonded through Watson-Crick G·C nucleobase, was fabricated to gain in responsiveness and selectivity (**Figure 24**).⁹⁶ A ROS-cleavable cinnamaldehyde (CA)-based thioacetal linker CASOH bearing a ROS generator was designed to benefit from a self-amplifying positive feedback loop of “ROS-activated CA release along with CA-induced ROS regeneration”. CASOH was functionalized with GEM to obtain a ROS-activatable self-immolative prodrug CAG, endowing selective activation in tumor cells and further achieving self-boosting “snowballing” activation via ROS compensation, while staying inactive in normal cells. Thanks to Watson-Crick G·C nucleobase H-bonding pair, CAG crosslinks with a designed guanine-rich, acyclovir (ACV)-modified hyaluronic acid conjugate HA-ACV, to self-assemble into pH/ROS dual-responsive H-bonded nano-prodrug HCAG. With high stability, tumor selectivity and pH/ROS-responsiveness, HCAG nano-formulation demonstrates excellent in vivo anti-tumor efficacy with a minimal systemic toxicity (**Figure 24**).⁹⁶

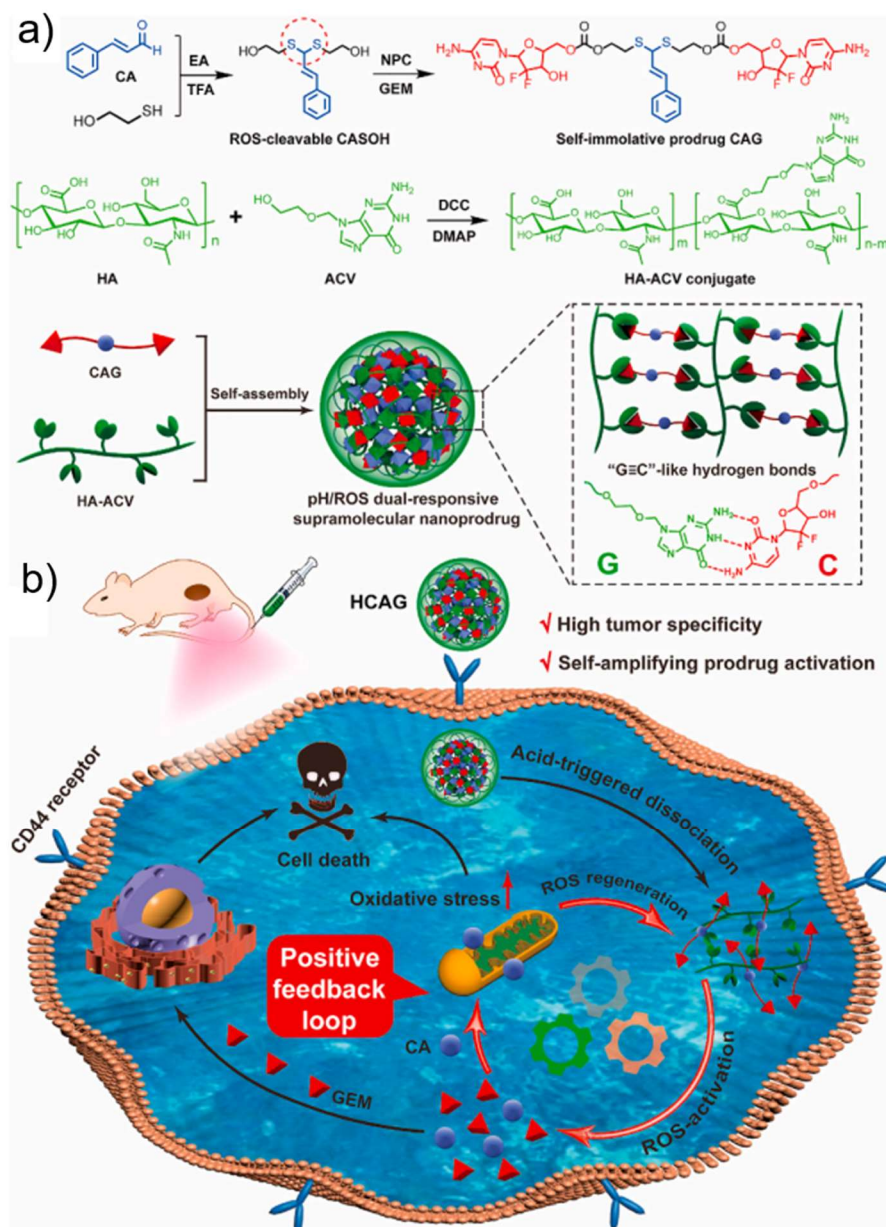


Figure 24: Preparation of CAG, HA-ACV conjugate, and pH/ROS dual-responsive H-bonded nano-prodrug HCAG (a), in vivo selective anti-tumor mechanism of HCAG by ROS regeneration positive feedback process, along with the cascade-amplifying “snowballing” prodrug activation (b). This figure has been reproduced from ref.⁹⁶ with permission from Elsevier, copyright 2021.

Summary and Outlook

The past decades have witnessed significant advances in the field of nanomedicine. A wide range of well-designed products have been extensively developed by means of nanotechnology, including precise cancer imaging and in vitro targeted cancer therapy. Currently, more than two

hundred nanomedicine products are undergoing clinical trials, and some of them have already been approved by FDA. These nanomedicines are considered safer and therefore endow better patient outcomes through reducing drugs side effects, as evidenced by several breakthroughs which have been made in the discovery of preclinical and clinical nanomedicine. Research at the interface of supramolecular chemistry and biomedical science significantly enriches nanomedicines portfolio. The dynamic nature of H-bonding interactions provides nanodrug systems with responsiveness, stability and multifunctionality with no need for tedious synthetic efforts, and so facilitating clinical translation of these products. Despite the rapid progresses in supramolecular cancer nanotheranostics, with more and more available examples of H-bonded nanomedicine, successful clinical translations of these nano-formulations are still scarce.

Several ways of future improvement can be envisioned. First, for efficiently targeting a tumor, an accurate imaging of it is mandatory. However, H-bonded nanomedicines and imaging probes stay so far uncombined in most reported systems. Promising strategies towards H-bonded nanomedicine combined with stable labelling will be of high interest to afford reliable theranostic platforms, in which diagnostic signals are responsive to drug release.

Another concern in clinical translation of nanomedicine stems from the safety of theranostic formulations, as their properties and the side effects are not completely understood yet. Nanomedicine must cross and overcome several complicated biological barriers, such as cellular membranes, air-blood and blood-brain barriers *in vivo*, prior to activating theranostic functions. Moreover, uncontrolled migrations and depositions of nanomedicine may also adversely affect patients. Thanks to the dynamic nature of non-covalent interactions, H-bonded nanomedicine used as delivery systems can be degraded into monomers, which are immediately excreted from the bodies. More interestingly, drugs can be directly assembled, or employed as building blocks to construct H-bonded theranostics, devoid of incorporation of unnecessary additives which may be source of potential adversely interactions with the immune system.

The prognosis of single therapy treatment is always unsatisfactory: tumor recurrence and metastasis still are the main causes of mortality. Combined therapy is considered as a feasible methodology to synergistically boost the antitumor efficiency by exploiting proper benefits of each therapeutic strategies, such as chemotherapy, phototherapy, radiotherapy, chemodynamic therapy, gene therapy and immunotherapy. However, the incorporation of such diverse strategies into one nanoplatform raises new synthetic challenges. Supramolecular chemistry, including those based on H-bonding interactions, provides straightforward routes to smart nanomedicines by directly using theranostic agents as building blocks.

Despite several obstacles to clinical translations of H-bonded nanomedicine, efforts have to be paid to overcome these difficulties to propose commercially-available nanomedicines that are more effective and less expensive comparing to existing products. As interest in this promising research field continues rising, it can be anticipated that clinical translations of H-bonded nanomedicine will materialize in a near future and will contribute to great progress in cancer diagnosis, therapy and ultimately human healthcare.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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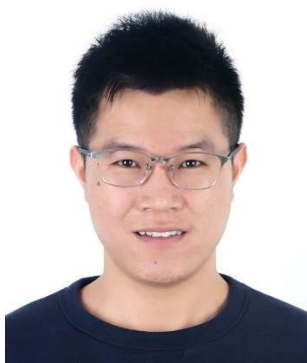
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The table of contents entry:

Hydrogen-bonds (H-bonds) bridge artificial and biological sciences, implementing dynamic properties into materials and (macro)molecules, which cannot be achieved via purely covalent bonds. In this review the current state-of-the-art for designing novel H-bonded nanomedicines for precise diagnosis, and targeted therapeutic drugs delivery are highlighted.

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Hydrogen-Bonds Mediated Nanomedicine: Design, Synthesis and Applications

ToC figure:

