DESIGNING NOVEL MATERIALS AND MOLECULAR MACHINES

Shuguang Zhang

By imitating nature, scientists are designing completely new molecular patterns that can serve as a blueprint of new materials and sophisticated molecular machines. In the emerging field of nanotechnology, basic natural building blocks such as amino acids are used to create structures such as peptides and proteins for applications in medicine and energy. Nanobiotechnologists have begun to exploit molecular self-assembly as a fabrication tool for building new nanobiostructures such as nanotubes for metal casting, nanovesicles for drug encapsulations, and nanofiber scaffolds for growing new tissues. They also have constructed an extremely high-density nanoscale photosystem and ultra-lightweight solar-energy-harvesting molecular machines. With better understanding of these seemingly intractable phenomena, one day mankind may be able to use nano devices to repair body parts or to rejuvenate the skin, enhance human capabilities, harness the unlimited solar energy, and achieve other feats that seem impossible today.

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About 10,000 years ago, humans began to domesticate plants and animals. Now it's time to domesticate molecules.

— Susan Lindquist, Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology

Biotechnology, which is known primarily by its medical and agricultural applications, is increasingly being focused on the building of new biological materials and machines in an astonishing diversity of structures, functions, and uses. The advent of nanotechnology has accelerated this trend. Learning from nature, which over billions of years has honed and fashioned molecular architectural motifs to perform a myriad of specific tasks, nanobiotechnologists are now designing completely new molecular patterns—bit by bit, from the bottom up—to build novel materials and sophisticated molecular machines. Over the next generation, advances such as new materials to repair damaged tissues and molecular machines to harness solar energy from the smallest molecular amino acids and lipids will likely have an enormous impact on our society and the world's economy.

Modern biotechnology has already produced a wide array of useful products, such as humanized insulin and new vaccines. But what lies ahead can be even more revolutionary. That is why governments small and large, and industries local and global, are increasingly seeking to attract biotechnology talent and investment. There is no doubt that biotechnology, helped by the tools of nanotechnology, is expanding at an accelerating rate, and that the best is yet to come.

IMITATING NATURE

Nature itself is the grandmaster when it comes to building extraordinary materials and molecular machines atom by atom and molecule by molecule. Shells, pearls, corals, bones, teeth, wood, silk, horn, collagen, muscle fibers, and extra-cellular matrices are just a few examples of natural materials. Multifunctional macromolecular assemblies, such as hemoglobin, polymerases, and membrane channels, are all essentially exquisitely designed molecular machines.

Through billions of years of molecular selection and evolution, nature has produced a basic set of molecular building blocks that includes 20 amino acids, a few nucleotides—the structural units of nucleic acids such as ribonucleic acid (RNA) and deoxyribonucleic acid (DNA)—a dozen or so lipid molecules, and two dozen sugars. From these seemingly simple building blocks, natural processes are capable of fashioning an enormously diverse range of fabrication units that can further self-organize into refined structures, materials, and molecular machines that not only have high precision, flexibility, and error-correction capacity, but also are self-sustaining and evolving. For example, the photosynthesis systems in some bacteria and all green plants take sunlight and convert it into chemical energy. When there is less sunlight, as, for example, in deep water, the photosystems must evolve to become more efficient to collect the sunlight.

In the early 1990s, biotechnologists began to learn how to manipulate natural building blocks with at least one relevant dimension being between one nanometer (one billionth of a meter) and 100 nanometers to fabricate new molecular structures, thus ushering science and technology into the age of designed molecular materials. Much like clay and water can be combined to make bricks with multiple uses that, in turn, can be used to build walls such as the Great Wall of China, houses, or roads, basic natural building blocks such as amino acids can be used to create structures such as peptides and proteins that can be used for a variety of purposes. For example, animals grow hair or wool to keep themselves warm, shellfish grow shells to protect their tissue from harm, spiders spin silk to capture insects, and our cells make a lot of collagens to keep cells together to form tissues and organs.

If we shrink the construction units one billion times to the nanoscale, we can construct molecular materials and machines from prefabricated units in a way similar to that in which a house is assembled from prefabricated parts.

Peptides formed from amino acids are molecular architectural units that are proving very useful in the development of new nanobiological materials. In water and in the body fluids, these peptides form well-ordered nanofiber scaffolds useful for growing three-dimensional (3-D) tissue and for regenerative medicine. For example, scientists have fabricated artificial cartilage and bones to replace damaged tissue using the biological scaffolds and cells.

A 3-D nanomaterial grown from tiny droplets of a liquid metal on a silicon surface.

Furthermore, scientists have also shown that the designer self-assembling peptide nanofibers can stop bleeding instantly, a characteristic useful in surgeries. New peptides are proving to be remarkably useful in drug, protein, and gene deliveries, because they can encapsulate some water-insoluble drugs and ferry them into cells and other areas of the body. They also are essential to fabricating bio-solar, energy-harvesting molecular machines that use the photosystem from spinach and tree leaves.

Molecular Self-assembly

All biomolecules, including peptides and proteins, naturally interact and self-organize to form well-defined structures with specific functions. By observing the processes by which these biological molecular structures are assembled in nature, nanobiotechnologists have begun to exploit self-assembly as a fabrication tool for building new nanobiostructures such as nanotubes for metal casting, nanovesicles for drug encapsulations, and nanofiber scaffolds for growing new tissues.

Molecular self-assembly involves mostly weak bonds—as does human handholding—that can be joined and disjoined quickly. This is in sharp contrast to the very strong bonds that join our arms to our body. Individually, weak molecular forces are quite insignificant. Collectively, weak interactions such as the hydrogen bond and the ionic bond play an indispensable role in all biological structures and their interactions. The water-mediated hydrogen bond, in which numerous water molecules work as a bridge to connect two separate parts, is especially important for biological systems, since all biological materials interact with water. The bond, found in all collagens, works to increase the moisture for an extended time.

As to molecular building blocks, the designed peptides resemble the toy Lego bricks that have both pegs and holes arranged in a precisely determined manner and can be assembled into well-formed structures. Often referred to as "peptide Legos," these new molecular bricks under certain environmental conditions spontaneously assemble into well-formed nanostructures.

In water, peptide Lego molecules self-assemble to form well-ordered nanofibers that further associate to form scaffolds. One such nanofiber scaffolding material that has been commercially realized is PuraMatrix, so called because of its purity as a biotechnologically designed biological scaffold. Biomedical researchers currently use it worldwide to study cancer and stem cells, as well as to repair bone tissue.

Since these nanofiber scaffolds contain 5 to 200 nanometer pores and have extremely high water content, they are of potential utility in the preparation of 3-D cell and tissue growth and in regenerative medicine. In addition, the small pore size of these scaffolds may allow drugs to be released slowly so people do not have to take their medicine several times a day but rather once over a longer period. A slow-release nanoscaffold device can be implanted on the skin with medicine supplies sufficient for months or years.

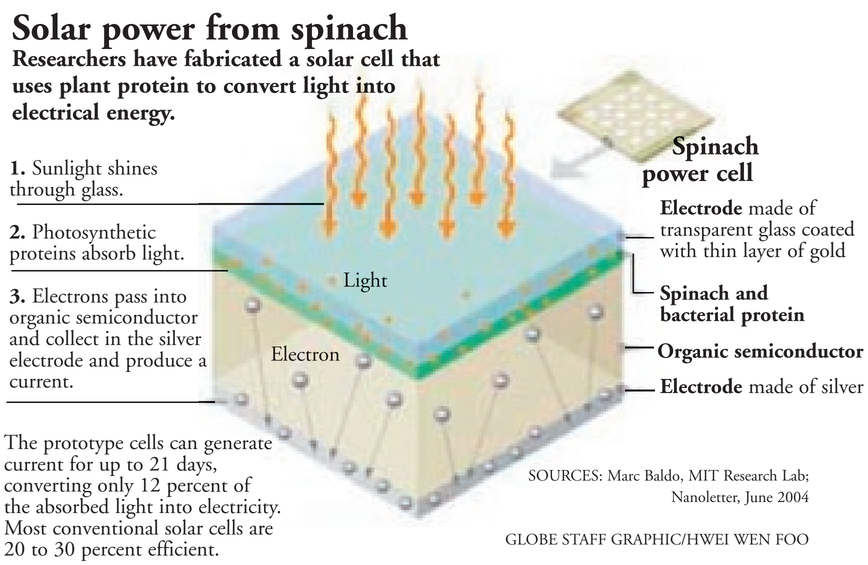
Creating More Building Blocks

Using nature's lipids as a guide, a new class of lipid-like peptide detergents has been designed. These peptides have seven to eight amino acids, giving them a length similar to naturally occurring lipids, which make up cell walls 20,000 times thinner than the diameter of a piece of human hair.

Simple lipid-like peptide detergents produce remarkably complex and dynamic structures in the same way that the assembly of numerous simple bricks can make many different and distinctive architectural structures.

Some peptide detergents have been found to be excellent materials for stabilizing notoriously hard-to-stabilize membrane proteins—protein molecules attached to or associated with the membrane of a cell—thus opening a new avenue for overcoming one of the biggest challenges in biology: obtaining clear pictures of the ubiquitous and vital membrane proteins.

Numerous drugs exert their effect through membrane proteins. But how these drugs interact with vital membrane proteins at the finest molecular level remains largely unknown. The designed peptide detergents promise to change this. If we can fully understand the interactions of these proteins, we may be able to produce more effective and efficient drugs with few or no side effects.



Courtesy of *The Boston Globe*

Figure 1. The spinach chip and bio-solar energy-harvesting molecular machine. The photons (either from the sun or any other light) can be directly converted into electric energy using the combination of a natural green plant photosynthetic system and semiconducting material carbon C_{60} and conducting materials—gold and silver electrodes.

Harnessing Solar Energy

Detailed molecular study of how membrane proteins function is just an exercise in understanding them. By deepening our knowledge of how cells communicate with their surroundings, we learn how all living systems respond to their environments. With this know-how, modern nanobiologists have begun to fabricate advanced molecular machines able to develop extremely sensitive sensors for medical detection or to harness bio-solar energy. For example, ancient Chinese doctors smelled a patient to diagnose a medical problem because they believed that an illness can change a patient's body odor or secretion. In modern medical science, a number of instruments are used to make an accurate diagnosis. In the future, a smell sensor as sophisticated as a dog's nose could help distinguish people with medical problems from healthy ones. In the United Kingdom, dogs have already demonstrated their ability to identify people suffering from cancer by sniffing their odors.

No one would argue that affordable, sustainable, and environmentally sound energy is requisite for the welfare of modern civilization. With environmental damages caused by fossil fuel pollution and the demand for energy burgeoning worldwide, the world's energy problems are now more urgent than ever. Alternative solutions, long debated but rarely seriously pursued, are now being pursued with a sense of urgency.

Further, the increasingly mobile nature of computing and communication, and the nanonization of materials and molecular machines, demand that smaller, lightweight, self-sustaining energy sources be developed. An obvious source of infinite energy is the sun. Nature has produced an efficient system to directly convert photons into electrons and further into chemical energy; green plants and other biological organisms have been using this system for billions of years.

Most energy on earth is obtained from photosynthesis through photosystems, the most efficient energy-harvesting system. If a way to harness the energy produced by natural photosystems can be developed, we will have a clean and nearly inexhaustible energy source.

Borrowing from the bacterial and green plant energy-harvesting photosystem, nanobiotechnologists have demonstrated that photons can be converted directly into electrons by newly designed bio-solar molecular machines. Through a combination of precision engineering and biological engineering of the photosystem, they have constructed an extremely high-density nanoscale photosystem and ultra-lightweight solar-energy-harvesting molecular machines.

Two key components are required to fabricate a bio-solar energy-harvesting molecular machine—a bio-solar energy production system (photosystem) from leaves of green plants, and the designed peptide detergents. For bio-solar energy production, a simpler photosystem was used. Scientists originally purified the photosynthesis system from spinach, and they have recently reported successfully purifying photosynthetic systems from maple, pine, and oak trees and from bamboo leaves. The entire photosystem complex—only about 20 nanometers in height—was anchored onto a gold surface with an upright orientation.

Experimentation is continuing to devise ways to increase the amount and duration of energy produced by this exciting new molecular-energy-harvesting machine (figure 1).

What Lies Ahead?

The continued development of nanobiotechnology materials and molecular machines will deepen our understanding of seemingly intractable phenomena. Nanoscale engineering through molecular design of self-assembling peptides is an enabling technology that will likely play an increasingly important role in the future of biotechnology and will change our lives in the coming decades. For example, aging and damaged tissues can be replaced with the scaffolds that stimulate cells to repair body parts or to rejuvenate the skin. We also might be able to swim and dive like dolphins or to climb mountains with a nanoscaffold lung device that can carry an extra supply of oxygen. It is not impossible to anticipate painting cars and houses with photosynthesis molecular machines that can harness the unlimited solar energy for all populations on every corner of the planet, not just for the wealthy few.

We are just at the beginning of a great journey and will make many unexpected discoveries. Although nanotechnologists face many challenges, they will actively pursue many issues related to the molecular fabrication of composite materials and molecular machines. Biotech self-assembling peptides can be considered the building blocks for emerging materials and for fabricating future man-made molecular machines. These peptides can also be designed in combination to incorporate other building blocks such as sugars, lipids, nucleic acids, and a large number of metal crystals. Nature has inspired us and opened the door to its secrets. It is up to our imagination to expand upon its materials and molecular machines. ■

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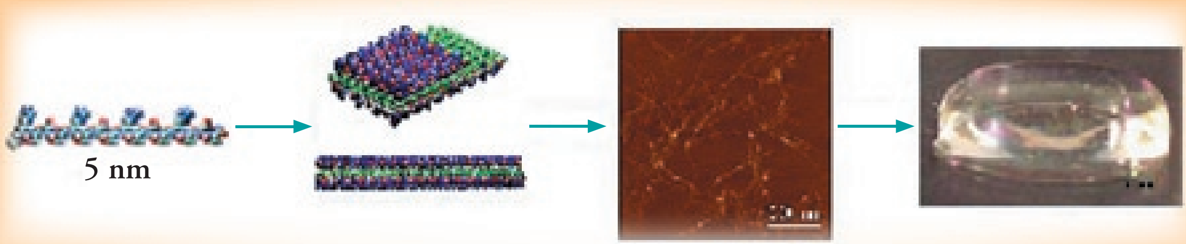
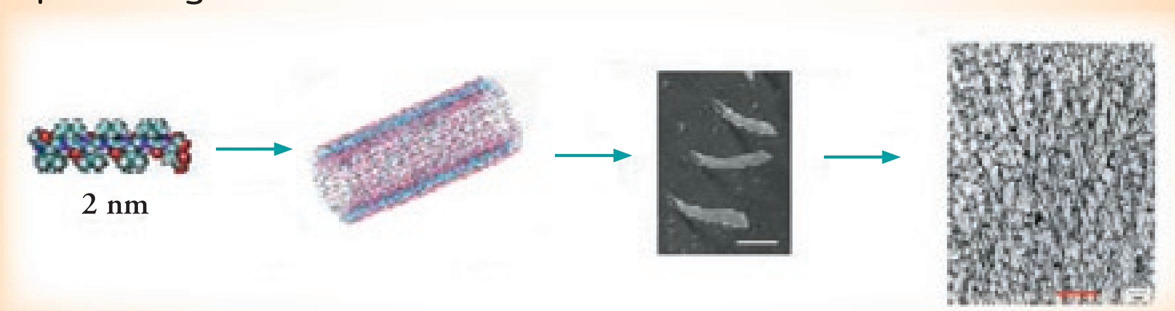
Examples of New Nanobiotechnological Materials

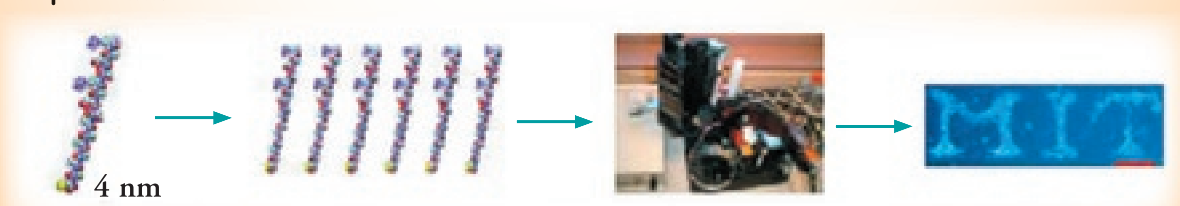
Peptide Lego



Peptide Detergents



Peptide Ink



Peptide Lego, also called ionic self-complementary peptide, has 16 amino acids, about five nanometers in size. Peptide Lego molecules form nanofiber scaffolds that can be used in studies of cancer cells and stem cells, as well as for bone tissue repair in medicine. **Peptide detergents**, about two nanometers in size, can self-assemble into nanotubes and nanovesicles with a diameter of about 30 to 50 nanometers. These nanotubes go on to form an interconnected network that can be used in the development of more effective and more efficient drugs with fewer side effects. **Peptide ink**, about four nanometers in size, can be used as ink for an inkjet printer to directly print on a surface, instantly creating any pattern. The peptide ink, like blue and red inks, is useful to instantly alter the surface property so that cells can directly attach on to it. It can be used for developing cell-based sensors and coating for medical implants. When the peptide ink is applied along a certain pattern or shape on the surface, rat neural cells can spell, for example, M.I.T., as shown here.

WHITHER NANOTECHNOLOGY?

Akhlesh Lakhtakia

"Think small, dream big" is a typical slogan about the promise of nanotechnology within the scientific research community. Once relegated to pure fiction, nanotechnology is becoming increasingly linked with advances in biotechnology and information technology. With annual expenditure for nanotechnology research in the United States estimated to be in excess of $2.6 billion in 2004, the word "nano" is even finding its way into popular culture, from daily horoscopes to newspaper cartoons.

Yet the relatively small number of applications that have made it through to industrial uses represent "evolutionary rather than revolutionary advances," according to a 2004 panel report from the Royal Society of London and the Royal Academy of Engineering.

"They found a defect in the new chip. Looks like someone was asleep at the itty-bitty, teeny-weeny switch."

www.cartoonstock.com

Nanotechnology is not a single process; neither does it involve a specific type of material. Instead, the term nanotechnology covers all aspects of the production of devices and systems by manipulating matter at the nanoscale.

Take an inch-long piece of thread and chop it into 25 pieces, and then chop one of those pieces into a million smaller pieces. Those itty-bitty pieces are about one nanometer long. The ability to manipulate matter and processes at the nanoscale undoubtedly exists in many academic and industrial laboratories. At least one relevant dimension must lie between 1 and 100 nanometers, according to the definition of nanoscale by the U.S. National Research Council. Ultra-thin coatings have one nanoscale dimension, and nanowires and nanotubes have two such dimensions, whereas all three dimensions of nanoparticles are at the nanoscale.

Nanotechnology is being classified into three types. The industrial use of nanoparticles in automobile paints and cosmetics exemplifies incremental nanotechnology. Nanoscale sensors exploiting the fluorescent properties of disks called quantum dots (which are 2 to 10 nanometers in diameter) and electrical properties of carbon nanotubes (which are 1 to 100 nanometers in diameter) represent evolutionary nanotechnology, but their development is still in the embryonic stage. Radical nanotechnology, the stuff of science-fiction thrillers, is nowhere on the technological horizon.

Material properties at the nanoscale differ from those in bulk because of extremely large surface areas per unit volume at the nanoscale. Quantum effects also come into play at the nanoscale. Nanoscale properties and effects should transform current practices in integrated electronics, optoelectronics, and medicine. But the translation from the laboratory to mass manufacturing is fraught with significant challenges, and reliable manipulation of matter at the nanoscale in a desirable manner remains very difficult to implement economically. And very little data exist on the health hazards of nanotechnology.

Nanotechnology is emerging at a crucial stage of our civilization. A remarkable convergence of nanotechnology, biotechnology, and information technology is occurring. Some of the extremely pleasant prospects of their symbiosis, among others, are new medical treatments, both preventive and curative; monitoring systems for buildings, dams, ships, aircraft, and other structures vulnerable to natural calamities and terrorist acts; and energy-efficient production systems that produce very little waste.

The convergence of the three technologies is to be expected. Protein molecules such as kinesin are being developed to transport cargo molecules over distances on the order of a millimeter on silicon wafers for eventual use in smart nanosensor systems and molecular manufacturing systems. Cells, bacteria, and viruses are being used to manufacture complex templates to precipitate medically useful molecules without producing medically harmful molecules in pharmaceutical factories. Nanotechnology also is being used to fabricate laboratories-on-a-chip to carry out tests of biological fluids, with the data being optically accessed and electronically stored and processed. Nano drug delivery systems are expected to be used inside living organisms to modify specific biological functions, for example, to develop or boost immunities against specific pathogens.

The convergence also makes urgent the need for better regulation and oversight. With most of the work being conducted under governmental auspices, citizen watchdog groups and nongovernmental organizations, as well as private-sector scientific panels, must be given greater authority to oversee this research. At the same time, laws must be formulated to guide the conduct of individuals in charge of government programs and private contractors on nanotechnology.

Nanotechnology today is probably like Mozart when he was five years old: bursting with promise, with the best yet to come after a few years of nurturance. ■

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