Self-assembled peptide nanostructures: the design of molecular building blocks and their technological utilization

Ehud Gazit*

Received 5th December 2006
First published as an Advance Article on the web 2nd May 2007
DOI: 10.1039/b605536m

In this *tutorial review* the process and applications of peptide self-assembly into nanotubes, nanospheres, nanofibrils, nanotapes, and other ordered structures at the nano-scale are discussed. The formation of well-ordered nanostructures by a process of self-association represents the essence of modern nanotechnology. Such self-assembled structures can be formed by a variety of building blocks, both organic and inorganic. Of the organic building blocks, peptides are among the most useful ones. Peptides possess the biocompatibility and chemical diversity that are found in proteins, yet they are much more stable and robust and can be readily synthesized on a large scale. Short peptides can spontaneously associate to form nanotubes, nanospheres, nanofibrils, nanotapes, and other ordered structures at the nano-scale. Peptides can also form macroscopic assemblies such as hydrogels with nano-scale order. The application of peptide building blocks in biosensors, tissue engineering, and the development of antibacterial agents has already been demonstrated.

Self-assembly and supramolecular chemistry

The spontaneous formation of ordered structures at the nano-scale or macroscopic objects with nano-scale order is a key issue in nanotechnology.[1–3] In a "bottom-up" process, simple building blocks interact with each other in a coordinated way to form large and more complex supramolecular assemblies (Fig. 1).[4,5] Processes of molecular recognition and self-assembly direct the way in which relatively simple building blocks recognize each other, associate, and form ordered one-dimensional, two-dimensional, and three-dimensional nanostructures and macroscopic objects with nano-scale order.

The organization of the building blocks into ordered structures is based on specific recognition that is facilitated by a combination of many different non-covalent interactions. These include electrostatic interactions, hydrogen bonds, hydrophobic interactions, and aromatic stacking interactions. The overall coordinated combination of the various molecular

Department of Molecular Microbiology and Biotechnology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv 69978, Israel. E-mail: ehudg@post.tau.ac.il; Fax: +972-3-640-5448; Tel: + 972-3-640-9030

Ehud Gazit

Ehud Gazit received his B.Sc. (summa cum laude) from Tel Aviv University after completing his studies in the Special University Program for Outstanding Students. He continued his studies at the Weizmann Institute of Science, where he received his Ph.D. (with distinction) in 1997. After three years as an EMBO and HFSP postdoctoral fellow at the Massachusetts Institute of Technology, he joined Tel Aviv University. He is a member of the editorial boards of Amyloid, Current Chemical Biology, Journal of Bionanoscience, PLoS ONE, and Nanomedicine. His research interests involve the study of protein folding, misfolding, and self-assembly, with special emphasis on amyloid fibril formation and peptide nanotechnology.

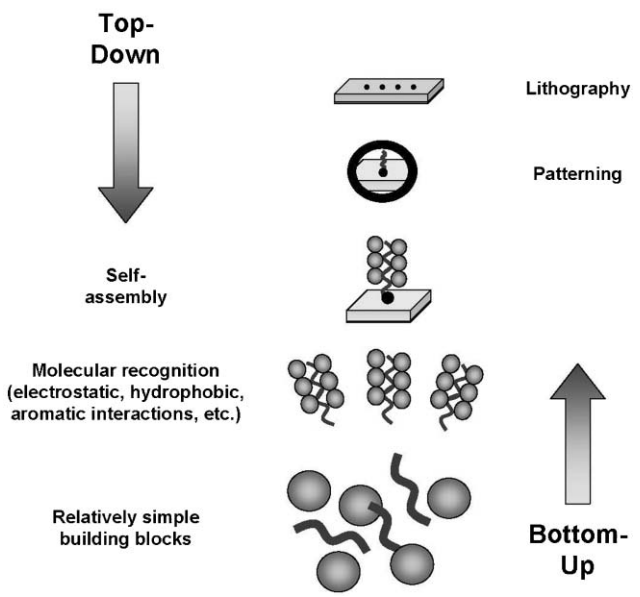

Fig. 1 The process of "top-down" as compared to "bottom-up" self-assembly. The top-down process as developed to superb efficiency by the microelectronics industry is based on the patterning of assemblies by lithographic definition. The "bottom-up" approach is based on the interaction of simple building blocks to form a well-ordered assembly by means of molecular recognition and self-assembly.

forces, which are quite weak individually, results in the process of self-organization from simple blocks into elaborate and ordered structures.

Nanotechnology in its "bottom-up" and self-assembly facets stems directly from earlier studies on self-association and self-organization (Fig. 1). The concept of "supramolecular chemistry", the chemistry of complex non-covalent structures at the nano-scale, began with the study of various organic polymers and sophisticated host–guest chemistry that was based on advanced organic chemistry. The pioneering work of Jean-Marie Lehn, who coined the term *supramolecular chemistry*, was directed towards the engineering of molecular cryptand cages with a desired shape whereby only a certain type of molecule was allowed to be lodged in the cage.[4,5] Lehn shared the 1987 Nobel Prize in Chemistry with Donald Cram and Charles Pedersen, two other eminent chemists who pioneered the development of crown ethers that are able to recognize and selectively bind ions of certain metal elements. The citation of their award reads: "For their development and use of molecules with structure-specific interactions of high selectivity". What these very talented chemists achieved synthetically is done in each living cell mainly by proteins.

Building blocks for nanotechnology vary considerably and include both organic and inorganic species. Classical nanotechnology emerged with the use of pure carbon structures of the buckminsterfullerene and carbon nanotubes, or modified analogs of these carbon structures.[6,7] This was later followed by the study of inorganic nanostructures, such as silicone nanowires[8,9] and inorganic nanotubes and fullerene-like structures from layered materials such as WS_2, MoS_2, and NbS_2.[10]

Other efforts in nanotechnology were directed towards the development of organic nanostructures. Organic chemistry offers very diverse chemical tools and elaborate molecular properties. A great deal of modern materials science is based on organic chemistry. Many of the materials that we use in everyday life are of course composed of organic polymers. These include plastics such as polyvinyl chloride, polypropylene, nylon (polyamide), Teflon® (polytetrafluoroethylene), and many other polymers (Fig. 2). As will be described below, peptides and proteins have much in common with polymeric organic materials, yet they offer many advantages.

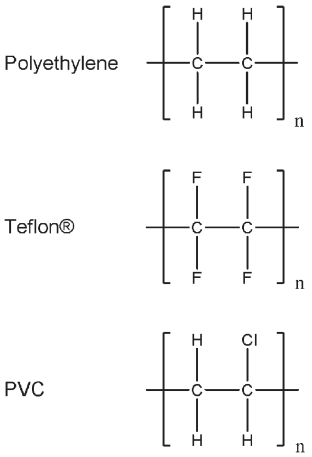

Fig. 2 Commercially available polymers. Some of the most useful polymers, such as Teflon®, PVC, and polyethylene, are formed from very simple molecular building blocks. Protein and peptide building blocks offer much more advanced and diverse molecular decoration to form "smart functional materials".

Self-assembly by proteins and peptides

Proteins and peptides serve as the major molecular scaffold material of the biological world at the nano-scale, micro-scale, and macro-scale. This starts from nano-scale elements such as the self-assembled actin cytoskeleton, the molecular structures that give the cell its physical rigidity, and the self-assembled microtubules that serve as nanoscopic protein railways that allow the transport of "cargo" within the micro-scale cell using nano-scale protein motors. Proteins also serve as the building blocks for macroscopic structural elements such as the collagen proteins in the skin and the keratin proteins in nails and hair. In addition, proteins serve as the building blocks for elaborate structures possessing unique physical properties such as silk, whose ratio of tensile strength to density is about five times higher than steel. Formation of inorganic biological structures such as bones and teeth and marine animal shells is directed by protein templates *via* the specific interaction of proteins and peptides with calcium or silicon.[11]

Proteins and peptides also facilitate biological recognition. The specific binding to various molecules is mediated by protein antibodies and receptors, whereas messages in the body are carried by polypeptide hormones such as insulin, vasopressin, and luteinizing hormone. In addition, almost all the enzymatic activities in every biological system are carried out by protein enzymes, ranging from simple reaction enzymes to multicomponent molecular synthesizers. Also, the mechanical components in biological systems, such as molecular motors at the nano-scale and muscles at the macro-scale, are composed of proteins. Thus, taken together, proteins serve both as the building scaffold as well as the functional entities in the biological world. Thus, many researchers view proteins and their peptide fragments as potential sources of engineered "smart function material".

As previously mentioned, most of the molecular recognition reactions in the biological world are facilitated by proteins and peptides. Proteins also have a direct connection to the polymeric material world, as described above (Fig. 3). They are basically polyamides: long polymers composed of tens, hundreds, or even thousands of amino acids, connected by amide bonds. This architecture resembles many of the organic materials around us. Polyamides include fibers such as the everyday nylon as well as the ultra-strong Kevlar® and Nomex® aromatic polyamides (aramids). Yet proteins offer a great advantage over organic polymers, namely their diversity (Fig. 4). Whereas synthetic polymers are usually formed by the polymerization of a single building block, proteins are composed of 20 different amino acids. The specific features of the protein stem from the composition of the amino acids, but also from their sequence. The number of combinations for a simple protein of 100 amino acids is 20^{100}, a number that is just impossible to grasp. It is possible to also make synthetically mixed polymers, known as co-polymers. However, in this case the co-polymer is a random mixture of polymers with the same composition, but not with the same sequence. In the case of

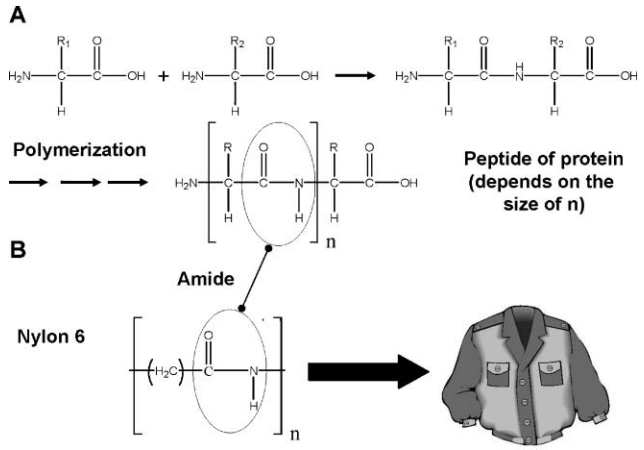

Fig. 3 Proteins and peptides as polyamide polymers. A. Polymerization of proteins and peptides. Proteins and peptides are formed by the interaction of amino-acid building blocks to form long linear polymers. The amino-acids differ one from another by the chemical identity of the R groups. The length of the polymer indicates whether it is a peptide or a protein. **B. Common synthetic polymers are polyamides.** Homo-polymers like nylon-6 are composed of aliphatic building blocks that are connected by amide bonds. This is the same planar bond of unique chemical properties that connects amino-acids in peptides and proteins.

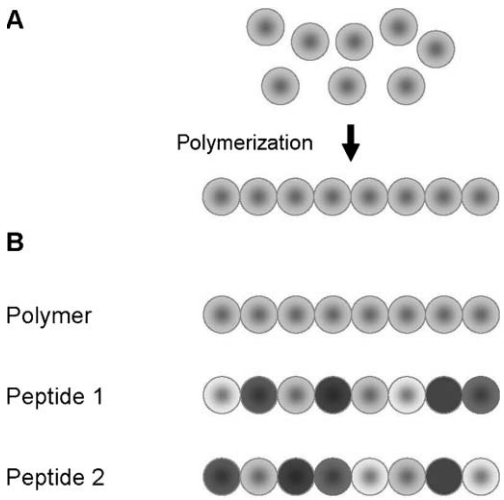

Fig. 4 The process of polymerization and the difference in the sequential organization of proteins or peptides and polymers. A. The process of polymerization. The polymerization of simple building blocks (monomers) into elongated linear chains occurs through the process of addition or condensation to form polymer (from the Greek roots: *polys* meaning *many*, and *meros* meaning *parts*). **B. Peptides and proteins as sequential polymers.** While most synthetic polymers are homo-polymers that are built from a single type of building block from each polymer, proteins and peptides are composed of a variety of building blocks in a specific order. The schematic *peptide 1* and *peptide 2* have the same amino-acid composition but in a different order and in real life probably have completely different properties.

proteins, the very precise order of building blocks is very easy to direct. The synthesis of such a complex polymer is simply mediated by bacterial over-expression using genetically engineered DNA vectors. Figs. 3 and 4 depict the similarities and differences between proteins, peptide polymers, and typical organic polymers.

As will be described in this review, the application of aromatic interactions as the driving force for the formation of self-assembled nanometric materials resulted in the assembly of the most rigid organic nanotubes, with a Young's modulus of about 20 GPa. Other concepts from the polymeric world can be used for further exploration of other protein and peptide nanostructures. One direction could involve the use of fluorinated building blocks to achieve properties similar to those of polytetrafluoroethylene (Teflon®), namely very low friction coefficients.

Although proteins offer many advantages owing to their self-assembly and molecular recognition processes, they are limited for technological applications such as consumer goods due to their instability and inability to be synthesized on a large scale. Peptides, which could be composed of 2–30 amino acids, offer an interesting alternative to proteins. Importantly, they can be synthesized on a large scale by conventional chemical techniques. Furthermore, when synthetic peptides are used, there is a greater tendency to use the 20 natural amino acids and therefore many more building blocks can be used. While the cost of peptide synthesis is still an issue, especially with large peptides, it may be reduced with large-scale solution phase methods. An optimized method for the synthesis of the aspartyl-phenylalanine-methyl ester (the Aspartame® sweetener) resulted in a cost of synthesis of a few cents per gram for ton-scale production.

There are of course endless variations for non-natural amino acids, with hundreds that are available as protected building blocks for chemical synthesis. If we go back to the simple "back-of-the-envelope" calculations, the number of combinations for pentapeptides with 100 amino acids is $100^5 = 10^{10}$. Peptides also offer excellent chemical and thermal stability because most peptide building blocks are stable at high temperatures, in the presence of organic solvents, and in extreme pHs. Although the current review is concerned with peptides, it should be noted that proteins from extermophiles can also be very stable and these bacteria, especially hypothermophiles, may still have various applications in nanotechnology. Extermophiles may actually serve as the equivalents of a rain-forest reservoir for new building blocks, ideas, and concepts for modern nanotechnology.

Tubular peptide nanostructures

The first engineered structures at the nano-scale were the cyclic peptide nanotubes, which were developed by M. Reza Ghadiri and coworkers.[12–14] In very elegant work, concepts from natural peptides were translated into technological applications. Ghadiri used the concept of alternating D- and L-amino acids in the context of a cyclic peptide to form a planar ring that could be self-assembled, one on top of the other, to form tubular structures of a desired diameter (Fig. 5).

Application of these nanotubes in diverse fields such as antibacterial agents and molecular electronics has already been demonstrated. Since the identity of the side-chains could be modulated, various residues including non-natural ones could be incorporated. A recent example from the group revealed the

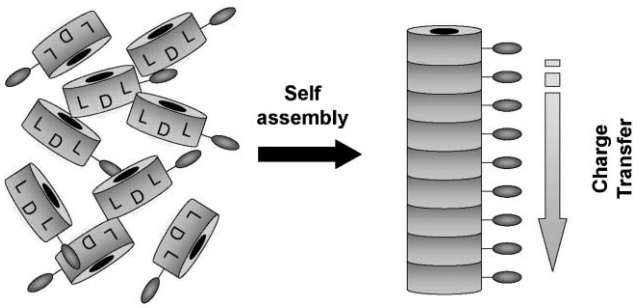

Fig. 5 The first peptide nanotubes. The first peptide nanotubes were developed in the 1990s by M. Reza Ghadiri and coworkers. These tubes are based on the precise assembly of alternating D- and L-amino-acid cyclic peptide to form elongated and hollow nanotubes. Decoration of the external parts of the nanotubes with functional moieties makes it possible to engineer them into functional nano-assemblies. For example, decoration with aromatic moieties that allow charge transfer is envisioned for molecular electronics applications.

ability to substitute the side-chains for 1,4,5,8-naphthalenetetracarboxylic acid diimide[14] to allow a charge transfer along the tubular system (Fig. 5). Other directions, which will be described next, include the design of novel antibacterial agents that are based on the interaction of the peptide nanostructures with bacterial membranes.

Another cyclic peptide that was shown to self-assemble into tubular structures is the Lanreotide growth hormone inhibitor.[15] Here, a naturally occurring cyclic peptide rather than a designed one self-assembles into well-ordered structures at the nano-scale by hydrophobic and aromatic interactions, which will be described in the aromatic nanostructures section.

Charge-complementary peptide nanostructures

Another very interesting approach to engineered peptide nanostructures originated from the concept of charge self-complementarity (Fig. 6). Peptides were designed in such a way that they will self-assemble due to the electrostatic interactions between positively charged and negatively charged moieties within the peptides.

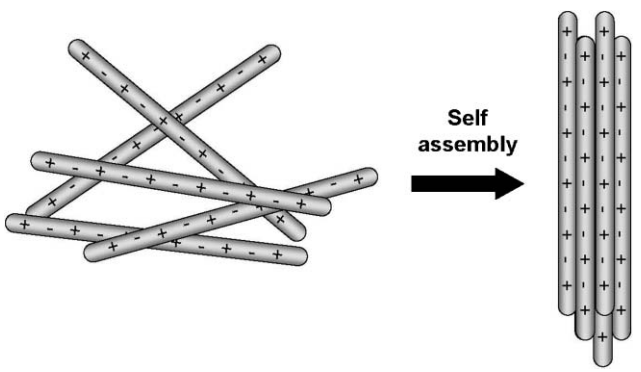

Fig. 6 Self-assembly as facilitated by charge complementarity. The design of peptide building blocks with opposing charges allows the efficient self-assembly of peptide monomers into well-ordered structures at the nano-scale. These peptide structures could be further fabricated to form macroscopic hydrogels that have nano-scale order.

The formation of charged peptide building blocks was demonstrated by Shuguang Zhang and coworkers in 1993.[16] The designed linear building blocks are composed of more than 50% charged peptides and include negatively charged glutamic acid and aspartic acids and positively charged lysines and arginines.[17] These peptides readily assemble in aqueous solution to form ordered fibrillar structures. Furthermore, by the process of extrusion the peptide can form macroscopic hydrogels. Application of these gels for tissue engineering and regeneration applications was demonstrated. For example, these gels allowed the growth of neural cells in an integrated network that showed synaptic activity.[18] In this case the charged properties of the peptide nanostructures served not only for their self-assembly but also for guidance of the cells, most likely by mimicking the RGD (arginine–glycine–aspartate) tripeptide motif that is found on the surface of various cells.

Surfactant-like and other hydrophobic nanostructures

One of the most important driving forces for biological self-organization is based on hydrophobic interactions. The formation of phospholipid membranes is specifically based on the organization of amphiphatic structures in aqueous solution (Fig. 7). These structures include both a hydrophobic tail and a hydrophilic head organized in the aqueous solution, where they form well-ordered structures.

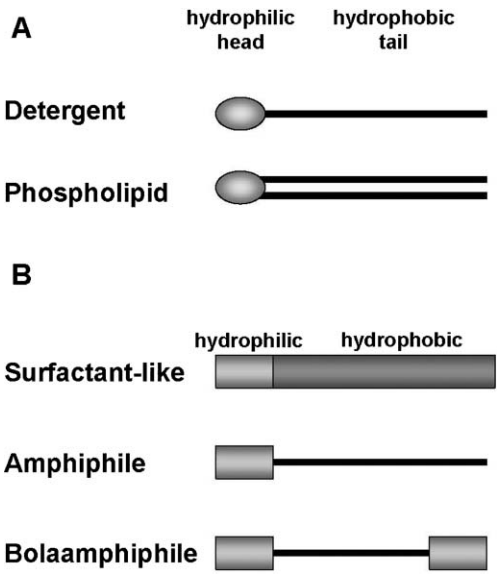

Fig. 7 The architecture of amphiphatic peptide building blocks. A. Detergents and phospholipids. The self-assembly of detergents and phospholipids is based on the architecture of a polar headgroup (in many cases inorganic) and a hydrophobic tail (mostly aliphatic). **B. Peptide-based amphiphiles.** Various peptide building blocks that are based on the formation of separated hydrophobic and hydrophilic domains were designed. The hydrophilic part is usually peptidic. Yet the hydrophobic part may be aliphatic. These peptide building blocks self-assemble into ordered nanostructures by a process that is similar to the molecular driving forces that allow formation of ordered phospholipid membranes.

Many peptide structures are based on similar principles of amphiphatic structure for their efficient molecular self-assembly. Whereas the surfactant-like peptides are basically a molecular mimicry of membrane phospholipids and detergents,[18,19] other organization schemes also exist. These building blocks include the bolaamphiphile peptides,[20,21] the peptide-conjugated amphiphiles,[22,23] and the conjugated peptides.[24] Fig. 7 depicts the relative organization of the various building blocks. As shown in the figure, the various amphiphatic building blocks utilize different geometries for the self-assembly process. This is a vivid demonstration of the way in which peptides and peptide-derived structures can be modulated to form various structures at the nano-scale.

In the case of the peptide-conjugated amphiphile building blocks, peptidic recognition motifs, such as the neurite-promoting laminin epitope IKVAV, have been integrated into the peptide head to mediate cell attachment and guidance for tissue engineering applications.[23] In a previous study, the building blocks were designed to direct mineralization of hydroxyapatite to form a composite material in which the crystallographic axes of hydroxyapatite are aligned with the long axes of the formed nanostructures.[22]

Amyloid fibrils as nano-materials

Amyloid fibrils are naturally occurring nano-fibrils that are associated with a large number of human diseases. Such disorders include Alzheimer's disease, Parkinson's disease, Type II diabetes and many others.[25,26] There are about 20 different human diseases that are associated with the formation of these 7–10-nm amyloid fibrils. These fibrils show remarkable order, as indicated by 4.6–4.8 Å X-ray fiber diffraction on the meridian. They also exhibit a typical β-sheet conformation and strong gold–green birefringence upon staining with the Congo red dye.

Amyloid fibrils may actually represent a much more fundamental structural state of protein, since some disease-unrelated proteins could form typical amyloid fibrils under various conditions. Furthermore, typical amyloid fibrils could be found in bacterial biofilm and other bacterial structural proteins.[27–29] Upon examination, amyloid fibrils were found to have very strong physical rigidity[30] and amyloid fibrils and silk were compared.[31] This suggests that indeed amyloid may represent a fundamental scaffold that supports physical structures with a nano-scale order. As will be further discussed, amyloid-derived peptides serve as major elements in peptide nanotechnology.

The use of yeast amyloid fibrils for nanotechnological applications has already been demonstrated.[32] The fibrils were genetically engineered to contain a cysteine residue that served as a nucleation site for the deposition of metal on the protein. The metal-coated fibrils were found to be conductive and may have applications in future nano-electronics and nano-wiring.[32]

Amyloid fibrils are usually formed by polypeptides of 30–40 amino acids, but they can also be formed by larger proteins. Yet recent studies have demonstrated the ability of much shorter peptides, namely tetra- to hexapeptides, to form typical amyloid fibrils that exhibit all the typical biophysical and ultrastructural properties of amyloid fibrils.[33,34] The change from larger polypeptides or proteins into short amyloid fragments now enables the large-scale synthesis of fibrils and their application in various nanotechnological settings.

Aromatic nanostructures

Another class of peptide nanostructures is based on the use of short aromatic peptides to form well-ordered nanostructures. The driving force for the discovery of the peptide was the study of very short amyloid-forming peptides. It was discovered that the core recognition motif of the β-amyloid polypeptide, the diphenylalanine polypeptide, forms discrete and hollow nanotubes in solution (Fig. 8).[35] These discrete nanotubes are extremely rigid[36] and form spontaneously and efficiently upon their dilution from organic solvents into aqueous solution or by heating and cooling of an aqueous solution of the peptides.[37]

A simpler analogue, the diphenylglycine peptide, forms nanospherical structures in aqueous solution (Fig. 8).[38] Other end-termini analogs such as the Fmoc-diphenylalanine form macroscopic hydrogels with nano-scale order,[39] whereas the Fmoc-diphenylalanine forms fibrils that are very similar to amyloid fibrils.[40] It was recently demonstrated that the dipeptide nanostructures could form vertical arrays in the form of a ''nano-forest'' of tubes or could be aligned horizontally upon modification with magnetic nanoparticles and the application of an external magnetic field.[41]

The peptide nanotubes were shown to be stable under extreme physical and chemical conditions including boiling, autoclave treatment, and exposure to various organic solvents.[42] This clearly demonstrates the robustness and stability of peptide structures that are not different from various organic polymers that were mentioned in the introduction (Fig. 9). An example of the modulation of the biological

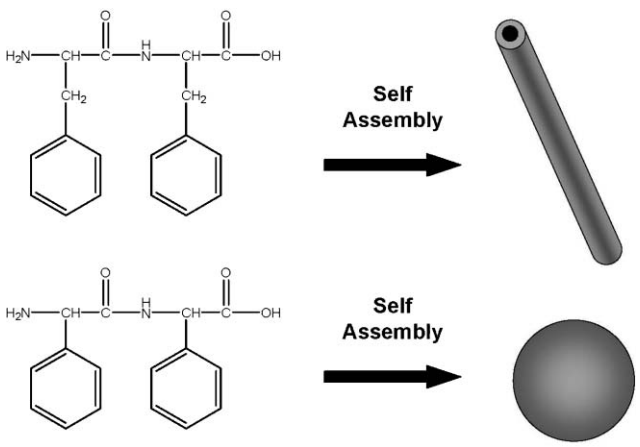

Fig. 8 Formation of ordered nanostructures by simple aromatic dipeptide. The diphenylalanine core motif of the Alzheimer's disease β-amyloid self-assembles into discrete peptide nanotubes of remarkable rigidity and chemical stability. The similar diphenylglycine peptide forms closed-caged nano-spheres that share common molecular characteristics with the peptide nanotubes. The alternative formation of tubular and spherical nanostructures resembles the tubular and spherical carbon and inorganic structures at the nano-scale.

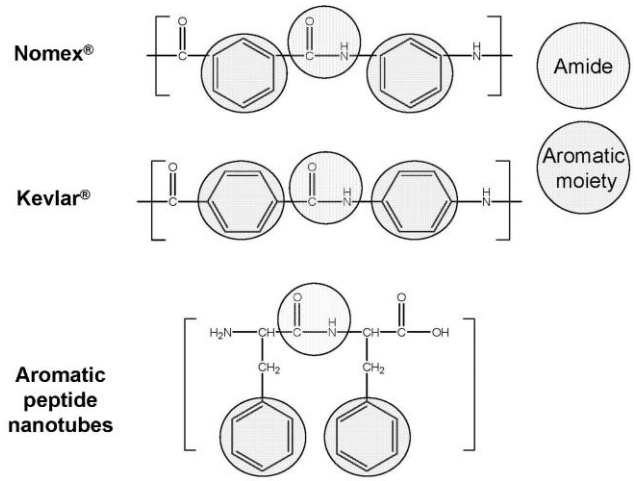

Fig. 9 Self-assembled peptide nanotubes and aromatic polyamides. The self-assembled peptide nanotubes show remarkable rigidity with a Young's modulus of about 20 GPa. The figure depicts the similarity between the building blocks of these self-assembled nanostructures and those of the commercially available aromatic polyamides (aramids), Nomex® and Kevlar®. The stacking of the planar amide bonds together with "molecular glowing" that is facilitated by aromatic pi–pi interactions is assumed to be the driving force for rigidity in both the case of the aromatic polyamides and the nanotubes.

stability of the peptide nanostructures was achieved by synthesizing the building block with either L- or D-amino acid isomers. While the L-isomers are recognized by natural enzymes and the structures are susceptible to degradation, the peptide building blocks that are composed of the non-natural D-amino acids are stable to proteolytic degradation.

The molecular basis for the formation of the dipeptide nanostructures by such short molecular building blocks most likely stems from the geometrically restricted interactions between the aromatic moieties in such a way that allows an order by such small molecular building blocks. Aromatic interactions were used in the past to design peptide-based materials that form macroscopic hydrogels with nano-scale order.[43] Indeed, also in the case of the peptide nanotubes, recent studies have begun to reveal the molecular organization of the peptide nanotubes using X-ray and electron diffraction.[41,44] It is likely that a striking three-dimensional aromatic stacking arrangement that serves as glue between the hydrogen-bonded cylinders as interpreted in the X-ray analysis of the peptide tubes[44] is the molecular basis for the remarkable rigidity of the peptide nanostructures similarly to the aromatic polyamides (Fig. 9).

Application of peptide nanostructures

Applications of peptide nanostructures are very diverse: they can include such unrelated fields as tissue engineering, on the one hand, and nanoelectronics on the other. One of the earlier applications of peptide nanotubes was the development of novel antibacterial agents.[13] The concept underlying this use was envisioned from naturally occurring antibacterial peptides that disintegrate the bacterial membrane, for example, the insect antibacterial Cecropins that are produced by various insects including the silk moth *Bombyx mori*. Interestingly, the nanotubes were able to form nano-scale channels in the membranes of bacteria, leading to their death by osmotic collapse.

Peptide nanotubes were used to fabricate 20 nm silver nanowires, by their use as a degradable casting mold at the nano-scale.[35] In this experiment silver ions were reduced to metallic silver in the lumen of the tube and the peptide template was removed by enzymatic degradation. This fabrication may have applications in molecular electronics as such small nano-wires could not be made by conventional lithography.

Another application of nano-order peptide structures, from a quite different angle, is in the field of neurological regeneration.[45] Peptide scaffolds were used to support neural growth in damaged optic nerves, leading to recovery of visual functions in model animals. This may pave the way to other forms of tissue engineering and regeneration where the peptide nanostructures provide both physical support and molecular guidance for the generation of macroscopic three-dimensional tissues.

Peptide nanostructures were also shown to have applications in the field of diagnosis and biosensors.[20,46] Peptide nanostructures were modified with antibodies to allow highly sensitive detection of binding for diagnosing of biological analytes. Other directions in the field of biosensors involve the modification of electrodes with native peptide nanostructures or with enzyme-modified ones to significantly increase the sensitivity of these devices.

Self-assembled peptide structures could be used for various biomaterials applications. One direction is the formation of macroscopic fibrils with nano-scale order.[47] The order and self-assembly process are important for ease of fabrication while the biological nature is key for biocompatibility. Such fibrils could be based on natural proteins or peptide fragments that could be useful for large-scale production. Among many directions, the fibers can be used for the fabrication of bandages, medical fabric that can allow slow release of various drugs, and degradable medical materials.

This is just a brief overview of selected applications of peptide nanostructures. In years to come, we expect many more applications in the fields of MEMS (micro-electro-mechanical systems), electronics, diagnostics, and medicine. It is important to keep in mind that most of these building blocks were developed in an academic setting during the 1990s and the beginning of the 21st century. The translation of academic studies into practical application may take a few more years. If we look back to parallels in polymer science, PVC was first discovered in the 1830s by Henri Victor Regnault, when he observed a white solid floating in flasks of vinyl chloride that were left in the sun. Yet it was only in the 1920s that Waldo Semon developed the methods to plasticize the polymer by blending it with various additives which paved the way to its widespread industrial application. We are witnessing the translation of the basic observation of peptide self-assembly into practical applications.

Summary

The formation of nanostructures by various peptide building blocks paves the way for large-scale bionanotechnology based

on simple building blocks that can be synthesized in large quantities and have a very diverse chemical profile.[48] The molecular basis for the assembly process is diverse and can be based on electrostatic interactions, amphipathicity, and aromatic interactions, to mention but a few. The application of peptide nanostructures in diverse fields, from antibacterial agents and neuroregeneration to molecular electronics, has already been demonstrated.

References

1 G. M. Whitesides, J. P. Mathias and C. T. Set, *Science*, 1991, **254**, 1312–1315.
2 S. Zhang, *Nat. Biotechnol.*, 2003, **21**, 1171–1178.
3 M. Lazzari, C. Rodriguez-Abreu, J. Rivas and M. A. Lopez-Quintela, *J. Nanosci. Nanotechnol.*, 2006, **6**, 892–905.
4 V. Berl, I. Huc, R. G. Khoury, M. J. Krische and J. M. Lehn, *Nature*, 2000, **407**, 720–723.
5 O. Ramstrom, T. Bunyapaiboonsri, S. Lohmann and J. M. Lehn, *Biochim. Biophys. Acta*, 2002, **1572**, 178–186.
6 H. W. Kroto, J. R. Heath, S. C. O'Brien, R. F. Curl and R. E. Smalley, *Nature*, 1985, **318**, 162–163.
7 S. Iijima, *Nature*, 1991, **354**, 56–58.
8 C. Yang, Z. Zhong and C. M. Lieber, *Science*, 2005, **310**, 1304–1307.
9 J. B. Hannon, S. Kodambaka, F. M. Ross and R. M. Tromp, *Nature*, 2006, **440**, 69–71.
10 R. Tenne and C. N. Rao, *Philos. Trans. R. Soc. London, Ser. A*, 2004, **362**, 2099–2125.
11 R. R. Naik, L. L. Brott, S. J. Clarson and M. O. Stone, *J. Nanosci. Nanotechnol.*, 2002, **2**, 95–100.
12 M. R. Ghadiri, J. R. Granja, R. A. Milligan, D. E. McRee and N. Khazanovich, *Nature*, 1993, **366**, 324–327.
13 M. R. Ghadiri, J. R. Granja and L. K. Buehler, *Nature*, 1994, **369**, 301–304.
14 W. S. Horne, N. Ashkenasy and M. R. Ghadiri, *Chemistry*, 2005, **11**, 1137–1144.
15 C. Valery, M. Paternostre, B. Robert, T. Gulik-Krzywicki, T. Narayanan, J. C. Dedieu, G. Keller, M. L. Torres, R. Cherif-Cheikh, P. Calvo and F. Artzner, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 10258–10262.
16 S. Zhang, T. Holmes, C. Lockshin and A. Rich, *Proc. Natl. Acad. Sci. U. S. A.*, 1993, **90**, 3334–3338.
17 T. C. Holmes, S. de Lacalle S, X. Su, G. Liu, A. Rich and S. Zhang, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 6728–6733.
18 S. Vauthey, S. Santoso, H. Gong, N. Watson and S. Zhang, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 5355–5360.
19 P. Kiley, X. Zhao, M. Vaughn, M. A. Baldo, B. D. Bruce and S. Zhang, *PLoS Biol.*, 2005, **3**, e230.
20 N. Nuraje, I. A. Banerjee, R. I. MacCuspie, L. Yu and H. Matsui, *J. Am. Chem. Soc.*, 2004, **126**, 8088–8089.
21 L. Yu, I. A. Banerjee, X. Gao, N. Nuraje and H. Matsui, *Bioconjugate Chem.*, 2005, **16**, 1484–1487.
22 J. D. Hartgerink, E. Beniash and S. I. Stupp, *Science*, 2001, **294**, 1684–1688.
23 G. A. Silva, C. Czeisler, K. L. Niece, E. Beniash, D. A. Harrington, J. A. Kessler and S.I. Stupp, *Science*, 2004, **303**, 1352–1355.
24 C. Madhavaiah and S. Verma, *Chem. Commun.*, 2004, 638–639.
25 B. Caughey and P. T. Lansbury, Jr., *Annu. Rev. Neurosci.*, 2003, **26**, 267–298.
26 R. Nelson, M. R. Sawaya, M. Balbirnie, A. O. Madsen, C. Riekel, R. Grothe and D. Eisenberg, *Nature*, 2005, **435**, 773–778.
27 M. R. Chapman, L. S. Robinson, J. S. Pinkner, R. Roth, J. Heuser, M. Hammar, S. Normark and S. J. Hultgren, *Science*, 2002, **295**, 851–855.
28 I. Cherny, L. Rockah, O. Levy-Nissenbaum, U. Gophna, E. Z. Ron and E. Gazit, *J. Mol. Biol.*, 2005, **352**, 245–252.
29 D. Claessen, R. Rink, W. de Jong, J. Siebring, P. de Vreugd, F. G. Boersma, L. Dijkhuizen and H. A. Wosten, *Genes Dev.*, 2003, **17**, 1714–1726.
30 J. F. Smith, T. P. Knowles, C. M. Dobson, C. E. Macphee and M. E. Welland, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 15806–15811.
31 J. M. Kenney, D. Knight, M. J. Wise and F. Vollrath, *Eur. J. Biochem.*, 2002, **269**, 4159–4163.
32 T. Scheibel, R. Parthasarathy, G. Sawicki, X. M. Lin, H. Jaeger and S. L. Lindquist, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 4527–4532.
33 K. Tenidis, M. Waldner, J. Bernhagen, W. Fischle, M. Bergmann, M. Weber, M. L. Merkle, W. Voelter, H. Brunner and A. Kapurniotu, *J. Mol. Biol.*, 2000, **295**, 1055–1071.
34 M. Reches, Y. Porat and E. Gazit, *J. Biol. Chem.*, 2002, **277**, 35475–35480.
35 M. Reches and E. Gazit, *Science*, 2003, **300**, 625–627.
36 N. Kol, L. Adler-Abramovich, D. Barlam, R. Z. Shneck, E. Gazit and I. Rousso, *Nano Lett.*, 2005, **5**, 1343–1346.
37 Y. Song, S. R. Challa, C. J. Medforth, Y. Qiu, R. K. Watt, D. Pena, J. E. Miller, F. van Swol and J. A. Shelnutt, *Chem. Commun.*, 2004, 1044–1045.
38 M. Reches and E. Gazit, *Nano Lett.*, 2004, **4**, 581–585.
39 A. Mahler, M. Reches, M. Rechter, S. Cohen and E. Gazit, *Adv. Mater.*, 2006, **18**, 1365–1370.
40 M. Reches and E. Gazit, *Isr. J. Chem.*, 2005, **45**, 363–371.
41 M. Reches and E. Gazit, *Nat. Nanotechnol.*, 2006, **1**, 195–200.
42 L. Adler-Abramovich, M. Reches, V. L. Sedman, S. Allen, S. J. Tendler and E. Gazit, *Langmuir*, 2006, **22**, 1313–1320.
43 A. Aggeli, M. Bell, N. Boden, J. N. Keen, P. F. Knowles, T. C. McLeish, M. Pitkeathly and S. E. Radford, *Nature*, 1997, **386**, 259–262.
44 C. H. Gorbitz, *Chem. Commun.*, 2006, 2332–2334.
45 R. G. Ellis-Behnke, Y. X. Liang, S. W. You, D. K. Tay, S. Zhang, K. F. So and G. E. Schneider, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 5054–5059.
46 M. Yemini, M. Reches, J. Rishpon and E. Gazit, *Nano Lett.*, 2005, **5**, 183–186.
47 A. Mitraki, K. Papanikolopoulou and M. J. Van Raaij, *Adv. Protein Chem.*, 2006, **73**, 97–124.
48 K. Rajagopal and J. P. Schneider, *Curr. Opin. Struct. Biol.*, 2004, **14**, 480–486.