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Review
doi.org/10.1002/cbic.202300018

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# Recent Progress on Cyclic Peptides' Assembly and Biomedical Applications

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Cyclic peptides are important building blocks for forming functional structures and have been applied in various fields. Considering the significant structural and functional roles of cyclic peptides in materials science and the attributed biophysical advantages, we provide an overview of cyclic peptide types that can self-assemble to form nanotubes, recent progress in stimuli-triggered cyclic peptide assembly, and methods to construct peptide and polymer conjugates based on cyclic peptides with alternative chirality. Specifically, we highlight the roles that stimuli-triggered cyclic peptides and their conjugates play in biomedical applications. Recent progress in other cyclic peptides acting as gelators in drug delivery and biomedicine are also summarized. These cyclic peptides with self-assembly properties are expected to act as adaptive systems for drug delivery and selective disease targeting.

## 1. Introduction

Supramolecular nanotubular structures are prevalent within membranes. They can facilitate intercellular communication and pathologies detection.[1] Various noncovalent interactions, such as hydrogen bonding, π–π stacking, hydrophobic interactions, and electrostatic interactions, stabilize the nanotubular structures. For most biological macromolecules, especially for proteins, tertiary structures are crucial for their biological functions.[2] Inspired by nature, synthetic nanotubular structures have drawn considerable attention from scientists with applications in ion channels,[3] sensors,[4] nanomedicine[5] (or tools for drug delivery[6]). Peptides and proteins are useful building blocks for accessing synthetic nanotubes because they can provide multiple hydrogen bond donors and acceptors, and their side chains can also offer multiple kinds of noncovalent interactions to stabilize the assembled architecture. Intermolecular hydrogen bonds between peptide monomers dominate in forming nanotubes.[7] Therefore, the peptide sequence should encode the primary information to reduce unnecessary intramolecular hydrogen bond formation and can shield the water molecules from hydrogen bonding competition. Among various secondary structures, β-stranded structures formed by peptides are more favorable to form nanotubular structures attributed to the preference to form intermolecular hydrogen bonds over intramolecular hydrogen bonds.[8]

Linear and cyclic peptides (CPs) can display significant differences in self-assembly behaviors and thermal stability due to the physical dissimilarities in topology.[9] Linear peptides are structurally flexible, dynamically exchanged in a variety of conformations in water, sensitive to enzyme cleavage, and less resistant to the endosome entrapment.[10] Therefore, they are less likely to accumulate enough to an effective concentration without causing severe off-target toxicity before reaching the target sites.[10c] However, cyclic peptides are structurally constrained to form much more stable structures in solution with higher efficiency to escape from the endosome,[11] and the self-assembly behaviors are more dependent on the multiple intermolecular hydrogen bonds array.[7,12] Cyclization can improve pharmacokinetics and targeting properties of peptides and promote the therapeutics accumulation in the tumor microenvironment.[2b,13] Nature has perfected this strategy by making numerous disulfide-bonded cyclic peptides.[14] Due to their cyclic nature, synthetic cyclic peptides have been widely used to deliver molecular cargo such as anticancer drugs or siRNA intracellularly.[15] Despite the significant progress, methods toward constructing cyclic peptides with sufficient structural diversity are appealing.

Most reported cyclic peptides possess a symmetrical backbone can self-assemble to result in nanotubular structures. Examples include cyclic alternative D/L peptides (**1**), cyclic peptides containing β-amino acids with $C_3$ symmetry (**2**), cyclic peptides containing pseudo amino acids with $C_2$ symmetry (**3**), and cyclic peptides consisting of α,γ-amino acids with $C_3$ symmetry (**4**; Figure 1).[7,12a,16] Cyclic alternative D/L peptides represent one of the most important structural units for forming nanotubular structures. Other classes of self-assembled cyclic peptides containing special amino acids, such as sugar moieties or furan derivatives, account for a small population among the self-assembled CPs. Besides, they need multiple steps to build the amino acid blocks,[17] which are synthetically challenging compared to the cyclic D/L peptides with all commercially available amino acids.

Several excellent reviews have summarized the design and applications of self-assembled peptides containing cyclic D/L peptides.[7,12a,18] However, less attention has been paid to the strategies to construct cyclic D/L peptides and their conjugates, and the roles they play in nanomedicines. New strategies toward constructing structurally and functionally diverse cyclic

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peptides are still increasing and in urgent need of nanomedicines. This review focuses on recent work on the design of stimuli-responsive peptide nanotubes derived from cyclic D/L peptides and the chemical approaches to their conjugates with applications in biomedicines. Other cyclic peptides with a small ring, such as cyclic dipeptides (heterocyclic 2,5-diketopiperazines), are already discussed somewhere,[19] which are not included here. Also, we draw special attention to cyclic peptides without self-assembly ability but can act as gelators to generate self-assembled linear peptides. As this field is just emerging, the potential applications in various fields are attractive, especially in nanomedicines.[20]

Pioneered by Ghadiri and co-workers,[21] substantial achievements have been obtained by using cyclic D/L peptides as scaffolds to build self-assembled nanotubes. For example, cyclo-[(L-Gln-D-Leu)$_4$] peptide monomers self-assembled to form large, rod-like structures with diameters reaching 2 μm.[22] The structures show equal or even higher stiffness and robustness than some of the known most robust peptide-based materials (i.e., amyloid fibrils). Some self-assembled fibers could reach hundreds of micrometers in length without losing nanoscale order. Cyclic D/L peptides can form nanotubes with rigorously controlled internal diameters by simply varying the ring size.[7] This feature is vital for designing artificial ion channels or transmembrane transporters for small molecules. Studies have shown that a decapeptide cyclo-[(L-Trp-D-Leu)$_4$-L-Gln-D-Leu] with an internal diameter of 10 Å exhibited high glucose transport activity, whereas its analogue octapeptide cyclo-[(L-Trp-D-Leu)$_3$-L-Gln-D-Leu] with smaller internal diameter did not.[23] These results suggested that the cyclic D/L peptides with appropriate ring sizes could be used for drug delivery. Wu et al. have showed the nanotubes formed by the self-assembly of cyclic peptide (cyclo-[L-Gln-(D-Leu-L-Trp)$_4$-D-Leu]) could mimic transmembrane channels to deliver a series of small anticancer drugs.[6] Structurally, the monomers of alternative cyclic D/L peptides with an even number of D/L amino acids adopt a flat conformation in which the backbone amides project along the ring plane to promote intermolecular stacking to form rod-like, cylindrical nanotubes.[7] These structures have shown a longer residential time in vivo when delivering drugs over their spherical counterparts and particles of comparable size.[24]

Another noteworthy advantage of cyclic peptides with alternative chirality is that the exposed surface could provide appropriate amino acid side chains for further modifications by incorporating natural or unnatural amino acids with functional groups.[25] The nanotubular structures in which all the side chains project perpendicularly toward the tube axis to provide ample spaces for conjugating with polymers or peptides. The report showed that cyclic D/L peptides could display superior solubility in water or lipophilicity to interact with biological membranes by tuning the hydrophilicity and hydrophobicity through side chains.[26]

After receiving his B.S. from Tianjin University, Huaimin Wang obtained his Ph.D. from Nankai University under the supervision of Professor Zhimou Yang. Before starting his independent research at Westlake University, he was a postdoctoral fellow with Prof. Bing Xu at Brandeis University. His research interests mainly focus on applying supramolecular assemblies of small molecules to explore and engineer living organisms, as well as designing functional supramolecular nanomaterial for applications in materials chemistry and biomedicine.

## 2. Stimuli-Response Cyclic Peptide Nanotubes

Stimuli-responsive nanomaterials have attracted considerable attention due to the controllable assembly and disassembly once exposed to the stimuli change. They have been widely applied in sensors,[27] actuators,[28] surface modifications,[29] and scaffolds,[30] and in drug delivery.[31] Although the nanostructures formed by the self-assembly of a cyclic peptide are controlled by a variety of factors, such as peptide concentration, side chain groups, pH values, reaction time and stirring intensity,[32] stimuli including pH adjustment,[33] enzyme,[34] and light,[35] or a combination of stimuli are necessary for the dynamic control of nanomaterials.[34c] As stimuli-responsive peptide nanomaterials are promising drug delivery systems, some recent examples about stimuli-triggered cyclic peptide self-assembly and their dynamic processes are summarized herein.

### 2.1. pH-triggered self-assembly

Due to the reversible protonation or deprotonation processes, peptides with chargeable groups are a class of pH-responsive materials. The responsiveness to pH has large effects on the solubility and electrostatic repulsion,[36] which could affect the stability of the self-assembled structures in an aqueous solution, thereby promoting drug release.[33f] The nanostructures can be tuned by a pH-driven or pH-sensitive method with controllable sizes and diameters by reversibly exchanging carboxylate and carboxylic acid in the side chain. For cyclic peptides with an even number of alternative D/L amino acids, the length and the primary sequence encode the diameter and secondary structure information in the solution.[37] However, selective incorporation of hydrophobic amino acids (i.e., Trp and Leu) and charged amino acids (i.e., Glu, His, Lys) could affect the aggregation of 1D nanotubes. For example, Montenegro and co-workers reported that a cyclic peptide (cyclo-[L-Gln-D-Leu-L-Trp-D-Leu-L-Glu-D-His-L-Gln-D-Glu-L-His]) capable of sequential 1D-to-2D self-assembly in aqueous solution.[33b,38] The cyclic peptide consists of four distinct domains: i) a hydrophobic tripeptide domain Leu-Trp-Leu; ii) two hydrophilic domains containing pH-sensitive amino acids (His-Glu) flanked on the two sides of the glutamine; iii) and a neutral hydrophilic glutamine on the opposite site of the tryptophan (Figure 2). This amphiphilic peptide nanotube is expected to form multiple intermolecular hydrogen bonds between peptide monomer rings, stabilizing a


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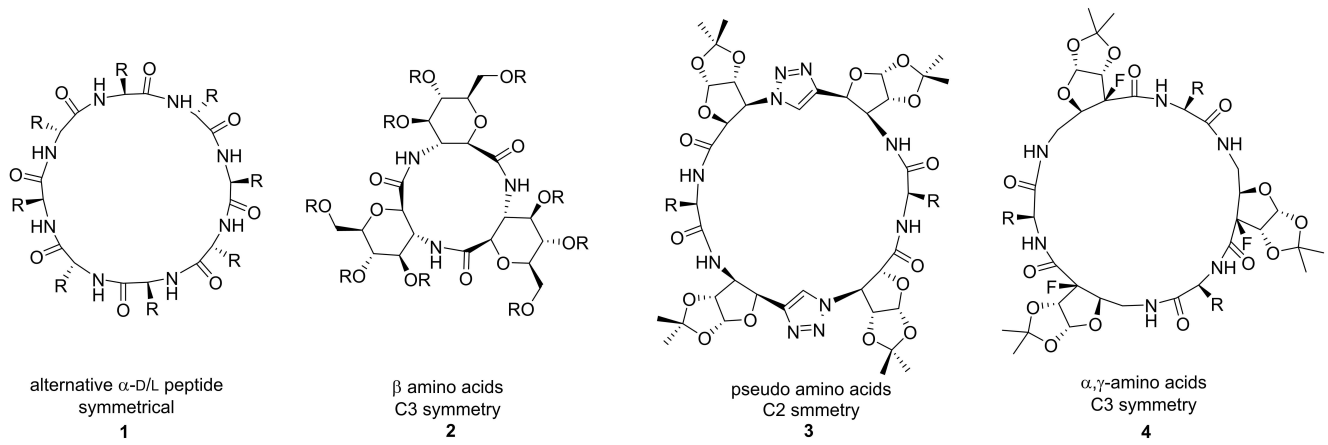


**Figure 1.** Self-assembled cyclic peptides with a symmetrical backbone.

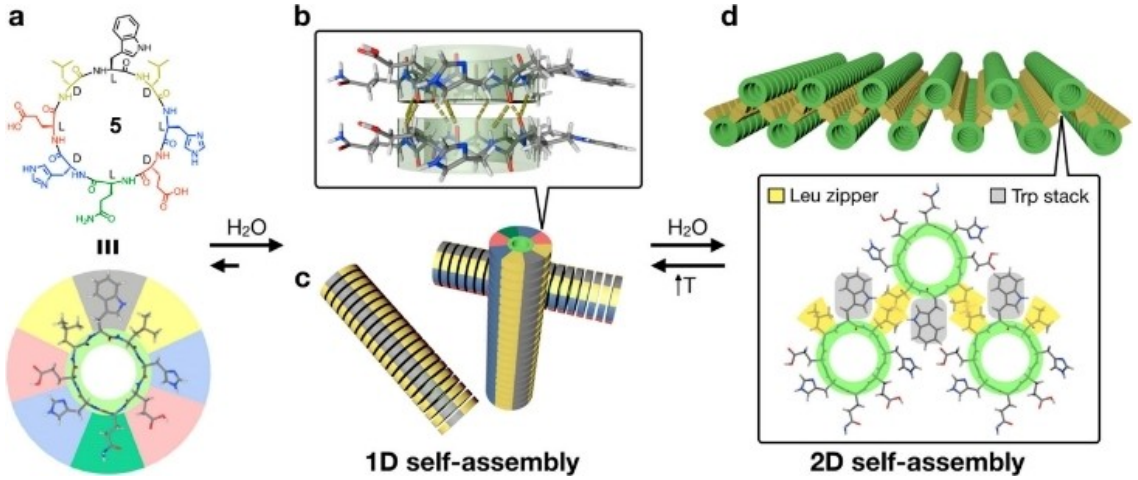


**Figure 2.** Proposed model for the sequential 1D-to-2D self-assembly of cyclic peptide **5**. a) Chemical structure of the cyclic peptide **5**. b) Parallel β-sheet formation stabilized by multiple intermolecular hydrogen bonds between monomer rings. c) 1D assembly of **5** to form amphiphilic nanotubes. d) 2D architecture formation stabilized by Leu zippers and Trp stacks. Reproduced with permission from ref. [33b]. Copyright: 2020, American Chemical Society.

parallel β-sheet secondary structure. A single nanotube would further self-organize into a nanotubular bilayer to bury its hydrophobic patch from the aqueous solution. Theoretically, at physiological pH, the surface of the tubular structures will have a highly anionic character due to the deprotonated state of the glutamic acids ($pK_a \approx 4.2$) and the neutrality of histidine residues ($pK_a \approx 6.0$). As a result, stabilized leucine zippers and π–π stacks from tryptophan indole rings formed owing to the shifting of one peptide tube to stagger the top and bottom layers. Meanwhile, the highly anionic surface prevented the aggregation of the individual layers of the 2D architecture, while the leucine zippers, π–π stacking together with the intermolecular hydrogen bonding between histidine and leucine side chains stabilized the architecture. Overall, this study revealed that pH and /or temperature as external stimuli allows the dynamic control of the supramolecular structure from 1D to 2D self-assembly.

### 2.2. Microfluidic controlled stimuli-triggered assembly

Very recently, the microfluidic controlled stimulus has been employed to adjust the packing degree and the spatial positioning of the microfibrillar bundles formed by cyclic peptide nanotubes.[33c,39] The nanotube and fibril formation (*'fibrillation' is a heart condition*) of supramolecular structures by cyclic peptide (cyclo-[L-His-D-Ala-L-Lys(pyrene-1-carbaldehyde)-D-Ala-L-His-D-Ser-L-Lys-D-Ser]) can be regulated by pH adjustment or ionic strength in confined aqueous droplets (Figure 3).[33c] Internally, the fibril formation process can be tuned by the peptide sequence containing pH-sensitive residues (His and Lys) and a side chain modified with a hydrophobic pyrene group conjugated via the oxime linkage. Externally, the confined spherical water droplets provided an environment to control fibril formation processes. Under acidic conditions (pH ≈4), the charged peptide monomer prevented the assembly due to the electrostatic repulsions owing to the protonation of Lys and His residues. Under basic conditions, the cyclic D/L


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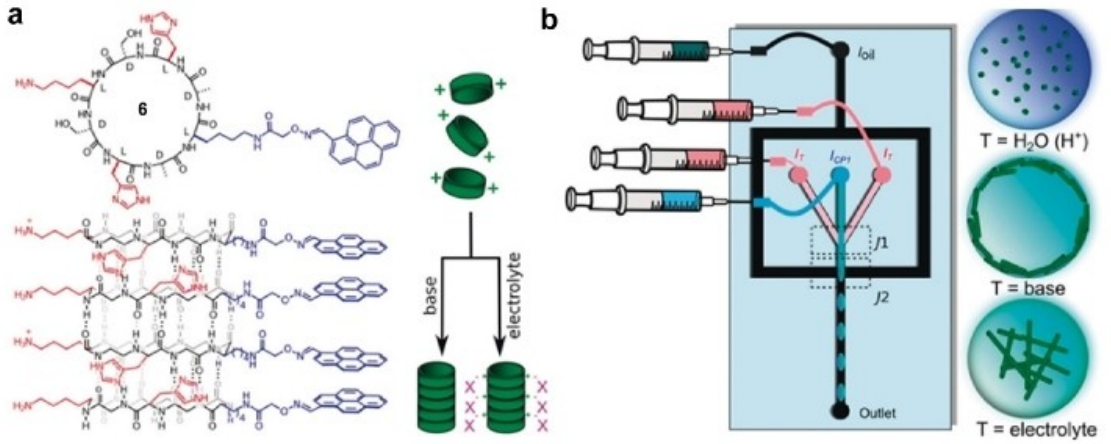


**Figure 3.** Microfluidic controlled supramolecular fibril formation. a) Chemical structure and the model of pH/ions-triggered self-assembly of cyclic peptide **6**. b) In-situ fibril formation induced in a microfluidic device under three different conditions. Reproduced with permission from ref. [33c]. Copyright: 2018, Royal Society of Chemistry

peptide formed the one-dimensional hierarchical arrangement that displayed perfect preservation from the nano to the micro-scale. A combination of noncovalent interactions, including intermolecular hydrogen bonding, π–π stacking, cation–π interactions, together with the deprotonation of the histidine side imidazole NH cooperative stabilize the supramolecular structure.

### 2.3. Light-fueled self-assembly and disassembly

Nature has perfected microtubules growth reversibly by switching the conformation of building blocks fueled by guanosine-triphosphate (GTP).[40] Traditionally, chemical fuels play a role in regulating electrostatic interactions between the building blocks to drive the switch between assembly and disassembly.[41] Recently, light-fueled cyclic peptide assembly and disassembly via controlling the charged state of the monomer has been reported.[42] The system used light as a clean source to fuel a spiropyran photoswitch to generate protons which subsequently converted the glutamate carboxylate to protonated state. The reduction of columbic repulsion facilitated the assembly of the cyclic peptide to form nanotubular structures. The hydrophobic pyrene group and intermolecular hydrogen bonds stabilize the nanostructures. However, the spiropyran would capture a proton from the carboxylic acid to disassemble the nanotubes. The rapid response to UV light and fast changes in pH could be applied in designing polymerization motors in the future.

### 2.4. Air-water interface-triggered peptide self-assembly

The backbone plays a crucial role in determining the self-assembly properties of cyclic D/L peptides. However, the side chains also have influence on the formation of nanotubes, with sterically hindered side chains destabilizing the formation of nanotubes.[18a] Studies have shown that a cyclic hexapeptide containing alternative 3-aminobenzoic acid and L-glutamic acid 5-isopropylester subunits (C6G) formed 2D crystallite structures at the air-water interface while the analog compound cyclo-octapeptide (C8G) did not.[43] The molecules tended to flip to a perpendicular state due to the surface suppression. Interestingly, unlike other alternative cyclic D/L peptides stabilized by intermolecular hydrogen bonds between backbone to backbone, the nanotubular structures formed by C6G were mainly stabilized by the backbone NHs and the CO groups of the side chains from a neighboring molecule.

## 3. Cyclic Peptide and Polymer Conjugates

Cyclic peptide nanotubes tend to form bundles and reach lengths of micrometer scale, giving rise to worse solubility,[37a] which limits their applications in biological systems. However, this drawback could be overcome by conjugating a cyclic peptide monomer with a polymer chain to tune peptide self-assembly, improving solubility in water,[44] and with extended applications[45] in transport[46] and transmembrane protein channel mimics.[45b,47] Besides, grafting polymeric chains can tune the nanotube length to some extent[33e,48] and introduce functional groups[45a,46] to coat the nanotubes. Notably, the conjugated nanotubes display additional superiority for drug delivery over typical spherical nanoparticles owing to the large surface area that they can span on cell membranes.[49] Several methods have been applied in conjugating a cyclic peptide and a polymer, such as radical chemistry, CuAAC, thio-ene reaction, condensation chemistry, ring-opening metathesis, or a cascade of reactions et al.[50] Most of the existing methods can be regarded as employing a convergent approach, which involves a single step to conjugate premade polymer chains to a cyclic peptide core.[51] Although dominant studies have focused on the symmetrical construction of peptide-polymer conjugates, recent research was also conducted on the self-assembly of


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unsymmetrically functionalized cyclic peptide-polymer conjugates.[52]

### 3.1. Copper-catalyzed peptide and polymers conjugation

Copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) has been widely used for peptide stapling[8,53] and peptide-polymer conjugates[54] since its discovery.[55] Blunden et al. applied this chemical strategy to synthesize the polymeric nanotubes which act as drug carriers (Figure 4).[56] The polymeric nanotubes were constructed by conjugating cyclic peptides and a bifunctional copolymer based on poly(2-hydroxyethyl acrylate) (pHEA) and poly(2-chlorethyl methacrylate) (pCEMA) via CuAAC reaction. The introduction of HEA increased the solubility in water, while the selection of CEMA provided a functional chlorine handle for ruthenium drug loading. The chlorine handle was readily converted to a ruthenium coordinate group by substituting the PTA (1,3,5-triazaphosphaadamantane) ligand. A ruthenium-based anticancer drug RAPTA–C was tightly bound to the polymer through the Ru-PTA coordinate bond. The nanotube carriers demonstrated efficient drug uptake (tenfold increase) in human ovarian A2780 tumor cells, although the drug was not releasable due to the strong coordination.

### 3.2. Amide coupling strategy

Amide coupling is probably the most efficient and economical method for peptide and polymer conjugation. By using the $NH_2$ group of the lysine side chain, Jolliffe and Perrier groups reported the generation of cyclic peptide-polymer conjugates via an amide coupling strategy,[51,57] by which a library of conjugates consisting of a cyclic peptide core and polymer shells were constructed.[51] The cyclic peptide core was wrapped with either hydrophobic or hydrophilic polymers. Based on the structure-channel formation relationship, they proposed that peptide-poly(N-isopropylacrylamide) conjugates could be regarded as a novel temperature-responsive system. The system allowed on-demand control over trans bilayer channel formation at 35 °C.

Later they developed a highly potent nanotube system for drug delivery by conjugating a pre-prepared biocompatible polymer poly(2-hydroxypropyl methacrylamide) (pHPMA) to a cyclic peptide (D-Leu-Lys-D-Leu-Trp)$_2$ through amide coupling (Figure 5).[58] The resulting nanotube systems were further functionalized with organoiridium anticancer complexes to afford cylindrical structures with an average length of about 20 nm. With respect to the nontoxic nanotubes themselves, the drug-loaded nanotubes displayed more potent antiproliferative activity toward A2780 cancer cells than the control groups with either free drug or drug-loaded polymers. Compared to the free drug, the drug-loaded nanotubes showed lower cell toxicity toward healthy human ovarian fibroblast cells. Studies on transport mechanisms suggested that the energy-dependent mechanisms are responsible for the higher accumulation of iridium in different organelles for drug-loaded conjugates than for the free drug.

#### *3.2.1. Thio-Michael reaction strategy*

Thio-Michael reaction has seen wide applications in small molecule synthesis and polymer modifications with tremendous successes in biological systems and materials functionalization.[59] This reaction provides one of the most popular methods for the synthesis of peptide polymer conjugates, despite the studies mainly on linear peptides.[59b] For example, an antimicrobial peptide $NH_2$-CGLFDIVKKVVGALC-$NH_2$ was conjugated to a hyperbranched polyglycerol (HPG) functionalized by maleimide.[60] Zhang et al. applied this reaction to conjugate PEG for the construction of DOX-loaded cyclic

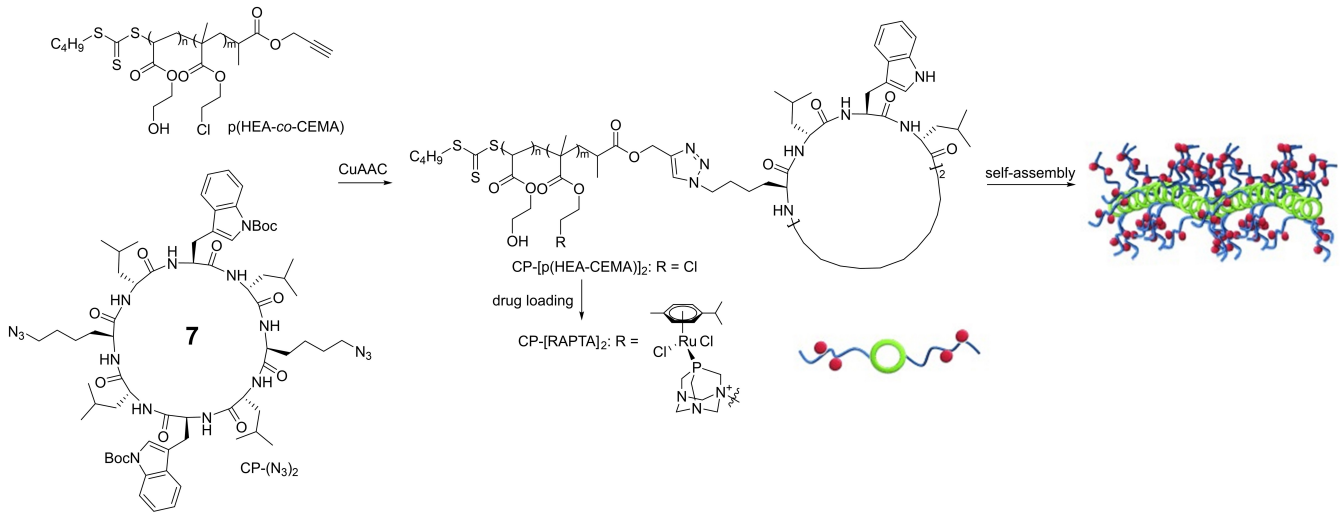


**Figure 4.** CuAAC strategy for the synthesis of cyclic peptide-polymer conjugates and the loading approach of an anticancer drug RAPTA–C. Reproduced with permission from ref. [56]. Copyright: 2014, John Wiley and Sons.


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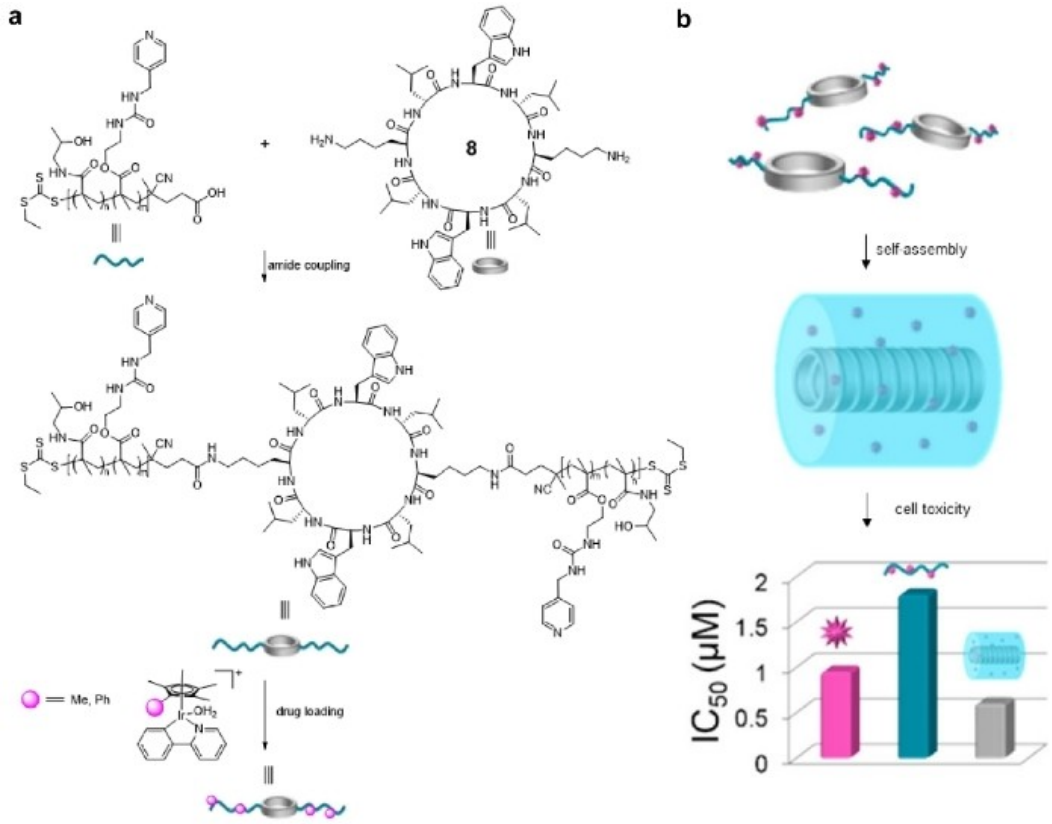


**Figure 5.** Amide coupling strategy for the construction of cyclic peptide-polymer conjugates as well as the application for drug delivery. Reproduced with permission from ref. [58]. Copyright: 2018, American Chemical Society.

peptide nanotube (CPNT) bundles, which acted as a nanocarrier for drug delivery.[61] The CPNT structures were based on an octapeptide cyclo-(L-Gln-D-Ala-L-Glu-D-Ala-L-Gln-D-Ala-L-Cys-D-Ala) monomer (**9**) with two functional groups, one glutamic acid and one cysteine on the opposite side. The peptide monomers formed CPNT at pH 2.0 by gradually decreasing the pH from 12.0. The single CPNT further self-aggregated to result in CPNT bundles. Functionally, the glutamic acid residue formed ion-pair complexes at pH 6–7 with a cationic anticancer drug, doxorubicin, while the other residue cysteine conjugated to the maleimide-PEG polymer in a thio-Michael reaction to afford the Dox-loaded CPNT bundles. The conjugated CPNT bundles displayed a high DOX loading ratio (66.7 %) at pH 6.0 and good dispersion in water with a length reaching about 200–300 nm and a diameter of about 50 nm. As for activity, the PEG-modified CPNT/DOX bundles demonstrated higher cell toxicity toward the human breast cancer MCF-7 cells and a multidrug-resistant MCF-7 cell line with respect to free DOX. Besides, the PEG-modified CPNT/DOX bundles showed a higher efficacy toward the multidrug-resistant MCF-7 cells than MCF-7 cells. Overall, the bundled system facilitated the cell uptake of DOX and influenced the intracellular distribution.

### *3.2.2. Double click reactions*

Click reactions have successfully conjugated small molecules and macromolecular substrates.[62] The reactions can be operated under mild conditions with high coupling efficiency, requiring no catalyst or excess of any coupling partner. Orthogonal double "click" reactions are very useful for the preparation of asymmetric amphiphilic peptide-polymer conjugates. Granja and co-workers[63] applied this strategy to install different hydrophobic and hydrophilic moieties to a modified cyclic D/L peptide based on the antimicrobial cyclo-[(L-Trp-D-Leu-L-Trp-D-Lys-L-Ser-D-Lys-L-Ser-D-Lys)].[64] Specifically, a propargylglycine (Prg) was used to attach aliphatic chains to increase the hydrophobicity through CuAAC reaction. Meanwhile, an *O*-alkoxyamine in the polar region was installed for condensing with various aldehydes. This click reaction allowed the conjugation of oligosaccharides to reduce hemolysis. The resulting cationic amphipathic nanotubes displayed a membrane-related mode of action and disrupted the bacteria membrane at MIC concentration or above.

Besides, another pair of click reactions, namely isocyanate-amine addition[65] and SPAAC[66] (strain-promoted azide–alkyne cycloaddition) reactions, were also employed for constructing cyclic peptide polymer conjugates (Figure 6).[52] The hydrophobic polymers (poly(*n*-butyl acrylate) (pBA)) and hydrophilic polymers (PEG chains (pPEGA)) were installed on the opposite


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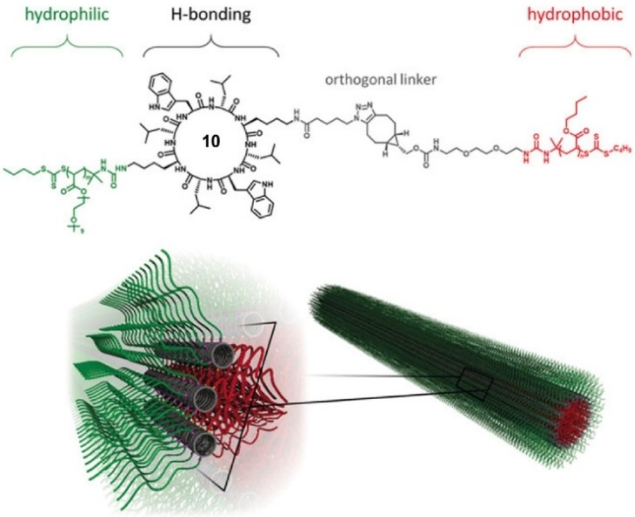


**Figure 6.** Chemical structure of the asymmetric cyclic peptide polymer 10 formed by orthogonal double click reactions. Reproduced with permission from ref. [52]. Copyright: 2018, John Wiley and Sons.

sides of the cyclic peptide. The conjugation process relied on the preprepared polymeric chains functionalized with an amine active isocyanate end group, which readily coupled with a commercially available amine-functionalized strained alkyne or lysine side chain amine. The amphiphilicity and the strong hydrogen-bonding interactions between the peptides core displayed unprecedented self-assembly in an aqueous solution. Detailed structural analysis by small-angle neutron scattering (SANS) and static light scattering (SLS) demonstrated single peptide nanotubes aligned in a barrel-shaped structure, which tended to form a large tubisome. Those tubisomes consisted of a hydrophobic internal channel and a hydrophilic shell. In vitro studies showed that the tubisomes were nontoxic, penetrated the cell membranes (HEK 293) by endocytosis, and further could insert into the lipid bilayer of lysosomes, which was different from the respective copolymer block. The tubisomes could be employed in drug delivery to facilitate the escape of molecules or drugs of similar sizes by disrupting the membrane or possibly creating transmembrane channels, as evidenced by a calcein escape assay. This kind of strategy has recently been applied in drug delivery.[67]

Other methods, such as ring-opening metathesis polymerization (ROMP), have also been applied to produce thermal-responsive cyclic peptide polymer conjugates by using a preinstalled olefin on the cyclic peptide N terminus.[68] Tunable control of the assembly and disassembly of nanotubular structures could switch on or off the functions of cyclic peptide-polymer conjugates, which play important roles in biomedicine. pH has been acting as a switcher in a few studies to control the assembly and disassembly.[32,36,69] A recent study also applied host-guest interactions to tune the processes.[70] The cyclic peptide-polymer conjugate disassembled due to the steric hindrance when introducing cucurbit[7]uril (CB[7]), which non-covalently hosted the phenylalanine residues. However, the supramolecular structures could be recovered when introducing a competitive guest molecule ADA (1-adamantanamine).

## 4. Other Cyclic Peptides in Nanomedicine

Supramolecular nanomedicines formed by molecular self-assembly are becoming attractive chemotherapeutic agents with increased solubility, low toxicity, enhanced resistance to blood clearance, and strong cell permeability.[71] Recently, peptide self-assembly has drawn significant attention for developing nanomedicines owing to its endogenous nature.[18b,72] Devoted efforts in designing such a system include employing linear peptides that self-assembled into pH/enzyme-triggered, monospecific, or bispecific nanomedicines.[20c] Despite the tremendous successes, the effectiveness using linear peptides was compromised mainly by the susceptibility to proteases and weak endosome escape.[10c] Taking advantages of the cyclic peptides, a prodrug platform based on a stimuli-responsive cyclic peptide may benefit the drug delivery efficiently.

Recently, Gianneschi and co-workers applied sterically constrained cyclic peptides into progelator materials platform for the treatment of heart post-myocardial infarction.[20b] The cyclic peptides are good candidates for minimally invasive catheter delivery with low resistance injection and negligible gelation ability when flowing through a syringe in an in vitro model system. They contained three functional fragments: i) a gellable core with the repeat sequence $(KXDX)_3$ (X indicates L or F), which acted as a non-immunogenic, non-hemolytic, and antimicrobial scaffold in tissue engineering materials;[73] ii) a substrate recognition sequence for MMP-2/9 and elastase (red) on the C terminus; iii) a fluorescent group (rhodamine) on the N terminus (Figure 7). The cyclic peptides could not self-assemble due to the conformational constraint. However, upon exposure to the MMP-2/-9 or elastase (PLG|LAG or PLGLA|G), the cyclic progelators resulted in linear conformation to generate self-assembled nanostructures forming resealable and viscoelastic hydrogels. The gelation ability is attributed to the salt bridges between the Lys and Asp residues and the hydrophobic interactions between the Leu or Phe residues. This study provided a strategy for using the cyclization method to deliver promising therapeutic peptides with self-assembly and the stimuli-responsive ability for treating injury or disease.

Di and Niu et al. identified a potent PLK1-PBD (Polo-like kinase-1 C-terminal polo-box domain) inhibitor Ac-ETΔDPPLHSpTA-$NH_2$ (Δ, L-3,4-dichlorophenylalanine) by pharmacophore mapping, virtual screening and molecular docking.[20c] The inhibitor showed a binding affinity of 39 nM to the receptor. Considering the low pharmacological abilities of the linear peptide, the cyclopeptide precursor C-1 was employed to increase the thermostability and pharmacological abilities before reaching the target. As shown in Figure 8, the cyclic peptide prodrug **11** (Ac-cyclo-(1,9)-CRRRRFΦECΔDPPLHSpTA-$CONH_2$) was designed with one cyclic ring and one functional tail for target binding. Specifically, the cyclic ring contained three distinct domains: i) a cell-penetrating


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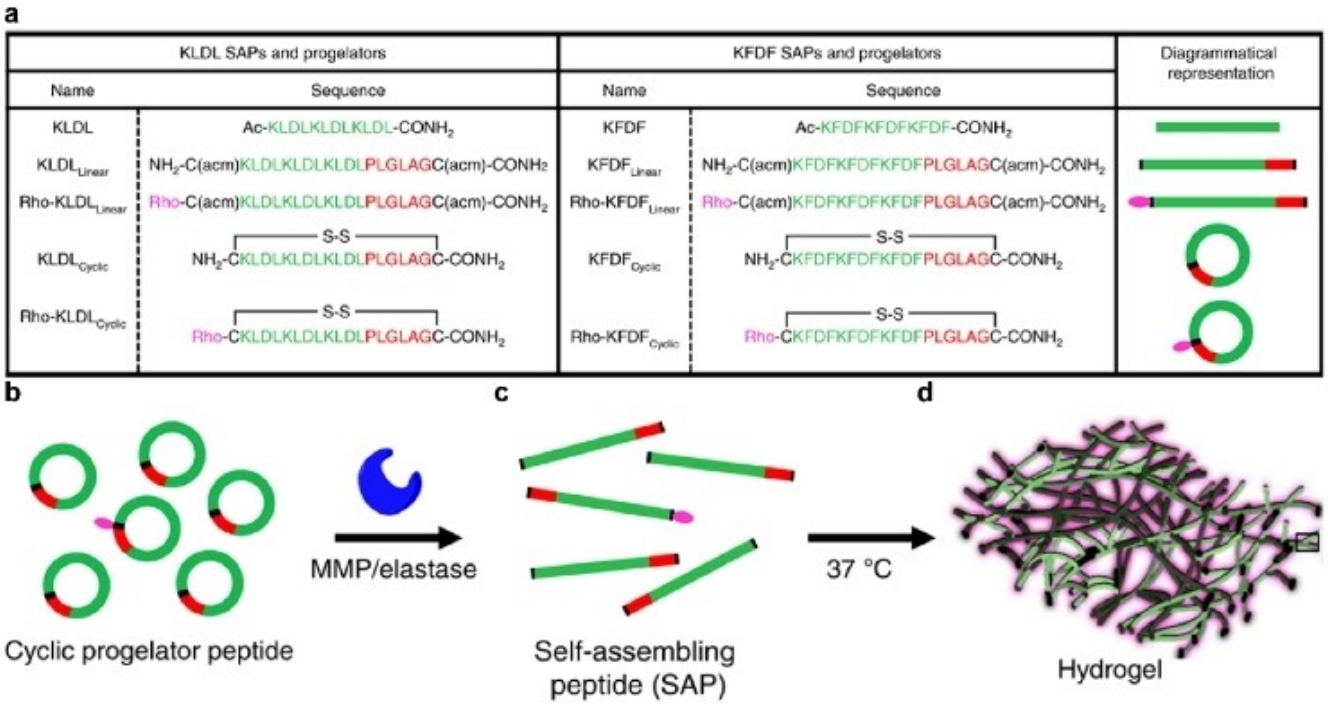


**Figure 7.** a) Sequences and design of self-assembled peptides and their corresponding cyclic, enzyme-responsive progelators. b) Cyclic peptide progelators. c) Enzyme cleavage resulted in self-assembled linear peptides. d) Linear peptides self-assemble into hydrogels. Reproduced with permission from ref. [20b]. Copyright: 2019, Springer Nature.

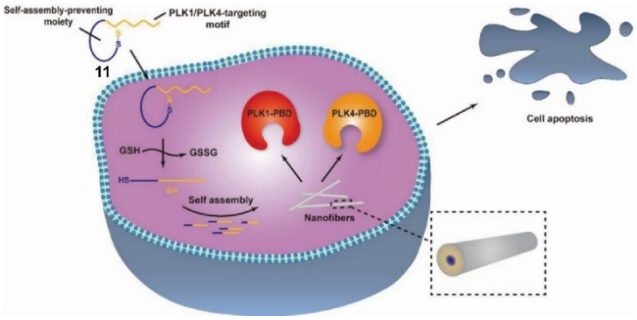


**Figure 8.** Cyclic peptide **11** as a redox-responsive bispecific PLK1/PLK4 nanomedicine progelator. Reproduced with permission from ref. [20c]. Copyright: 2020, John Wiley and Sons.

tetrapeptide consisting of four sequential Arginine (RRRR); ii) a hydrophobic dipeptide FΦ to promote peptide self-assembly; iii) two cysteines flanked at positions 1 and 9 to form a reduction-responsive disulfide bond, which prevents the self-assembly of C-1 before exposed to GSH. The cyclic precursor could be reduced in a tumor environment with a high concentration of glutathione. After entering the cytosol of the cancer cells, the linear peptide generated in situ self-assembled into nanostructures. The nanostructures could bind to PLK1 and PLK4 specifically, further promoting the cancer cells entry into apoptosis process. This approach could be useful for treating cancers with the overexpression of PLK1 and PLK4.

## 5. Summary and Outlook

Since the earliest report in the mid-1970s, cyclic peptides with the ability to self-assemble have attracted substantial study as they have applications in various areas, including ion channels, antibacterial agents, sensors, and drug delivery. These kinds of cyclic peptide have a large backbone diversity ranging from α- to β-amino acids, α,γ-amino acids, and even pseudo-amino acids. Moreover, the side chains provide ample spaces and numerous opportunities for modification with polymers, peptides, or other molecules. Among all the cyclic peptides with propensity to self-assemble, cyclic alternative D/L peptides are the best studied and characterized. New methods for the construction of cyclic peptides of this kind of and their conjugates will continuously draw significant attention, which will benefit drug delivery and the development of nanomedicines. By contrast, some cyclic peptides constructed through disulfide bonds have a low assembly ability due to conformational constraints, but can act as progelators, which could be converted to linear peptide gelators. Having the advantages of cyclic peptides, such as increased cell permeability and higher stability, the progelators can be converted to linear peptides gelators by certain stimuli-triggered (i.e., redox conditions or highly expressed enzymes in tumor environment) cleavage, thus acting directly as nanomedicine. As this field is just emerging, with the size of cyclic peptide libraries increasing and new methods for peptide and polymer conjugation emerging, we envision that cyclic peptides and their conjugates


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will be inherently useful scaffolds for the construction of stimuli-responsive and adaptive systems for drug delivery.

## Acknowledgements

*This project was supported by the National Natural Science Foundation of China (82272145).*

## Conflict of Interests

The authors declare no conflict of interest.

**Keywords:** cyclic peptides · self-assembly · peptide polymers · drug delivery · nanomedicine

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Manuscript received: January 10, 2023
Revised manuscript received: March 26, 2023
Accepted manuscript online: April 5, 2023
Version of record online: June 28, 2023


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