

Self-assembly of Functional Nanostructures by Short Helical Peptide Building Blocks



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Abstract: The self-assembly of short peptide building blocks into well-ordered nanostructures is a key direction in bionanotechnology. The formation of  $\beta$ -sheet organizations by short peptides is well explored, leading to the development of a wide range of functional assemblies. Likewise, many natural proteinaceous materials, such as silk and amyloid fibrils, are based on  $\beta$ -sheet structures. In contrast, collagen, the most abundant protein in mammals, is based on helical arrangement. Similar to  $\beta$ -sheet structures, short helical peptides have been recently discovered to possess a diverse set of functional ities with the potential to fabricate artificial self-assembling materials. Here, we outline the functional roles of self-assembled nanostructures formed by short helical peptides and their potential as artificial materials. We focus on the association between self-assembled mesoscale structures and their material function and demonstrate the way by which this class of building blocks bears the potential for diverse applications, such as the future fabrication of smart devices.

Keywords: Self-assembly, short peptide, helical conformation, nanostructure, nanotechnology,  $\beta$ -sheet structure.

#### **1. INTRODUCTION**

Biomolecular self-assembly into controllable nanostructures has recently emerged as an exciting direction of research to fabricate materials with novel functional properties [1-4]. In natural biological systems, self-assembled proteins nanostructures play diverse key roles, such as the selfassembled molecular structure of the actin cytoskeleton, which provides physical rigidity to the cell, self-assembled microtubules that allow the transport of cargo within the cells, and self-assembled collagen fibers, the most abundant component in the Extracellular Matrix (ECM), which play an essential role in cell adhesion and growth [5-7].

Inspired by this ubiquitous use of proteins by nature, a number of self-assembled artificial materials have been developed. However, the exploitation of protein self-assembly to fabricate desired materials is extremely challenging due their complex nature and the difficulties in controlling the self-assembly process. In this context, peptides are attractive building blocks because of their simple synthesis, rich chemical diversity and inherent biocompatibility. In addition, the wide range of available amino acids allows to modify the physical and chemical properties by varying the primary structures, adjusting them to specific applications. The selfassembly of peptides and their various analogues has been employed to prepare diverse interesting nanostructures, including fibers, tubes, ribbons, vesicle, films, and threedimensional (3D) networks, which have been utilized for diverse functional purposes, such as drug delivery, tissue engineering, sensing, optoelectronics, catalysis, and biotechnology [1-3, 8-11].

The self-assembly is mainly driven by different noncovalent interactions such as hydrogen bonding, electrostatic attraction, and van der Waals forces. These interactions underlie the formation of two major secondary structural motifs designated as  $\alpha$ -helix and  $\beta$ -sheet. Based on the wealth of existing knowledge regarding the effects of these noncovalent interactions, it has been possible to design  $\alpha$ -helical or  $\beta$ -sheet peptide sequences that self-assembled into tailor nanostructures. The  $\beta$ -sheet structure is well known for its occurrence in amyloid fiber forming peptides initially related with several neurodegenerative diseases [12]. However, it was later realized that amyloid fibrils play various crucial roles in nature as cellular and extracellular materials [3, 13, 14]. Thus, most of the studied artificial peptides were designed to fold into  $\beta$ -sheet secondary structure and their selfassembled nanostructures and functions have been extensively demonstrated [15-17].

Yet, the most common secondary structure found in globular proteins is  $\alpha$ -helix. The natural functional roles of helical proteins have recently opened a new avenue of research aimed to design highly controllable artificial proteinous nanomaterials with predictable functional properties.

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#### Self-assembly of Functional Nanostructures by Short Helical Peptide

The self-assembling peptides were designed either by mimicking natural sequences of helical proteins or by incorporating non-coded amino acids with higher helical propensities into sequences. The understanding of sequence-to-structure relationships of helical peptides and their functional roles opens a new direction of molecular engineering and development of future functional materials.

# 2. FUNCTIONAL PROPERTIES OF HELICAL PRO-TEINS/PEPTIDES IN NATURE

The  $\alpha$ -helical coiled-coil structural subunit is a ubiquitous protein folding motif estimated to occur in 5-10% of all proteins [18, 19]. Coiled coil structures are an association of two or more  $\alpha$ -helices packed together *via* interlocking of side chains, known as hydrophobic knob-into-hole packing, as well as complementary electrostatic interactions. They play important roles in protein machineries that intervene several key biological processes ranging from gene transcription and molecular recognition to viral infection. They also provide mechanical stability to cells and are involved in movement processes.

Another important helical structure protein family is collagen, the most abundant protein in the human body [20-22]. They are found in the ECM in a wide variety of tissues such as cartilage, bones and skin. All the proteins in this family fold into a common structural arrangement known as collagen triple helix. This structure is constructed by three polypeptide chains, known as alpha chains, which adopt a lefthanded helical conformation and interact with each other to form a tightly packed right-handed super-helix. Despite of their similar secondary structure, collagen proteins selfassemble to generate a wide variety of supramolecular structures adapted to their specialized functions [22]. The most common collagen assembly structure is fibrils, which provide structural stability to most connective tissues. The sheet morphologies of collagen are found to constitute basement membranes, Descemet's membrane, worm cuticle, and organic exoskeleton of sponges. Beside these, collagen also plays a crucial role of connecting different tissue components. For example, the Fibril Associated Collagens Containing Interrupted Triple helices (FACIT) connect fibrils to other matrix elements. In addition, collagen self-assembles into anchoring fibrils that bind epithelial basement membranes and entrap collagen fibrils from the underlying stroma to glue the two structures together, and thin-beaded filaments forming collagen interacts with fibrils and cells.

Apart from the functions of coiled-coil and collagen, electron transfer through helical proteins is also a fundamental process in many biological metabolic cycles [23]. Mitochondrial respiratory electron transfers to produce Adenosine Triphosphate (ATP), as well as photosynthetic processes in which ATP is created by the use of sunlight, are two central examples of electron transfer processes. In all these processes, electrons generally travel over long distances *via* proteins with predominately  $\alpha$ -helical secondary structures.

### 3. NANOSTRUCTURES OF HELICAL PEPTIDES FOR DIVERSE FUNCTIONAL APPLICATIONS

The characteristics of helical peptides and their natural uses make them attractive building blocks for the fabrication of artificial functional materials. Several de novo design principals were adopted for long peptide sequences contained 20 or more amino acids to fold into helical conformation and self-assembled into tailored functional materials. The α-helix based coiled-coil protein structure has been extensively exploited in the design of self-assembled, onedimensional nanofibrous materials [24, 25]. The most common strategy is design based on the "sticky-end" concept in which  $\alpha$ -helical peptides interact, leaving dangling ends that can nucleate the addition of further helices at both ends and support growth in axial direction. Using this strategy, Woolfson and coworkers have designed 28 residue coiled coil peptides and explored their self-assembled fiber formation and subsequent hydrogelation for the development of biomaterials [26, 27]. Slight modification of the building blocks resulted in unique supramolecular nanostructures, including linear, waved, kinked, and branched morphologies [28, 29]. Using a 21-residue peptide, Hartgerink and colleagues have designed self-assembled coiled coil nanofibrils without "sticky ends" features [24]. Coiled coil peptides were also designed to use as mild temperature triggers and pH sensitive triggers for the controlled release of encapsulated molecules from liposomes [30, 31]. Other study demonstrated supramolecular assembly of a coiled coil structure into helical nanotubes [32]. The sticky-ended assembly of long peptides has also been explored for the development of several collagen mimetic peptides that self-assembled into hydrogels and other functional biomaterials [33, 34]. So far, most of the design principles of peptide folding into helical structures and self-assembly into tailored functional materials have been exploited for long peptide sequences, and several excellent reviews have nicely described their design principles and the resulting self-assembled functional nanostructures [1, 35]. However, recent studies found that ultra-short peptide sequences also possess the ability to fold into similar helical conformations and aggregate to a variety of supramolecular nanostructures with promising potential for multifarious pharmaceutical and nanotechnological applications. In this focus review, we will discuss the different types of nanostructures produced by self-assembled short helical peptide sequences and their diverse biomedical and electronical applications.

# 3.1. Helical Peptide-based Nanostructures as Delivery Vehicles

Recent works suggest that nanostructures fabricated by the self-assembly of ultra-short helical peptides can serve as carriers for various cargos. Haldar and co-workers reported the formation of supramolecular helical column through intra- and intermolecular hydrogen bonding interactions and interdigitated helical bundle structures by a hydrophobic pentapeptide [36]. The peptide self-assembled into mesoporous vesicles in methanol solution, with the diameter



**Figure 1. a)**, Supramolecular helical column structure; **b,c**), Vesicle morphologies; and **d,e**), drug binding of a pentapeptide [36]. **f,g**), Lowest energy structures obtained from the NMR structure refinement of  $\beta$ -peptides and **h,i**), their corresponding vesicle morphologies [39]. **j**), Schematic model of drug binding and release mechanism in vesicle nanostructure [36]. Figure reproduced with permission from respective references.

increasing in a concentration-dependent manner (Figure 1). The authors exploited the mesoporous vesicular structures for the encapsulation of a potent bacteriostatic antibiotic, sulfamethoxazole. They were also able to control the release of encapsulated drug depending on the pH of the medium. In other studies, this group reported the formation of supramolecular parallel double helical structures using capped  $\gamma$ -peptide [37, 38]. Solvent interactions were found to have a significant effect on the molecular folding and structural diversity that lead to a change in the initial helical conformation. By changing the solvent from methanol to chloroform, the higher order assembly of the helical strand changed from supramolecular sheet to double helical structure. The nanostructures obtained from different solvents also showed significant diversities in morphology. This helical peptide also strongly interacted with sulfamethoxazole.

Vesicle nanostructures were also obtained from helical  $\beta$ peptide oligomers, as reported by Fülöp and co-workers [39-41]. Alternative H10/12 helix stabilization of a  $\beta$ -peptide was achieved through the utilization of aromatic side-chains [39]. Nuclear Magnetic Resonance (NMR) and Circular Dichroism (CD) spectroscopic characterization clearly indicated the presence of the H10/12 helix in organic solvents. The stability of the helix was found to depend on the chain length. In methanol solution, all the studied oligomers formed a vesicle structure (Figure 1). The effect of modified side-chains containing six-membered alicyclic rings of the  $\beta$ peptidic H10/12 helix was also studied [40]. Conformational polymorphism was observed upon changing the side chain as demonstrated by chemical exchange between the major lefthanded H10/12 helix and a minor folded conformation. The helical peptides were self-assembled to produce vesicles ~100 nm in diameter. These vesicle structures can be potentially used as drug delivery systems.

Our group recently reported the ability of a non-coded amino acid,  $\alpha$ -aminoisobutyric acid, to stabilize very short peptides in helical conformation and designed the first-ever self-assembling single heptad repeat module [42]. Morphological analysis of the self-assembled helical peptide indicated the presence of fiber structures. Modification of the minimal building block with helix favoring leucine at the *a* and *d* positions and a positively charged lysine residue in place of serine resulted in tight DNA binding ascribed to the combined features of helicity, hydrophobicity and positive charge. Secondary structure analysis revealed that the backbone of the modified peptide also adopted a similar helical conformation. The distinctive formation of toroid and rodlike structures revealed in TEM images of peptide-DNA conjugates indicated peptide-induced condensation of plasmids.

Kim and co-workers utilized the stimulus-responsive conformational conversion of a  $\alpha$ -helical peptide on the surface of mesoporous silica nanoparticles to prepared peptide gatekeepers [43]. Without any external stimulus, the helical peptide gatekeepers were shown to block the release of the entrapped drugs. Addition of Glutathione (GSH) resulted in a reduction of the intramolecular disulfide bond into two thiols, resulting in a conformational change from  $\alpha$ -helix to random structure allowing the released of the entrapped drug. The peptide-nanoparticle conjugate was also found to disrupt a liposome membrane. Therefore, this stimulusresponsive  $\alpha$ -helical peptide gatekeeper provided a direction for the construction of mesoporous delivery vehicles with enhanced therapeutic efficacy *via* membrane disruption.

# 3.2. Helical Peptide Mediated Nanostructures to Fabricate Hybrid Materials

One of the important applications of peptide nanostructures is utilization of their functional surfaces to produce hybrid nanomaterials. Peptide nanotubes and fibers are an important class of self-assembled nanostructure found to have potential applications in casting metal nanowires from metal ions, as well as several other applications [44-48]. The group of H. N. Gopi investigated the supramolecular assembly of various artificially folded 12-helical architectures composed of  $\gamma^4$ -Val,  $\gamma^4$ -Leu and  $\gamma^4$ -Phe residues (Figure 2) [49]. Self-aggregation study in aqueous environment showed the self-assembly of a peptide with  $\gamma$ Val residues into uniform nanosheets, while a peptide with yLeu residues displayed a variety of self-assembled structures, including nanoscale cubes, hexagons, and pyramids. Replacement of  $\gamma$ Val or  $\gamma$ Leu residues with  $\gamma$ Phe residue significantly altered the nanostructures and the peptide displayed a unique elongated nanotubular morphology (Figure 2). The authors also demonstrated that irrespective of the type of  $\alpha$ -amino acids in the sequence, other three 12-helices hybrid peptides with yPhe residues also assembled into nanotubular superstructures. The discovery of elongated nanotube morphologies motivated the authors to investigate whether the new nanotubes had the potential to act as templates for casting metal nanowires from metal ions. Dilution of the nanotubes with silver nitrate and the reducing agent citric acid revealed that the nanotubes acted as templates to form silver nanowires from the silver ions.

In an interesting study, Banerjee and coworkers designed pseudopeptide-based molecular building blocks to construct helical nanofibers [50]. In single crystal structure, the pseudopeptide with S-chirality formed hydrogen bonded supramolecular right-handed helical structure which converted to a left-handed helix upon changing the chirality to R. The (S)-pseudopeptide self-assembled in MeOH/H<sub>2</sub>O (1:1) to form a right-handed helical nanofiber (Figure 2). The handedness of the helicity of the nanofibers was found to be reversed when enantiomeric molecular scaffold was used. Modification of the parent pseudopeptide resulted in  $\beta$ -sheet secondary structures and breakage of the chirality of the assembled nanofibers by forming straight nanofibers. A sixmembered intramolecular hydrogen-bonded [NH---

O(amide)] turn played an intrinsic role in the formation of supramolecular helical secondary structures and helical nanofibers, and was absent in the  $\beta$ -sheet and straight nanofiberforming modified pseudopeptides. This study clearly indicated that along with molecular structure and chirality, the supramolecular structure formed from the corresponding molecular scaffolds also played an important role in directing the final shape and chiral nature of the assembled nanostructures. The self-assembled helical nanofibers were utilized as templates for fabricating dipeptide-capped gold nanoparticles in definite arrays.

Moretto and colleagues reported the 3D structure of a terminally protected hydrophobic dipeptide [51]. In crystal, the molecules arranged into left-handed, supramolecular six fold helix that was characterized by a very narrow lumen, about 2.5 Å in diameter. The dipeptide self-assembled from either ethyl acetate, acetonitrile or acetone into long, aligned rods which were found to comprise an overall parallelepiped shape and an empty inner cavity (Figure 2). Heating of a mixture of citrate passivated gold nanoparticles and peptide nanorods to 400°C led to the formation of gold nanorods. In addition, the peptide formed organogel in toluene after a gentle heating followed by a cooling process. The organogel was exploited to incorporate guest molecules such as C60 fullerene and Multiwalled Carbon Nanotubes (MWCNTs). Moreover, by a simple vacuum-drying process, the authors fabricated an ordered, robust, carbon-based non-covalently assembled material from an organogel composed of the dipeptide, C60 and MWCNTs. This assembled material was found to display high performances as catalyst in reduction reactions. Several other studies also reported the fabrication of ribbon and elongated fibrillar morphologies by short synthetic helical peptides [52-54].

Haldar and colleague used a central nonchiral spacer to connect two tripeptide fragments with intrinsic  $3_{10}$  helical folding propensity stabilized by multiple intramolecular hydrogen bonds, thereby mimicking the  $\alpha$ - $\alpha$  corner motif of a protein super secondary structure [55]. The peptidomimetic compound initially self-assembled to a rod-like supramolecular structure which latter converted to uniform toroids through end-to-end like cyclization reaction. These superstructures were utilized for exfoliation of graphene from graphite.

#### 3.3. Helical Peptides as Modular Surfactants

Surfactant based emulsifiers are a unique class of materials with applications in various fields, including the food, cosmetic, pharmaceutical and biomedical industries. However, commonly used food-grade surfactants, such as Tween-80 and carboxymethyl cellulose, were found to induce lowgrade inflammation and obesity-metabolic syndrome in wildtype hosts [56]. Peptide-based emulsifiers have thus been explored as biocompatible and biodegradable alternatives. Several hydrogel forming short peptide sequences with preferential  $\beta$ -sheet secondary structures were reported to provide functional emulsion-stabilization [57, 58]. Based on the utilization of robust conformation, Middelberg and colleagues developed a 21-amino acids helical peptide containing surfactant which could produce oil-in-water emulsions [59, 60]. The  $\alpha$ -helical polypeptides were also used to fabri-



**Figure 2.** a), X-ray structure of  $\alpha, \gamma^4$ -hybrid peptide; b), Nanotube morphology observed using SEM; c), Adsorption of gold nanoparticles on the surface of the nanotube [49]. d,f), AFM images of right-handed and left-handed helical nanofiber of (S)-pseudopeptide and (R)-pseudopeptide respectively; e.g., SEM images showing the corresponding helical fibers used as templates for fabricating dipeptide-capped gold nanoparticles [50]. h), Nanorod morphology of hydrophobic helical dipeptide; i), TEM images of the dipeptide/C60 organogel nanostructure. Inset: Vials before and after organogel formation. j), TEM image showing the presence of small particles on the structure network [51]. Figure reproduced with permission from respective references.

cate emulsion-templated self-assembled microcapsules [61]. Recently, our group has employed a minimalistic design approach to fabricate a rigid helical conformation [62]. Single crystal structure showed the designed building blocks organized in super helical assemblies and the sequence was found amenable to structural modularity (Figure 3). In acidic pH, the peptide self-assembled into uniform high aspect ratio nanofiber morphologies, independently of peptide concentration. The minimal designed helical peptide demonstrated excellent surface activity of oil-in-water emulsion formation and delivered the highest stable emulsions reported for peptide and protein emulsifiers. In contrast, modification of the peptide sequence to a non-aggregated surrogate failed to form stable emulsion signifying the important role of robust backbone conformation for favorable interactions.

### 3.4. Helical Peptide Based Porous Biomaterials

Porous biomaterials have been widely used in a variety of orthopedic applications. There are increasing number of evidence that helical peptides can serve as useful motifs to modulate porous bio-material design. Anita and colleagues designed three pseudopeptides comprised of a single pyridinedicarboxylic acid and a flexible dipeptidyl fragment containing a combination of L-Ala, L-Tyr and L-Ile [63]. In single crystal structure, all three pseudopeptides displayed supramolecular preference for double helices, characteristic of



Figure 3. a), Canonical helical conformation of heptapeptide observed in crystal as cylindrical helices; b), Packing of adjacent head-to-tail helical columns; c), Cryo-TEM micrograph of cylindrical micelles-like nanofibers morphologies; d), Photographic image of silicone oil (20%) and water (80%) emulsions before and after emulsifications; e), Fluorescence micrograph demonstrating the formation of oil-in-water emulsion [62].

pyridine carboxamides, employing intermolecular H-bonding and  $\pi$ - $\pi$  analogy (Figure 4). Morphological analysis revealed that the pseudopeptide comprised of L-Ala and L-Ile formed rod-like aggregates, whereas the L-Tyr containing pseudopeptide self-assembled into a nanoporous morphology, clearly indicating the role of H-bonding side-chain in the formation of nanoporous materials. Gas adsorption studies of evacuated pseudopeptides revealed Tyr-containing porous aggregates displaying fifteen times more N<sub>2</sub> sorption than the rod-like aggregates.

The folding and self-assembly properties of three isomeric hybrid Boc-Phe-x-aminobenzoic acid (x = o/m/p) peptides were illustrated by the group of Haldar [64]. In higher order assembly, the o-aminobenzoic acid containing peptide formed supramolecular noncanonical herringbone helix, whereas the m-surrogate showed a single helical architecture (Figure 4). From a 1:1 MeOH/H<sub>2</sub>O solution, the o-isomer self-assembled into rose-like morphology and the m-isomer gave rise to a twisted fiber (Figure 4). Gas adsorption study showed higher N<sub>2</sub> uptake of the former, indicating that the supramolecular herringbone-like helical packing provided a larger void (3.02 nm) than the supramolecular single helical packing. This group also reported N<sub>2</sub>-uptake by a doublehelical tripeptide, indicating the formation of porous biomaterials from a helical peptide [65].

## 3.5. Helical Peptide Based 2D Soft Nanomaterials

One of the most important applications of self-assembled helical peptides is their organization into 2D soft nanomaterials. Although  $\beta$ -sheet forming peptide sequences were conventionally used as building blocks for constructing two dimensional (2D) nanostructures, the resulting assemblies were found to possess inhomogeneous structures composed of bundled fibrils and could be produced only with a micrometer scale thickness. Recently, Nam and co-workers designed pentapeptide with cysteine in the middle of the sequence and two tyrosine residues at the termini [66]. The peptide formed dimers *via* a disulfide bridge which stabilized the helical conformation of the resulting dimer (Figure 5).

Immediately after placing a peptide-containing water droplet on hydrophobic siliconized glass, a very thin transparent peptide film started growing on the entire surface of the droplet. Over time, the peptide assembly induced flattening of the initially round water droplet due to the large driving force for 2D assembly and the high elastic modulus of the resulting sheet. Dimerization of the reported peptide monomers was found to be a decisive parameter for determining the assembled structures and facet formation. The nanosheets formed by the dimer were flat and uniform with a thickness of 10 nm, whereas the monomer films exhibited a nonuniform, wrinkled morphology composed of bundled fibrillary fragments. The morphological conversion of the



**Figure 4. a),** Schematic representation of supramolecular double helix formation from pseudopeptide; b), Porous morphology; c),  $N_2$  sorption isotherm [63]. **d,e**), Supramolecular noncanonical herringbone helix and single helical structure of o- (**d**) and m (**e**) hybrid peptides; **f,g**), Rose-like and twisted fiber morphologies; **h**),  $N_2$  sorption isotherm [64]. Figure reproduced with permission from respective references.



Figure 5. a), NMR solution structure of dimer pentapeptide; b), AFM image of dimer sheets; c), AFM image of monomer films; d-f), Optical images of a water droplet containing pentapeptides at various timepoints; g), Top view of the droplet containing monomer films at the air/water interface [66]. Figure reproduced with permission from the respective reference.

helical peptide assembled structures from fibrils to giant sheets accelerated the facet formation kinetics at the air/water interface. This work thus opened an avenue of selfassembling helical peptide design for the fabrication of transferable and giant 2D architectures with minimal molecular elements.

#### 3.6. Electron Conductivity in Helical Peptides

The combination of bioelectronic materials with synthetic electronic entities has a broad range of applications such as wearable or implantable devices, portable and biocompatible power sources, real-time and miniaturized sensors, and bionic neural interfaces. In the last couple of decades, a vast majority of biological Electron Transfer (ET) studies focused on helical peptides [23]. Electron transport through a monolayer of helical peptides adsorbed onto metal surfaces was found to be particularly important. Electron conductivity and tunneling in nanomaterials has been studied for wide range of helical constituents, ranging from nonenzyme proteins to short peptides. By using self-assembled nanostructures, long range electron conductivity has been established in bacterial protein fiber appendages, called pili [67]. The combination of the side chains orientation, hydrogen bonds, and most significantly  $\alpha$ -helical secondary structure, was identified as important for hopping and tunneling conductivity in these peptides. They were also found to be one order of magnitude more conductive than B-sheet forming amyloid fibers [68]. In another study, the conductance of fiber nanostructures produced by the self-assembly of short helical peptide was reported to improve after the selfassembly process [69]. Recently, Hochbaum and colleagues designed peptide sequences based on conductive protein fibers [70]. In solid state crystal and in solution, the peptide formed a coiled-coil hexamer in which aromatic residues orientated in the hydrophobic core. In aqueous solution, the coiled-coil hexamer induced end-to-end electrostatic interactions and assembled into elongated fibers (Figure 6). In this medium, the electrochemical transport measurement of selfassembled nanofibers showed ohmic electronic transport and a metallic-like conductance. The most promising factor was the observed conductivity facilitated entirely by amino acids lacking extended conjugation,  $\pi$ -stacking, or redox centers usually observed in organic and biohybrid semiconductors. At higher concentrations, the peptide formed a hydrogel and could not self-assemble into an ordered fibrous structure. Surprisingly, the hydrogels exhibited a remarkable decrease in conductivity with increasing peptide concentration. These findings clearly indicated that the supramolecular order nanostructures and  $\alpha$ -helical secondary organization of the peptides are critical structural features for the resulting electronic conductivity.

#### **CONCLUSION AND FUTURE OUTLOOK**

The ability to design and arrange peptides into a controllable secondary structure and their chemical diversity gives rise to a class of self-assembled materials with sophisticated functions. Although most of the design rules of helical peptides have so far been envisioned from the mimicking of natural coiled-coil or collagen proteins for the design of long peptide segments, several non-coded and synthetic amino acids have been employed to design a large number of ultrashort helical peptides. Assisted by self-assembly, these helical peptides could form a diverse range of nanostructures, including nanofibers, nanotubes, and nanosheets. As discussed in this focus review, many promising demonstrations



**Figure 6. a,b)**, Atomic force micrograph of a drop-cast film of peptide nanofibers, inset of (b) shows a z-height line-scan across the fiber; c), Proposed nanofiber self-assembly mechanism based on X-ray crystal structures of peptide and their deposition onto interdigitated electrodes; d), Current-voltage (I–V) characteristics of peptide fibers [70]. Figure reproduced with permission from the respective reference.

of these functional materials have already emerged, with great promise for applications ranging from cell culture materials to sensors and storage structures. Other intriguing applications of helical peptide-based nanostructures are yet to be comprehensively explored. The understanding of the mechanical properties of helical peptide-based nanomaterials, mainly nanotube and nanofibers, will make them interesting building blocks for structural applications. The piezoand pyro-electric properties of short  $\beta$ -sheet forming peptide nanostructures are well explored. Although  $\alpha$  -helical peptides were reported to show electron conductivity an order of magnitude higher than  $\beta$ -sheet peptides, the piezo- and pyroelectric response of short helical peptides are not well studied. These molecules have a significant potential as a framework for the fabrication of future smart devices. The combination of a helical peptide layer and a solar panel will allow the design of a smart chargers to work with pressure, temperature and sunlight only, without requiring any external source of electricity.

#### **CONSENT FOR PUBLICATION**

Not applicable.

#### **CONFLICT OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

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