DRUG DELIVERY APPLICATIONS OF PEPTIDE SELF-ASSEMBLED NANOSTRUCTURES

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ABSTRACT

Peptide self-assembled nanostructures are most popular in many biomedical applications. Drug delivery is one of the most enterprising applications among them. The enormous advantages for peptide self-assembled nanostructures include good bio-compatibility, low cost, tunable bioactivity, high drug loading capacities, chemical diversity, specific targeting, biodegradability and stimuli responsive drug delivery at disease sites. Peptide self-assembled nanostructures such as nanoparticles, nanotubes, nanofibers, and hydrogels have been investigated by many researchers for drug delivery applications(ref). In this review, the underlying mechanisms for the self-assembled nanostructures based on peptides with different types and structures are introduced and discussed. Peptide self-assembled nanostructures associated promising drug delivery applications such as anticancer drug and gene drug delivery are emphasized. Furthermore, peptide self-assembled nanostructures for targeted and stimuli responsive drug delivery applications are also reviewed and discussed.

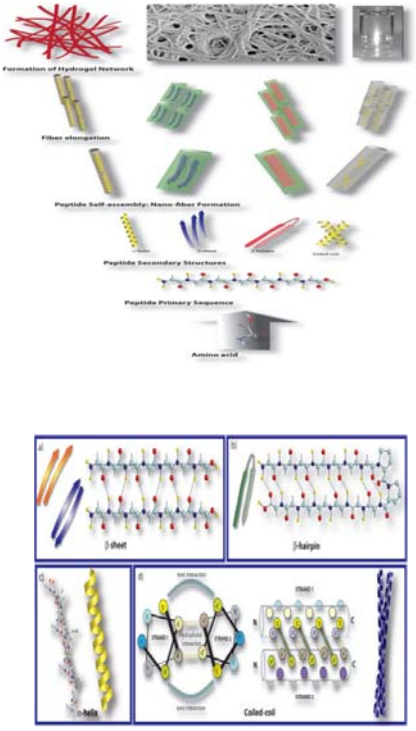
Key words : Peptide, Hydro-gel, Bio-compatibility, Biodegradability

I INTRODUCTION

Hydrogels can be formed by the self-assembly of dipeptides in water. The ability of peptide molecules to adopt specific secondary, tertiary and quaternary structures provides unique opportunities for design of nanoscale materials that are not easily available with traditional organic molecules and polymers. Self-assembly of small molecules are governed by the presence of following factors: (a) hydrophobic interaction, (b) p–p stacking, (c) hydrogen bonding, (d) electrostatic interactions. H-bonding interactions can be formed between amino acids, and aromatic groups can interact together via π-π stacking interactions. These interactions lead to the formation of one-dimensional structures that grow and entangle to form fibers, which entraps the water to form a hydrogel. These type of interactions are weak individually, but they can together lead to self-assemble and form a stable hydro-gel[1, 2, 6, 7, 9, 10, 17, 20, 21]. Proper sequencing of amino acids in a peptide molecule could easily establish self-assembly. It has been reported that a change of the order may lead to significant change to the hydrogelation process[7, 8, 17]. For instance, if we compare between dipeptides that have similar amino acids and different substitution positions of a bromine atom, we note that they have different gelation results.

The self-assembly of peptides leading to hydrogelation is a hierarchical process and could be simplified as shown in Fig.(1)Moreover, the self-assembly process is also very important in the functions of cell-penetrating peptides that could play an important role in delivering the drugs inside the cell membrane and transporting genes into the nucleus. In solution, peptide molecules adopt a specific secondary conformation and in the presence of appropriate stimuli or favorable physical conditions these secondary structures then self-assemble to form nanofibres. Elongation of these fibers in three-dimensional space leads to thicker and longer fibers, which further assembles to a fibrillar network. These 3D networks of peptides capable of entrapping water molecules provide a self-supporting hydrogel. Manipulation of the physical properties of these hydrogels can be fine-tuned by playing with the amino acid

sequences. Thus, control over the synthesized materials is achieved. In the last two decades, several attempts have been made to prepare and understand peptide-based hydrogels which contain different secondary structural motifs such as a-helix, b-sheet, b-hairpin and coiled coil. Even though a-helix based fibrous and a-helix-containing gelling materials have been explored to some extent, 14–19 much of this effort has been engaged to the assemblage of b-structured systems.

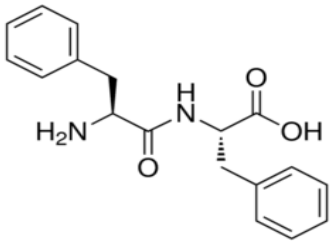


(figure number 1)

II PEPTIDE TYPES AND STRUCTURES FOR SELF-ASSEMBLY

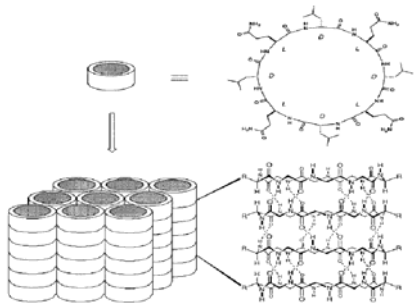
Peptides can be assembled into different nanostructures including nanotubes, nanofibers, and nanovesicles based on their design and self-assembly conditions [9]. Different types and structures of peptides including dipeptides, cyclic peptides, amphiphilic peptides, α-helical peptides, and β-sheet peptides have been utilized to self-assemble into nanostructures.

A. Dipeptide. Recently, researchers have claimed that short peptides have the ability to self-assemble into many different nanostructures that can minimize the difficulty and cost of the fabrication process and simultaneously enhance the stability [11, 12]. Among them, dipeptide self-assembled nanostructures are investigated intensively for various biomedical applications including drug delivery. Diphenylalanine(fig. number 2) , Phe- Phe (FF), the first reported dipeptide that has been used for the self-assembly of different nanostructures, is a core motif of the amyloid-β polypeptide segment [13]. It has been Reproduced from [9] with permission from the Royal Society of Chemistry. Recognized as the core recognition motif to drive self assembly in Alzheimer's disease. Many studies have been carried out to self-assemble FF dipeptides into different nanostructures including nanoparticles, nanotubes, nanovesicles, and nanowires [10, 14–18].



(figure number 2) *Diphenylalanine*

B. Cyclic Peptide. Cyclic peptides with alternating D type and L type amino acids that could self-assemble into nanotubes were determined theoretically as early as 1974 [74]. However, the first self-assembled nanotube using cyclo-(LGln-D-Ala-L-Glu-D-Ala)2 cyclic peptides was achieved in 1993 based on that theory [22]. The cyclic peptide self assembly is formed through aggregating cyclic peptides as basic building blocks to a flat conformation structure(fig. number 3)where the amino and carbonyl side chains are arranged perpendicular to the ring [23]. The cyclic peptide self-assembled nanotubes were self-assembled and stabilized by hydrogen bonding between amide groups [24]. Due to the alternating D type and L type amino acids, the peptide side chains could be formulated on the outside area that can create a nanotube structure. There are many cyclic peptide sequences that can be used for the self-assembly, including alternating D type and L type α-amino acids, alternating α- and β-amino acids, β-amino acids, and δ-amino acids [22, 23, 25, 26].



(figure number 3)*Cyclic peptides with alternating D type and L type amino acids adopted flat ring*

C. Amphiphilic Peptide. Amphiphilic peptides have many different types such as linear peptides, ionic complementary peptides, peptide phospholipids, and long-chain alkylated peptides [27, 28]. Amphiphilic peptides are generally formed from hydrophilic peptide head groups and hydrophobic tails that could be used to form various secondary and tertiary conformations [29, 30]. These peptides could self assemble into nanostructures with many different morphological structures including nanovesicles, nanotubules, and nanomicelles [28, 31]. The electrostatic and hydrophobic interactions are thought to be the main factors that drive the self-assembly for amphiphilic peptides [32].Linear peptides with hydrophobic tails and hydrophilic heads have the ability to self-assemble into different nanostructures depending on their chemical properties and physical properties. For the hydrophobic tail, A, G, L, and F amino acids are good candidates. On the other hand, the amino acids D, E, H, and R are always utilized in the hydrophilic domains [33]. For example, lipid-like peptides similar to surfactants, such as G4DD, G6DD, G8DD, A6D, A6 K, and KA6 sequences, can self-assemble into various nanostructures once they reach the critical aggregation concentration [32, 33]. Because they are very similar to phospholipids, those peptides have the potential to stabilize membrane proteins.

D. α-helical peptide. For decades, it has been well known that biological and physical properties can enhance the self assembly of peptides into helical structures. Actuarially, there are only several major molecules that have been discovered with the purpose of self-assembling these helical structures into nanostructural biomaterials. The α-helical peptides have drawn researchers' attention because they can form nanostructures that are very common in the cytoskeleton and extracellular matrix in biological systems [35]. For example, these filamentous nanostructures could be formed from α- helical peptides with 25–50 amino acids [36]. The α-helical peptides with 2–5 helices can aggregate around each other to form nanofibers [37, 38]. These α-helical peptides can also self-assemble into nanofibers using around 30-amino-acidlong peptides through helical coiled-coils structures [39]. The hydrophobic residues could promote the helix oligomerization through hydrophobic collapse. Another nanofibrous structure could also be formed using the peptides with central Glu amino acid and Lys amino acid at the end of the sequence through ionic interactions [40].

*E. β-Sheet Peptide.*The β-sheet is one of the most useful naturally occurring motifs that can be used for peptide self assembly [41]. Tremendous peptides have been studied for self-assembling β-sheet secondary structures. The β-sheet consists of alternating hydrophilic and hydrophobic amino acids in the peptide sequence, which can provide amphiphilic property to the peptide that drives the self-assembly of β- sheets [75]. The β-sheet peptides also could be utilized to form many different nanostructures including nanotubes, mono layers in nanoscale order, and nanoribbons [42–46]. For example, β-sheet peptide QQRFEWEFEQQ can self assemble into a pH responsive hydrogel using peptides' ionizable side chains from Glu and Arg amino acids. These peptides are soluble in neutral pH condition and transform to a hydrogel structure at low pH conditions [42].The reason is that anti parallel β-sheet tapes were formed at lower pH values and then stacked together to form nano fibrils in hydrogels. The β-hairpin peptides were also found to self-assemble into various nanostructures at the water and air interfaces [47]. The self-assembly of β-hairpins in proteins is based on the arrangement of two β-sheets in antiparallel formats. A β- hairpin peptide with the sequence of VKVKVKVKVDPPTKVKVKV was utilized to form responsive hydrogels. This material could be formed from the increase of the pH values. The underlying mechanism is that the hydrogels could be formed from the hairpin structure that

was self-assembled from β-sheets formation after the increase of the pH values[48].

III.PEPTIDE SELF-ASSEMBLY MECHANISMS

Electrostatic interaction, hydrophobic interaction, hydrogen bonding, and π-πstacking (fig. number 4)are the key contributors of peptide self-assembly [49]. Nonpolar amino acids, such as aromatic and aliphatic amino acids, are mainly responsible for hydrophobic aggregation through π-πstacking and hydrophobic interactions. Polar amino acids result in either electrostatic interactions or hydrogen bonding depending on whether they have uncharged or charged residues [50]. Besides individual amino acids, the peptide backbone itself also provides considerable stability through hydrogen bonds.

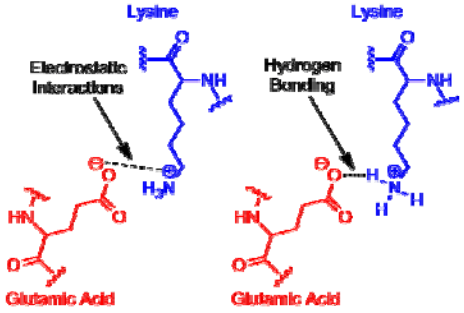
A. Electrostatic Interaction. Electrostatic interactions involve both attractive and repulsive forces between charged residues from amino acids in the peptide self-assembly, which also have strong effects on many other self-assembly processes. Positively charged peptides have the ability to aggregate with negatively charged peptides or even drugs by electrostatic interactions. After that, they could form a stable nanostructure that could be used for drug delivery applications [51]. For instance, a multi functionalized peptide self assembled nanostructure was designed and synthesized using cRGD-BSA and KALA cell-penetrating peptides through electrostatic interaction. These nanostructures could be used for targeted and pH responsive anticancer drug delivery applications [52].

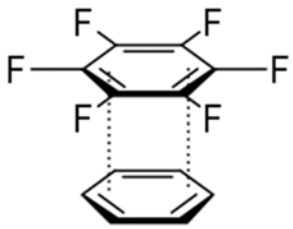
B. Hydrophobic Interaction. The hydrophobic interaction isone of the most important effects among various noncovalentinteractions in the peptide self-assembly process.The self-assembly of amphiphilic peptides could be readilyaccomplished through micro phase separation driven bythermodynamics because of the coexistence of polar andnonpolar regions inside the peptide sequences. In the aqueousreaction condition, the nonpolar segments of the basic units will collapse and cluster together to try to hide the hydrophobic area from water. Meanwhile, the polar areas attempt to enhance their contact with water [53, 54]. For instance, amphiphilic drugs that can be self-assembled into nanostructures were developed based on hydrophobic interactions. The amphiphilic drugs are composed of a tau proteinderived peptide conjugated with a hydrophobic anticancer drug camptothecin. These materials could be self-assembled into fibril structures through hydrophobic interactions and intermolecular hydrogen bonding [55].

C. Hydrogen Bonding. Naturally occurring hydrogen bonding patterns such as those found in α-helices, β-sheets, and coiled coils are utilized for the design of various peptide sequences to self-assemble into nanostructures. Hydrogen bond is the electrostatic attraction between H atom and a highly electronegative atom nearby, such as N and O. Hydrogen bonding has a key role in the formation and stabilization of the peptide secondary structure and protein folding. Actually, among different noncovalent interactions, hydrogen bonding is probably the most important one in peptide self-assembly. The stabilization of multiple peptide backbone arrangements is based on hydrogen bonding interactions through the amide and carbonyls groups in the backbone. After that, they can self-assemble into β-sheet structures. These structures could be in parallel or antiparallel arrangements according to the direction of the peptide sequences. Peptide is typically designed to contain repeating amino acid residues for hydrophobic and hydrophilic regions. Therefore, the hydrophobic part will be buried within the self-assembled nanostructure while the hydrophilic region is exposed to the aqueous environment [56]. Unlike β-sheets, α-helices are formed by individual peptide chains where backbone amide components are intramolecularly hydrogen bonded. This arrangement leads to the presentation of side chains from amino acids on the surface of each helix and further facilitates the accessibility of them in the solvent.

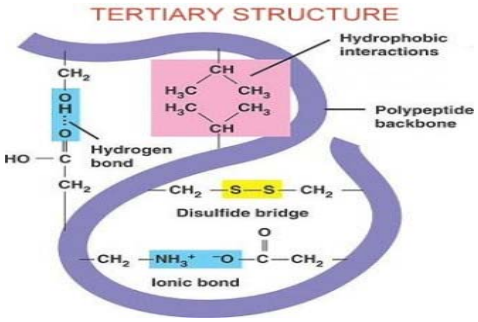
*D. π-πStacking.*The π-π stacking can promote the peptide self-assembly, especially for aromatic peptides. The interactions for π-π stacking can drive directional growth and they are robust in water due to their limited solubility of molecules containing aromatic groups [57]. The π-π stacking is also a more distinct driving force in pure organic solvents such as toluene

and TFA. These solvents can make the π-π stacking more dominant than other self-assembly effects [16]. For the dipeptide FF self-assembly process, π-π stacking from the aromatic groups and hydrogen bonding stabilized the self assembled FF nanostructures, which have been demonstrated for various applications including drug delivery [19, 58]. In summary, noncovalent interactions play very important roles in the peptide self-assembly processes. As these noncovalent interactions are easily affected by the external stimuli, these factors including pH values, temperature, and reaction solvent polarity can also trigger the self-assembly and manipulate the self-assembly process and even the final formed nanostructures. For example, pH values are very important for peptides with charged amino acids such as Glu, Asp, Lys, His, and Arg. The status of these peptides with negative or positive surface charges could be sensitively affected by the pH values and then self-assembled into different nanostructures [5]. Tunable management of the physical and biological properties of peptide self-assembled nanostructures is highly desired for their successful utilization in drug delivery applications. When designing peptide self-assembled nanostructures for drug delivery, noncovalent interactions, as well as peptide types and structures, should be taken into consideration and be rationally applied in the strategies.





Pi-pi stacking



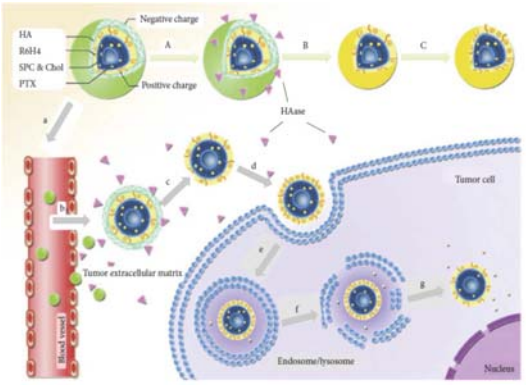
(figure number 4)

IV. DRUG DELIVERY APPLICATIONS OF PEPTIDE SELF-ASSEMBLED NANOSTRUCTURES

In the past decades, peptide self-assembled nanostructures with various sizes and shapes have been fabricated and utilized for many biomedical applications such as tissue regeneration, biosensors, bio-imaging, and drug delivery. In this section, peptide self-assembled nanostructures for anticancer drug and gene drug delivery as well as targeted and stimuli responsive drug delivery are illustrated and discussed in detail. The most desired properties for self-assembled nanostructures are biocompatibility, biodegradability, and multi functionality for drug delivery applications [4, 58]. Compared to other organic materials for drug delivery, peptide self-assembled nanostructures are more suitable due to their intrinsic physical and biological properties.

A. Anticancer Drug Delivery. Although tumors are one of the most deadly diseases worldwide, the proper therapy strategy is still far away from the real demand. Therefore, there is still a need for new materials or methods for cancer therapy. Nanomaterials as drug delivery carriers have many advantages including high efficiency for drug loading, a low ratio for drug loss, and high stability to avoid body clearance [60]. For example, nanostructures could be used for anticancer drug delivery because they have the ability to both enhance the therapeutic efficiency and decrease unwanted negative reactions. Among various nanostructures, peptide self-assembled nanostructures have attracted increasing attention for anticancer drug delivery and are believed to be a promising strategy for cancer treatment. The peptide has the ability to self-assemble into many different nanostructures such as nanoparticles, nanotubes, nanovesicles,

and nanofibers that form hydrogels [61]. All of them could be used to deliver different types of anticancer drugs for cancer therapy. For instance, the peptide with amphiphilic properties could self-assemble into nanovesbeen demonstrated to deliver hydrophobic anticancer agents for cancer therapy. icle structures, which have Meanwhile, the outside layer of these nanostructures could be tuned to achieve specific drug delivery purposes [62]. Peptide self-assembled hydrogel with injectable properties could also be used to directly come into contact with the tumor sites to enhance the efficacy and safety of tumor therapy [63]. The peptide self-assembled nanofibers that form injectable hydrogels could be the most interesting materials for anticancer drug delivery applications, because, in this way, the chemotherapeutic drugs could directly come into contact with the targeted cancer tissues at higher local concentrations compared with traditional cancer therapy methods. These peptide hydrogels could be more safe and controllable due to their slow release rates. Peptide-based hybrid nano structures were also fabricated from polylactide (PLA) and VVVVVVKK (V6K2) peptides [34].These nanostructures could conjugate with doxorubicin and paclitaxel for anticancer drug delivery in cancer therapy applications. The pure PLA nanoparticles have a diameter of around 130 nm, but the PLA-V6K2 self-assembled nanoparticles only have a diameter of around 100 nm. The encapsulation and anticancer drug releasing ratios for PLAV6K2 nanoparticles are significantly higher and slower than the pure PLA nanoparticles. Moreover, the experiments have demonstrated that the PLA-V6K2 nanoparticles conjugated with anticancer drugs have higher toxicity to cancer cells and no toxicity to normal cells compared with free doxorubicin or paclitaxel and pure PLA nanoparticles conjugates. Therefore, this study demonstrated the higher efficacy of these PLAV6K2 nanoparticles for anticancer drug delivery that could be potentially useful in cancer therapy [64].

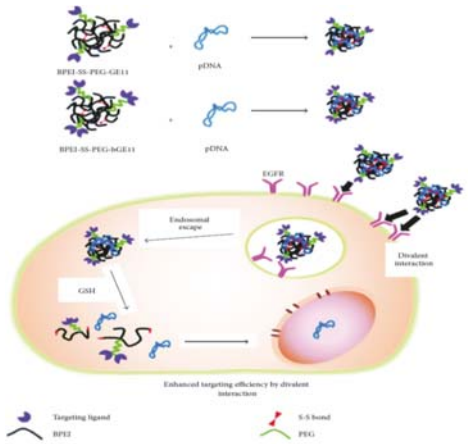


(figure number 5)

Schematic design of the multifunctional nanostructures for tumor-targeted drug delivery

B. Gene Drug Delivery. The great progress in biotechnology, as well as many other fields with better acknowledgment of the pathology mechanisms for various diseases from the gene levels, has promoted a big change in many different diseases' diagnosis and therapy. Researchers have used recombinant plasmid DNA as a gene drug for delivery to the specific target for gene therapy. In this way, the functional proteins from the related gene encoding could be applied to heal patients. The gene drug delivery needs cost-effective methods and noninvasive approaches for this specific gene disease therapy [65]. Although more and more attention has been paid to gene therapy, there is still huge enhancement needed for the study of nonviral gene drug delivery platforms currently. For example, the nanocarriers for gene drug delivery should be improved through different perspectives including toxicity, immunogenic response, and poor uptake into cells and the nucleus [66, 67]. Therefore, attention for the design and fabrication of nanostructures for gene drug delivery should be paid to the enhancement of cellular delivery, specific delivery, and improvement of loading efficacy. Cationic nanostructures have been intensively studied and utilized because they are easier to be delivered into cells and because of their high loading capacity for nucleic acids [68]. Most importantly, peptide self-assembled nanostructures present a very promising and efficient method for gene drug delivery due to their intrinsic properties and precisely controllable fabrication approaches. Peptide self-assembled nanotubes also could be used for gene

drug delivery through the transforming of nanotube structures into nanovesicles in the endocytosis process [69]. Therefore, many conjugations of gene drugs and peptide self-assembled nanostructures have been developed recently for the gene drug delivery systems [70]. One of the most important properties of peptide selfassembled nanostructures for gene drug delivery is the conjugation between these nanostructures with DNA. Moreover, because of the easier modification and tunability of the peptide building blocks, these peptide self-assembled nanostructures could also increase the DNA uptake through cell membrane and nucleus. They also have the ability to control the gene drug release and enhance gene expression [71]. Therefore, researchers could focus on developing vectors with improved efficiency, safety, and specificity. Although there are several studies using peptide self-assembled nanostructures or gene drug delivery, it is still far away from the real demand.



(Figure number 6)
Schematic of gene drug delivery by using GE11 peptide-based self-assembled nanostructures

C. Targeted Drug Delivery. For drug delivery applications, specific targeting with desired sites is very important for the nanocarriers to deliver or transport the drugs efficiently [72]. For this purpose, peptides self-assembled nanostructures have many advantages such as easier modification properties and tunable design of the recognition motifs. For example, cell-penetrating peptides are cationic peptides with less than 30 amino acids, which could be used to promote the penetration of the cell membrane to make the drug or gene delivery more efficient [73]. Most importantly, the self-assembly mechanism is also very important for the enhanced membrane transport using cell-penetrating peptides. Besides that, there are also many other proteins or aptamers that could be used to enhance cell penetrating or specific targeting especially for cancer cells or disease sites. For example, dipeptide WF self-assembled nanoparticles have been developed for targeted drug delivery for cancer therapy [3].

V. CONCLUSIONS AND PERSPECTIVES

Peptide self-assembled nanostructures could construct well defined structures through the noncovalent forces including electrostatic interaction, hydrophobic reaction, hydrogen bonding, and π-πstacking. The morphology and function of the peptide self-assembled nanostructures can be manipulated from the molecular level by tuning the types and structures of peptides, or external triggers such as temperature, pH value, and electric field. Recent studies have shown that these peptide self-assembled nanostructures have been utilized for many different biomedical applications. The examples presented in this paper highlight the potential role of peptide self-assembled nanostructures for drug delivery applications. One peptide self-assembled nanostructure could include multiple functions such as cell penetration, specific targeting, release responsive mechanism, and endosomal escape motifs. However, people are still facing many challenges such as predicting precise molecular or higher structures, functional properties, and bio-safety from the peptide self-assembly. Another major challenge is the high yield of the peptide nanomanufacturing. This is also very important for the clinical applications. In conclusion, with multidisciplinary efforts, peptide self-assembled nanostructures for drug delivery applications have much potential and are very promising to treat human diseases.

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