8

Molecular Design of Biological and Nano-Materials

Shuguang Zhang, Hidenori Yokoi, and Xiaojun Zhao

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8.1 DESIGN, SYNTHESIS, AND FABRICATION OF BIOLOGICAL AND NANO-MATERIALS AT THE MOLECULAR SCALE

Nature is the grandmaster when it comes to building extraordinary materials and molecular machines — one atom and one molecule at a time. Masterworks include such materials as minerals, well-ordered clays, and photonic crystals, and in the biological world, composites of inorganic or organic shells, pearls, corals, bones, teeth, wood, silk, horn, collagen, muscle fibers, and extracellular matrices. Multifunctional macromolecular assemblies in biology, such as hemoglobin, polymerases, ATP synthase, membrane channels, the splicesome, the proteosome, ribosomes, and photosystems are all essentially exquisitely designed molecular machines (Table 8.1).

Through billions of years of prebiotic molecular selection and evolution, Nature has produced a basic set of molecules that includes 20 amino acids, a few nucleotides, a dozen or so lipid molecules, and a few dozens of sugars as well as naturally modified building blocks or metabolic intermediates.

Table 8.1 What do they have in Common? Machines and Molecular Machines

Machines (Made by Humans)	Molecular Machines (Made by Nature)
Car, train, plane, space shuttle	Hemoglobin
Assembly lines	Ribosomes
Motors or generators	ATP synthases or photosystems
Train tracks	Actin filament network or intermediate filaments
Train controlling center	Centrosome
Digital database	Nucleosomes
Copy machines	Polymerases
Chain couplers	Ligases
Bulldozer or destroyer	Proteases or proteosomes
Mail-sorting machines	Protein sorting system
Electric fences	Membranes
Gates, keys, or passes	Ion channels, pumps, or receptors
Internet or World Wide Web	Neuron synapses

With these seemingly simple molecules, natural processes are capable of fashioning an enormously diverse range of fabrication units, which can further self-organize into refined structures, materials and molecular machines that not only have high precision, flexibility, and error correction, but also are self-sustaining and evolving.

Indeed, Nature shows a highly-flavored bottom-up design, building up molecular assemblies, bit by bit, more or less simultaneously on a well-defined scaffold. Take for example egg formation in oviparous animals. The fabrication of an egg involves not only the creation of the ovum, its various protective membranes, and accompanying nutritive materials (e.g., yolk) but also simultaneous synthesis of the eggshell from an extremely low concentration of calcium and other minerals, all in a very limited space. Oviparous animals synthesize eggshell against an enormous ionic and molecular concentration gradient due to the high levels of minerals at the site of eggshell assembly. Dental tissue formations face similar challenges not only when sharks repeatedly form new teeth, but also when humans form teeth during early childhood.

Nature accomplishes these feats effortlessly, yet recreating them in the laboratory presents an enormous challenge to the human engineer. The sophistication and success of natural bottom-up fabrication processes inspire our attempts to mimic these phenomena with the aim of creating new and varied structures, with novel utilities well beyond the gifts of Nature.

8.1.1 Two Distinctive and Complementary Fabrication Technologies

Two distinctive and complementary fabrication technologies are employed in the production of materials and tools. In the "top-down" approach, materials and tools are manufactured by stripping down an entity into its parts, for example, carving a boat from a tree trunk. This contrasts sharply with the "bottom-up" approach, in which materials and tools are assembled part by part to produce supra-structures, for example, building a ship using wooden strips (Figure 8.1) and complex architectures, construction of a building complex. The bottom-up approach is likely to become an integral part of materials manufacture in the coming decades. This approach requires a deep understanding of individual molecular building blocks, their structures, assembling properties, and dynamic behaviors. Two key elements in molecular material manufacture are chemical complementarity and structural compatibility, both of which confer the weak and noncovalent interactions that bind building blocks together during self-assembly. Following nature's leads, significant advances have been made at the interface of materials, chemistry and biology, including the design of helical ribbons, peptide nanofiber scaffolds for three-dimensional cell cultures and tissue engineering, peptide surfactants, peptide detergents for solubilizing, stabilizing, and crystallizing diverse types of membrane proteins and their complexes.

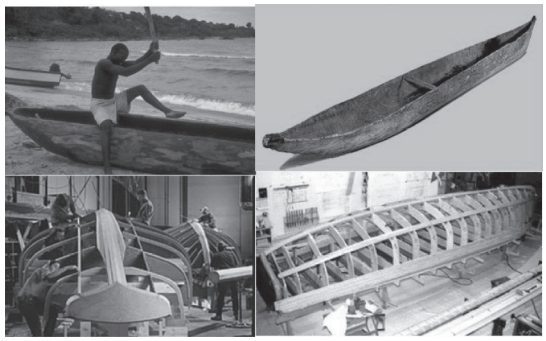

Figure 8.1 Two distinctive and complementary fabrication technologies: Top-down vs. bottom-up. In the top-down approach, the boat is limited by the size of the tree. On the other hand, the bottom-up approach, the boat is built with smaller parts of the tree. There is no size limit to the boat for which parts are used to build it.

8.2 NANOBIOTECHNOLOGY THROUGH MOLECULAR SELF-ASSEMBLY AS A FABRICATION TOOL

Design of molecular biological materials requires detailed structural knowledge to build advanced materials and complex systems. Using basic biological building blocks and a large number of diverse peptide structural motifs (Branden and Tooze, 1999; Petsko and Ringe, 2003), it is possible to build new materials from bottom-up.

One of the approaches is through molecular self-assembly using these construction units (Branden and Tooze, 1999; Petsko and Ringe, 2003). Molecular self-assembly is ubiquitous in nature, from lipids (that form oil droplets in water) and surfactants (that form micelles and other complex structures in water) to sophisticated multiunit ribosome and virus assemblies. Molecular self-assembly has recently emerged as a new approach in chemical synthesis and materials fabrication in polymer science, nanotechnology, nanobiotechnology, and various other engineering pursuits. Molecular self-assembly systems lie at the interface of molecular and structural biology, protein science, chemistry, polymer science, materials science, and engineering. Many self-assembling systems have been developed. These systems range from organic supramolecular systems, bi-, tri-block copolymers (Lehn, 1995), and complex DNA structures (Seeman, 2003, 2004), simple and complex proteins (Petka et al., 1998; Nowak et al., 2002; Schneider et al., 2002) to peptides (Aggeli et al., 2001; Hartgerink et al., 2001; Zhang et al., 1993, 1995, 2002; Zhang, 2003). Molecular self-assembly systems represent a significant advance in the molecular engineering of simple molecular building blocks for a wide range of material and device applications.

8.3 BASIC ENGINEERING PRINCIPLES FOR MICRO- AND NANO-FABRICATION BASED ON MOLECULAR SELF-ASSEMBLY PHENOMENA

Programmed assembly and self-assembly are ubiquitous in nature at both macroscopic and microscopic scales. The ancient Great Wall of China, the Pyramids of Egypt, the schools of fish in the ocean, flocks of birds in the sky, herds of wild animals on land, protein folding and oil droplets on water are all such examples. Programmed assembly describes predetermined planned structures. On the other hand, self-assembly describes the spontaneous association of numerous individual entities into a coherent organization and well-defined structures to maximize the benefit of the individual without external instruction (Figure 8.2).

Just like the construction of a wall, a house, or a building, many other parts of structures can be prefabricated and program assembled according to architectural plans (Figure 8.3). If we shrink

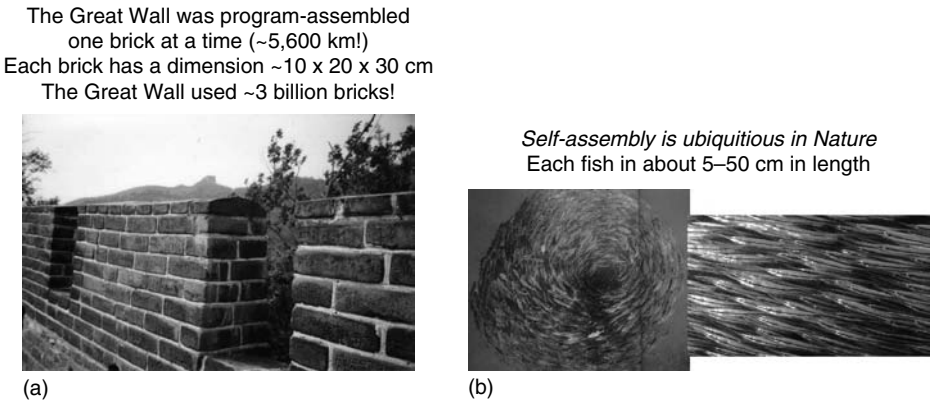

Figure 8.2 The programmed assembly and self-assembly. (a) The Great Wall was program-assembled over 2200 years ago, one brick at a time, with a defined plan, thus an ordered structure, using approximately 3 billion bricks (similar in number to the DNA bases in the human genome). (b) On the other hand, numerous individual fish self-assembled into well-ordered structure without external instructions. The power and ubiquitousness of self-assembly is witnessed everywhere in nature (images of the fish are courtesy of the National Geographic Society).

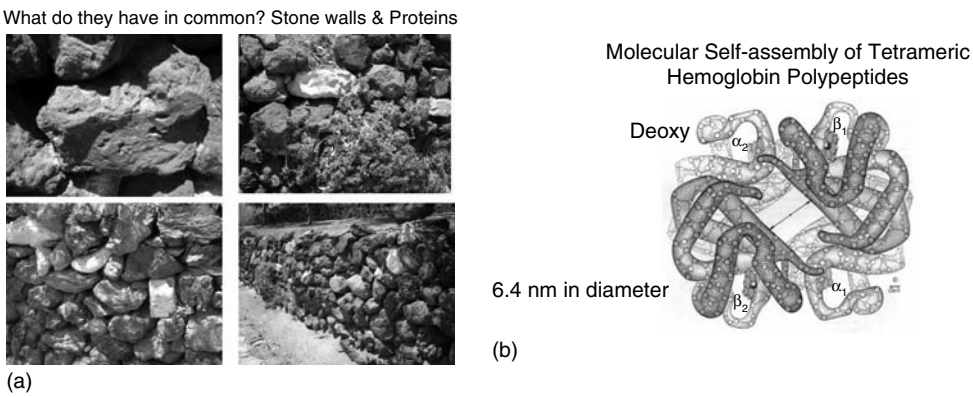

Figure 8.3 (See color insert following page 302) (a) The stone wall is built one stone at a time with different sizes and colors of stones. It has a defined function. (b) The protein — hemoglobin consisting of four chains — is built one amino acid at a time with 20 amino acids of all shapes and chemical properties. It also has a defined function to carry oxygen.

construction units by many orders of magnitude into nano-scale, such as structurally well-ordered protein fragments, or peptides (Fields, 1999; Yu et al., 1997), we can apply similar principles to construct molecular materials and devices, through molecular self-assembly and programmed molecular assembly. This field is growing at a rapid pace and it is impossible to summarize all aspects of the work being done by others in this limited space, and hence this chapter focuses on a few examples especially from the author's laboratory.

In this chapter, two distinct classes of self-assembling peptide construction motifs are described (Figure 8.4). The first class belongs to amphiphilic peptides that form well-ordered nanofibers (Zhang et al., 1993, 1995). The first member of such self-assembling peptides, EAK16, was discovered in a segment from yeast protein, zuotin (Zhang et al., 1992). These peptides have two distinctive sides, one hydrophobic and the other hydrophilic. The hydrophobic side forms a double sheet within the fiber and hydrophilic side the outside of the nanofibers that interact with water molecules. The hydrophilic side can form extremely high water content hydrogel, containing as high as 99.9% water similar as the water content of a jhellyfish. At least three types of molecules can be made, with $-$, $+$, $-/+$ on the

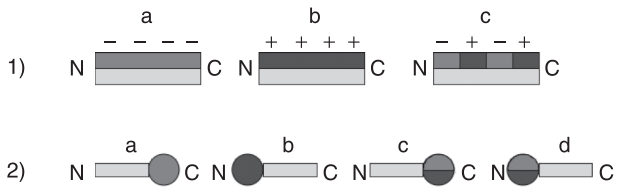

Figure 8.4 (See color insert) Two distinct classes of self-assembling peptide construction motifs are shown here. (a) The first class belongs to amphiphilic peptides that form well-ordered nanofibers. These peptides have two distinctive sides, one hydrophobic and the other hydrophilic. The hydrophobic side forms a double sheet inside of the fiber and hydrophilic side forms the outside of the nanofibers that interact with water molecules and they can form extremely high water content hydrogel, containing as high as 99.9% water. At least three types of molecules can be made, with $-$, $+$, $-/+$ on the hydrophilic side. (b) The second class of self-assembling peptide belongs to surfactant-like molecules. These peptides have a hydrophilic head and a hydrophobic tail, much like lipids or detergents. They sequester their hydrophobic tail inside of micelle, vesicles or nanotube structures and expose their hydrophilic heads to water. At least three kinds of molecules can be made, with $-$, $+$, $-/+$ heads.

hydrophilic side (Zhang and Altman, 1999; Zhang, 2002). The second class of self-assembling peptide belongs to a surfactant-like molecule (Vauthey et al., 2002; Santoso et al., 2002; von Maltzahn et al., 2003). These peptides have a hydrophilic head and a hydrophobic tail, much like lipids or detergents. They sequester their hydrophobic tail inside of micelle, vesicles or nanotube structures and expose their hydrophilic heads to water. As in the previous case, at least three kinds of molecules can be made, with $-$, $+$, $-/+$ heads.

The first class includes: "Peptide Lego" that forms well-ordered nanofiber scaffolds and can be used not only for 3-D tissue cell culture but also for regenerative medicine, namely to promote healing and replacing damaged tissues. The second class includes peptide surfactants and detergents that can be used not only for drug, protein and gene deliveries, but also for solubilizing, stabilizing, and crystallizing membrane proteins. Membrane proteins are crucial for biological energy conversations, cell–cell communications, specific ion channels and pumps including our senses, sight, hearing, smell, taste, touch, and temperature sensing.

Like bricks and architectural construction units, these designed peptide construction motifs are structurally simple, versatile for a wide spectrum of applications.

8.4 CHEMICAL COMPLEMENTARITY AND STRUCTURAL COMPATIBILITY THROUGH NONCOVALENT WEAK INTERACTIONS

Molecular self-assembly, by definition, is the spontaneous organization of numerous molecules under thermodynamic and kinetic conditions into structurally well-defined and rather stable arrangements through a number of noncovalent interactions. These molecules undergo self-association forming hierarchical structures. The ribosome is one of the most sophisticated molecular machines nature has ever remarkably self-assembled (Figure 8.5). It has more than 50 different kinds of proteins and 3 different size and functional RNAs, all through weak interactions to form the remarkable assembly line (Stillman, 2002). The other molecular machines include the photosystems I and II that collect photos to convert into electrons in order to produce energy needed for nearly all living systems on Earth (Barber, 1992).

Molecular self-assembly is mediated by weak, noncovalent bonds — notably hydrogen bonds, ionic bonds (electrostatic interactions or salt bridges), hydrophobic interactions, van der Waals interactions, and water-mediated hydrogen bonds. Although these bonds are relatively insignificant in isolation, when combined together as a whole, they govern the structural conformation of all biological macromolecules and influence their interaction with other molecules (Pauling, 1960). The water-mediated hydrogen bond is especially important for living systems as all biological materials interact with water (Ball, 2001).

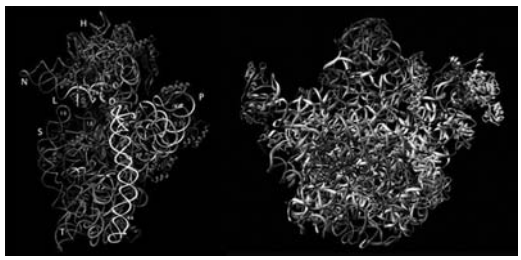

Figure 8.5 (See color insert) The bacterial ribosome. 30S ribosome (left panel) and 50S ribosome (right panel). The ribosome is one of the most sophisticated molecular machines nature has ever self-assembled. It has more than 50 different kinds of proteins and 3 different size and functional RNAs, all through weak interactions to form the remarkable assembly line. (*Source*: http://www.molgen.mpg.de/~ag_ribo/ag_franceschi/.)

These weak interactions promote the assembly of molecules into units of well-defined and stable hierarchical macroscopic structures. Although each of the bonds or interaction is rather weak, the collective interactions can result in very stable structures and materials. The key elements in molecular self-assembly are chemical complementarity and structural compatibility. Like hands and gloves, both the size or shape and the correct orientation, that is chirality, are important in order to have a complementary and compatible fitting (Schnur, 1993).

The key engineering principle for molecular self-assembly is to artfully design the molecular building blocks that are able to undergo spontaneously stepwise fine-tuned interactions and assemblies through the formations of numerous noncovalent week chemical bonds.

8.5 SELF-ASSEMBLING SYSTEMS — MODELS TO STUDY MOLECULAR ANTENNA FOR PROGRAMMED ASSEMBLY, SURFACE ENGINEERING, AND FABRICATION OF NANOSCAFFOLD TO NANOBIOTECHNOLOGY

8.5.1 Fabricating Nanowires using Bioscaffolds

In the computing industry, the fabrication of nanowires and nanofeatures using the "top-down" approach increasingly faces tremendous challenges. Thus, the possibility of molecular fabrication of conducting nanowires using DNA (Braun et al., 1998; Keren et al., 2003) peptides and protein scaffolds is of particular interest to electronics industry. One can readily envision that nanotubes, nanofibers, actin filaments, yeast prion nanofibers made from self-assembling peptides and proteins may serve as templates for metallization (Djalali et al., 2002; Scheibel et al., 2003; Reches and Gazit, 2003; Mao et al., 2003). Once the organic scaffold is removed, a pure conducting wire is left-behind and immobilized on a surface. There is great interest in developing various methods for attaching conducting metal nanocrystals to DNA, peptides, and proteins for such a purpose. Furthermore, the coupled DNA, peptides and proteins may not only respond to electronic signals but may also be used as antennae for a wide range of applications including to study detailed molecular interactions and fabricate miniature devices (Hamad-Schifferli et al., 2002; Sung et al., 2004).

8.5.2 Molecular Ink and Nanometer Coatings on Surfaces

Molecular assembly can be targeted to alter the chemical and physical properties of a material's surface (Whitesides et al., 1991; Mrksich and Whitesides, 1996; Whitesides and Grzybowski, 2002). Surface coatings instantly alter a material's texture, color, compatibility with, and responsiveness to the environment. Conventional coating technology is typically accomplished through

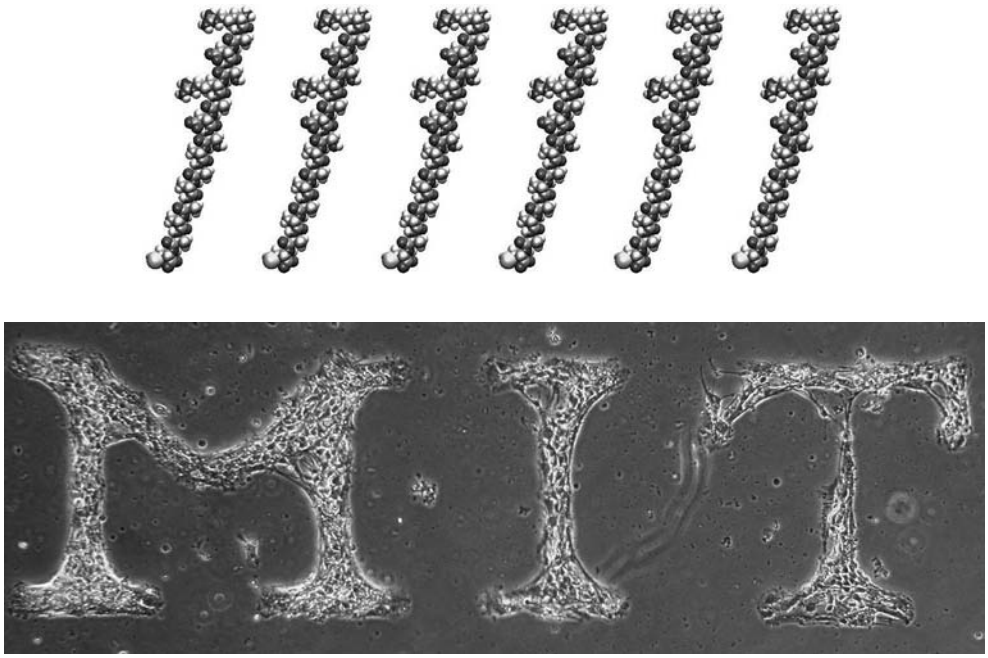

Figure 8.6 Self-assembling peptide molecular ink and the printed MIT. The ink molecules are 4 nm long with a linker that can be directly anchored on surface (Top). The molecular ink was used to print specific patterns for cells and neurons (Bottom). The MIT letters are ~400 μm tall.

painting or electroplating. These coatings are usually in the tens and hundreds micron range and the interface is often not complementary at the molecular level. Thus, erosion is common.

We have developed a class of biologically active molecular ink (Figure 8.6), self-assembling peptides with linkers that anchor on surfaces (Zhang et al., 1999). In conjunction with self-assembled monolayers prepared through microcontact printing, we can place molecules (nanometer scale) and cells (micron scale) into complex patterns. This approach may facilitate research into detail molecular interactions and cell–cell communication. Recently, we have moved one step further: using peptides and proteins as ink, we have directly microprinted specific features onto the nonadhesive surface of polyethylene glycol to fabricate any arbitrary patterns rapidly without preparing a mask or stamps. The process is similar to using an ink pen for writing — here, the microprinting device is the pen and the biological or chemical substances are the inks (Sanjana and Fuller, 2004).

8.5.3 Nanofiber Peptide and Protein Scaffolds

We have also focused on fabricating three-dimensional peptide scaffolds using the self-assembling peptides (Figure 8.7) by exposing them to a salt solution or to physiological media that accelerate the formation of macroscopic structures (Zhang et al., 1993, 1995; Holmes et al., 2000). Scanning electron microscopy (SEM), transmission EM (TEM), and atomic force microscopy (AFM) (Marini et al., 2002) reveal that the matrices formed are made of interwoven nanofibers having a diameter of ~10 nm and pores of ~5 to 200 nm in size. If the alanines are changed to more hydrophobic residues, such as valine, leucine, isoleucine, phenylalanine, or tyrosine, the molecules have a greater tendency to self-assemble and form peptide matrices. These simple, defined and tailor-made self-assembling peptides have provided the first *de novo* designed scaffolds for three-dimensional cell culture, with potential implications for basic studies of cell growth and applied studies in tissue engineering and ultimately regenerative medicine (Kisiday et al., 2002; Zhang, 2004).

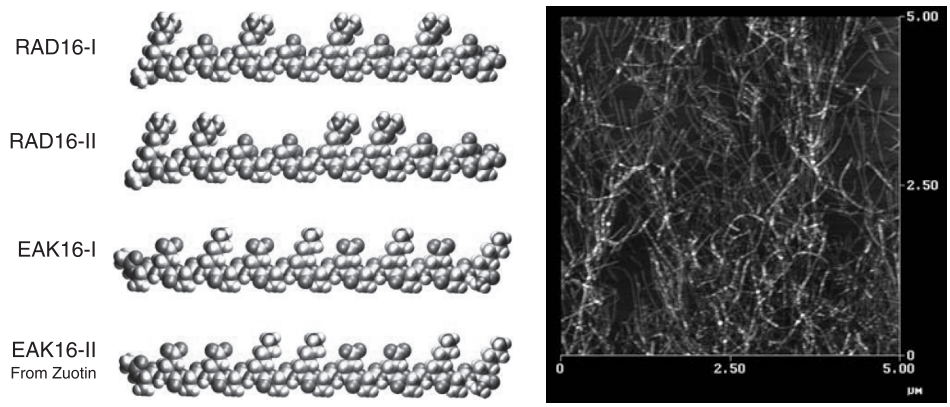

Figure 8.7 The individual self-assembling peptide molecules are 5 nm long (left). The first such peptide, EAK16-II, was discovered from a yeast protein, zuotin (Zhang et al., 1992). This peptide inspired us to design a large class of self-assembling peptide construction motifs. Upon dissolving in water in the presence of salt, they spontaneously assemble into well-ordered nanofibers, further into scaffolds. The AFM image of peptide RAD16-I nanofibers and PuraMatrix scaffold is shown (right).

We have shown that a variety of tissue cells encapsulated and grown in three-dimensional peptide scaffolds exhibit interesting functional cellular behaviors, including proliferation, functional differentiation, active migration, and extensive production of their own extracellular matrices (Kisiday et al., 2002; Zhang, 2003, 2004). When primary rat hippocampal neuron cells are allowed to attach to the peptide scaffolds, the neuron cells not only project lengthy axons that follow the contours of the scaffold surface, but also form active and functional synaptic connections (Figure 8.8). (Holmes et al., 2000). Furthermore, when the peptide scaffold was injected into brain of animals, it bridged the gap and facilitated the neural cells to migrate across the deep canyon. The animals regained their visual function. Without the peptide scaffold, the gap remains, and the animals did not regain visual function (Ellis-Behnke et al., unpublished results).

8.5.4 Designer Peptide Surfactants or Detergents

We designed another new class of peptide surfactants or detergents with short hydrophobic tail and hydrophilic head (see Figure 8.4, lower panel), taking advantage of the self-assembly properties in water (Vauthey et al., 2002; Santoso et al., 2002; von Maltzahn et al., 2003). Several peptide surfactants have been designed using the nature lipid as a guide. These peptides have a hydrophobic tail with various degrees of hydrophobicity and a hydrophilic head, either negatively charged aspartic and glutamic acids or positively charged lysine or histidine (Figure 8.9). These peptide monomers contain 7 to 8 amino acid residues and have a hydrophilic head composed of aspartic acid and a tail of hydrophobic amino acids such as alanine, valine, or leucine. The length of each peptide is approximately 2 nm, similar to that of biological phospholipids (Vauthey et al., 2002; Santoso et al., 2002; von Maltzahn et al., 2003). The length can also be varied by adding more amino acid, one at a time to a desired length as shown in Figure 8.9.

Although individually these peptide surfactants or detergents have completely different compositions and sequences, these peptides share a common feature: the hydrophilic heads have 1 to 2 charged amino acids and the hydrophobic tails have four or more consecutive hydrophobic amino acids. For example, A_6D (AAAAAAD), V_6D (VVVVVVD) peptide has six hydrophobic alanine or valine residues at the N-terminus followed by a negatively charged aspartic acid residue, thus having two negative charges, one from the side chain and the other from the C terminus; likewise, G_8DD (GGGGGGGGDD), has eight glycines followed by two asparatic acids with three negative charges. In contrast, KV_6 (KVVVVVV) and V_6K (VVVVVVK) have one positively charged lysine as the

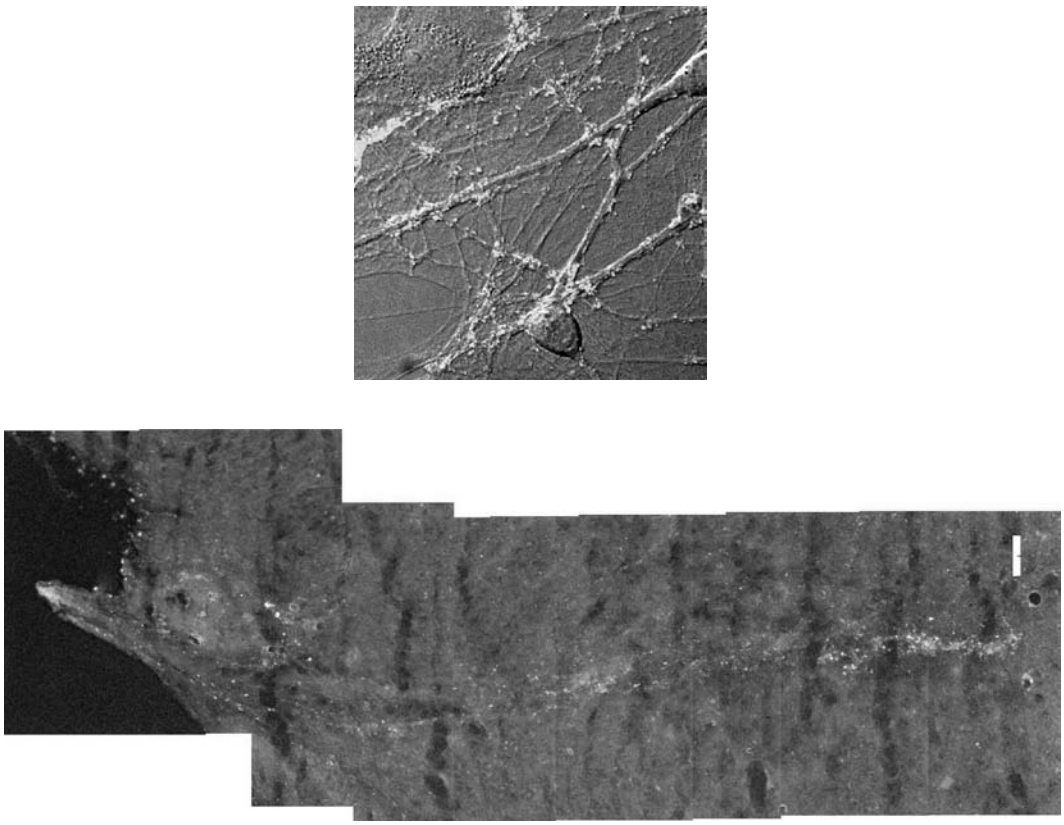

Figure 8.8 (See color insert) When primary rat hippocampal neuron cells are allowed to attach to the peptide scaffolds, the neuron cells not only project lengthy axons that follow the contours of the scaffold surface, but also form active and functional synaptic connections, each green dot is a functional neuronal connection (upper panel). Furthermore, when the peptide scaffold was injected into brain of animals, it bridged the gap and facilitated the neural cells to migrate across the deep canyon (lower panel). The animals regained their visual function. Without the peptide scaffold, the gap remains, and the animals did not regain visual function.

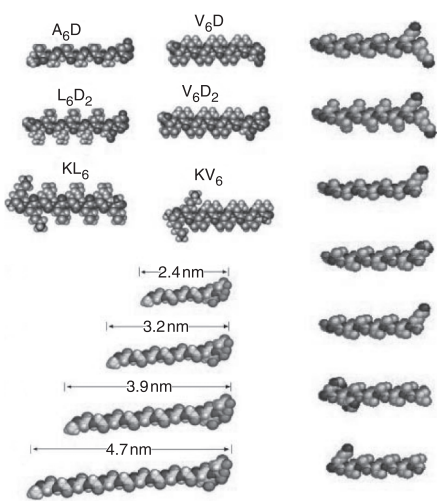

Figure 8.9 A few of the self-assembling peptide surfactant or detergent molecules are modeled here. These peptides have a hydrophilic head and a hydrophobic tail, much like lipids or detergents. They sequester their hydrophobic tail inside of micelle, vesicles or nanotube structures and their hydrophilic heads expose to water. At least three kinds of molecules have been made, with $-$, $+$, $-/+$ heads.

hydrophilic head and six valines as the hydrophobic tail. Leucine and isoleucines are also used as tails. Positively charged lysine and histidine and negatively charged aspartic acid and glutamic acids have also been used as heads. (Vauthey et al., 2002; Santoso et al., 2002; von Maltzahn et al., 2003).

These peptides undergo self-assembly in water to form nanotubes and nanovesicles having an average diameter of 30 to 50 nm (Vauthey et al., 2002; Santoso et al., 2002; von Maltzahn et al., 2003). The tails consisting of alanines and valines produce more homogeneous and stable structures than those of glycines, isoleucine, and leucine. This property may be due to their hydrophobic and hydrophilic ratios. These monomer surfactant peptides were used for molecular modeling. The negatively charged aspartic acid is modeled as red and positively lysine is blue with the green as the hydrophobic tails.

Quick-freeze or deep-etch sample preparation where the sample is instantly flash-frozen below -190°C produced a 3-D structure with minimal structural disturbance. Using transmission electron microscopy, it revealed a network of open-ended nanotubes with three-way junction to connect the nanotubes (Figure 8.10) (Vauthey et al., 2002; Santoso et al., 2002; von Maltzahn et al., 2003). They seem to be dynamic molecular entities overtime. Likewise, A_6K cationic peptide also

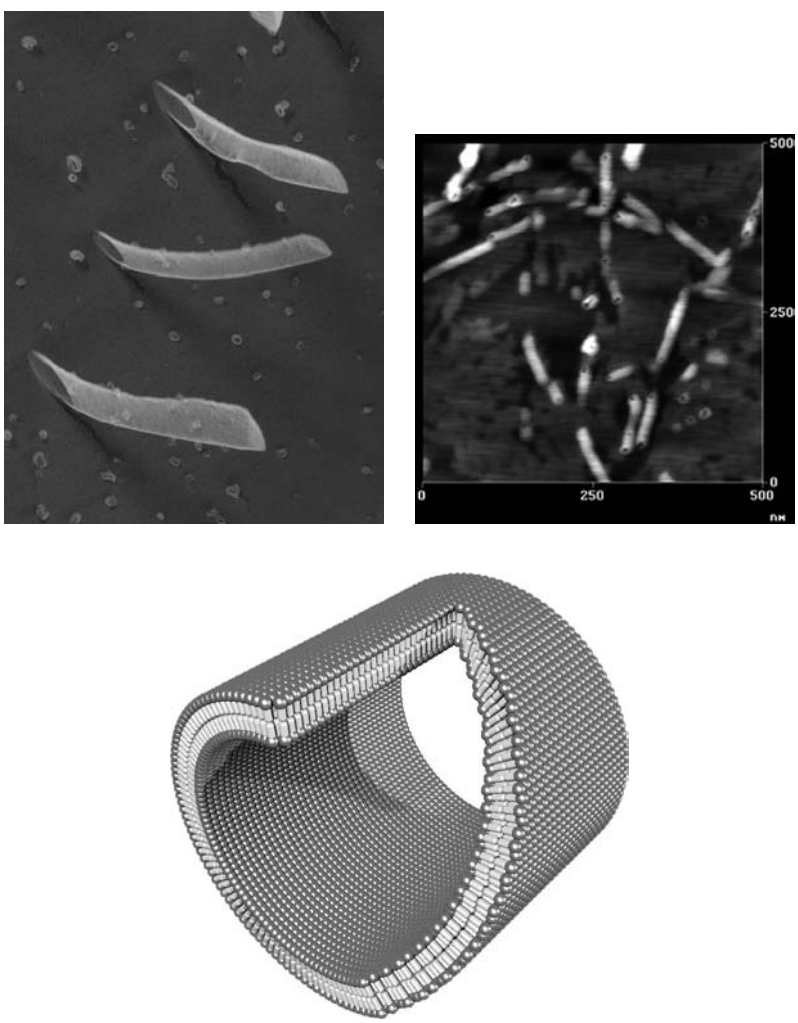

Figure 8.10 (See color insert) Self-assembling peptide nanotubes. Peptide detergents: V_6D with the tube diameter ~30 to 50 nm (left panel), A_6K with the tube diameter ~20 to 30 nm (middle panel) and the model for V_6D. The openings of the nanotubes are clearly visible. The wall of the tube has been determined using neutron scattering as ~5 nm, suggestive of a bi-layer structure modeled here.

exhibited similar nanotube structures with the opening ends clearly visible. The wall of the tube has been determined by neutron scattering as ~5 nm, suggestive of a bi-layer structure modeled here.

It is interesting that these simple peptides surfactants can produce remarkable complex and dynamic structures. This is another example to build materials from the bottom-up.

One may ask how could these simple peptide detergents form such well-ordered nanotubes and nanovesicles? The answer may lie in the molecular and chemical similarities between lipids and the peptides since both have a hydrophilic head and a hydrophobic tail. Organic detergents have been well studied over last few decades. The key lies in the molecular packing. However, the packing between lipids and peptides is likely to be quite different. In lipids, the hydrophobic tails pack tightly against each other to completely displace water, without formation of hydrogen bonds at all. On the other hand, in addition to hydrophobic tail packing between the amino acid side chains, peptide detergents also interact through intermolecular hydrogen bonds along the backbone. Some of these peptide detergents displayed typical beta-sheet structures, implying the backbone extended. Thus, the tails are likely packed in the beta-sheet form with certain curvature due to the repulsion charged heads.

8.6 PEPTIDE DETERGENTS STABILIZE MEMBRANE PROTEINS AND COMPLEXES

Many grand challenges remain in the postgenomic era, one of which is the fundamental understanding of membrane biology, namely, the study of the structure and function of membrane proteins, and specifically, the elucidation of high-resolution structures of integral membrane proteins.

Nearly all cellular signal transduction cascades occur through membrane proteins (Brann, 1992; Haga et al., 1999; Wess, 1999). All our senses including sight, smell, hearing, taste, touch, and temperature sensing, use membrane proteins for us to communicate with the external world. Many important drugs used as human therapeutics act through their interaction with membrane proteins. Yet, despite much effort in last few decades, very little is known about the intricacies and function of many membrane proteins. Thus, meticulous and systematic determination of high-resolution membrane protein structure will not only further our understanding of proteins as a whole, but will also enhance our knowledge of signal transduction and accelerate development of ultra-sensitive sensing devices.

Although membrane proteins are composed of approximately one-third of total cellular proteins (Wallin and von Heijne, 1998; Loll, 2003) and carry out some of the most important functions in cells, only ~170 membrane protein structures have been elucidated. This is in sharp contrast to over 30,000 nonmembrane protein structures that have been solved (http://www.rcsb.org/pdb/). The main reason for this delay is difficulty to purify and crystallize membrane proteins because removal of lipids from membrane proteins affects protein solubility and conformation stability. Despite a variety of detergents and lipids as surfactants being used to facilitate, solubilize, stabilize, purify, crystallize, and manipulate the membrane proteins for over the several decades, how detergents interact with membrane protein to impact its structure and functions and how to choose good detergents for the right membrane proteins remain largely unknown. This is partly due to complexity of membrane protein–detergent–lipid interactions and lack of "magic material" detergents. Therefore, the need to develop new material is urgent.

Recent experiments show that these peptide detergents are excellent materials for solubilizing, stabilizing (Kiley et al., 2005), and crystallizing several classes of diverse membrane proteins (Figure 8.11). These simply designed peptide detergents may now open a new avenue to overcome one of the biggest challenges in biology — to obtain large number of high-resolution structures of membrane proteins.

Study of the membrane proteins will not only enrich and deepen our knowledge of how cells communicate with their surroundings since all living systems respond to their environments, but these membrane proteins can also be used to fabricate the most advanced molecular devices, from energy harness devices, extremely sensitive sensors to medical detection devices, we cannot now even imagine. Following nature's lead, as the late legendary Francis Crick best put it: "*You should always ask questions, the bigger the better. If you ask big questions, you get big answers.*"

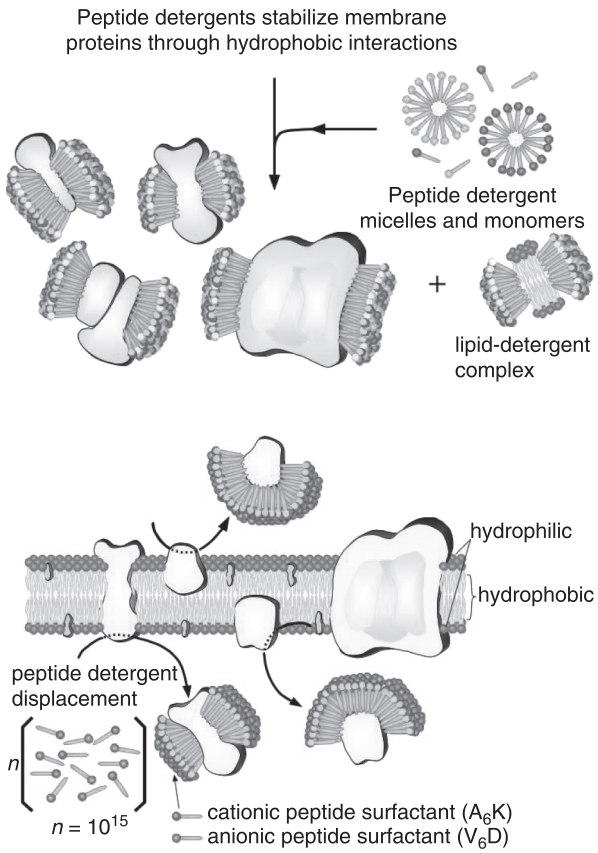

Figure 8.11 (See color insert) Schematic illustration of designed peptide detergents used to solubilize and stabilize membrane proteins. When mixed with membrane proteins, they solubilize and stabilize them, presumably at the belt domain where the membrane proteins are embedded in lipid membranes.

ACKNOWLEDGMENTS

We also would like to thank members of the lab, past and present, for making discoveries and conducting exciting research. We gratefully acknowledge the supports by grants from ARO, ONR, DARPA (BioComputing), DARPA or Naval Research Labs, DARPA or AFOSR, MURI or AFOSR, NIH, NSF-MIT BPEC and NSF CCR–0122419 to MIT Media Lab's Center for Bits and Atoms, the Whitaker Foundation, DuPont-MIT Alliance, Menicon, Ltd, Japan, Olympus Biomaterials Corp. and Mitsubishi Corp. Research Center. We also acknowledge the Intel Corporation's educational donation of computing cluster to the Center for Biomedical Engineering at MIT.

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