NANOTECHNOLOGY

Biology Offers Nanotechs A Helping Hand

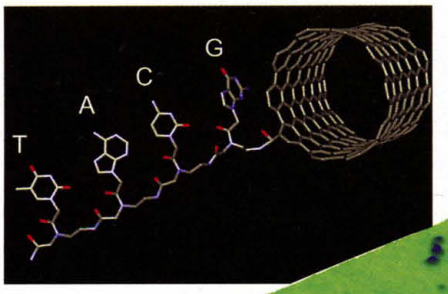
Rather than building tiny devices atom by atom, nanoscientists are raiding biology's molecular toolbox in hopes of revolutionizing sensors, medical diagnostics, and electronics

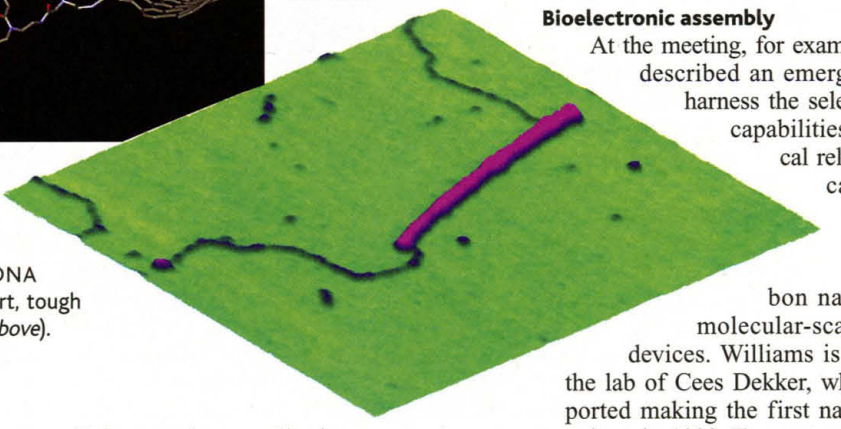
BOSTON, MASSACHUSETTS—When it comes to nanotechnology, physicists, chemists, and materials scientists can't hold a candle to the simplest bacteria. Billions of years of evolution have outfitted organisms of all stripes with a wealth of nanomachines—from the information-storage medium of DNA to the proteins that capture sunlight and copy DNA during cell division. Early nanotech visionaries dreamed of crafting their own versions of nanomachinery and even went so far as to draw up molecular specs for tiny gears and motors. But at the Materials Research Society meeting here earlier this month,* it was clear that as nanotechnology begins to leave its infancy and find its feet, most nanobuilders are looking to biology not just for inspiration but also a little practical help.

In labs around the globe, researchers are working to marry biology and nanotechnology, fusing useful biomolecules to chemically synthesized nanoclusters in arrangements that do everything from emitting light to storing tiny bits of magnetic data. The result is a merger that attempts to blend biology's ability to assemble complex structures with nanoscientists' capacity to build useful devices.

That merger hasn't created any Fortune 500 companies yet. But for basic researchers, blending biology and nanotech is a white-hot field. "It's gaining huge momentum right now," says Chad Mirkin, a chemist and nanoscience expert at Northwestern University in Evanston, Illinois. And that momentum, say many researchers, could lead to the development of a wide range of applications, from novel medical diagnostics and sensors to data-storage materials and nanomanufacturing tools. "There are a lot of ideas emerging right now," says Günter Schmid, a chemist at the University of Essen, Germany.

One of the biggest drivers behind nanotechnology's enthusiasm for biological systems revolves around an organism's impressive ability to manufacture complex molecules such as DNA and proteins with atomic precision. Chemists create molecules up to hundreds of atoms in size without too much trouble, controlling the position of every atom. But beyond that, traditional synthetic schemes become unwieldy and too inefficient to be practical.





Welded. In this micrograph, a carbon nanotube (purple) trails DNA anchored by short, tough PNA molecules (*above*).

Computer chip engineers—the most advanced materials makers—do much better. They can craft chips with 200 million transistors, each with features on the order of 100 nanometers, or 100 billionths of a meter.

"There's a big gap in between those two," says Joseph Jacobson, a physicist at the Massachusetts Institute of Technology (MIT) in Cambridge—but not for biology. "The champions of that [size range] are the pieces of machinery of biology, DNA and proteins." So as a stopgap, nanotechnologists are looking to see what they can appropriate. "There is an incredible toolbox [of biomolecules] that we can incorporate for our own ends," says Paul Alivisatos, a chemist at the University of California, Berkeley.

Complex biological machines also show an uncanny knack for homing in on and binding to molecular targets amid a sea of other molecules. "Biomachinery is a powerful way of bringing organization into a system," notes Keith Williams, a physicist and nanotech expert at the Delft Institute of Technology in the Netherlands. By contrast, engineered nanosized objects such as carbon nanotubes and tiny spherical metal and semiconducting particles lack any guidance mechanism. That makes it extremely difficult to put those tubes and particles where you want them to go. "As materials become so small, they become difficult to handle with traditional methods such as lithography," the technique used to pattern computer chips, says Williams.

As a result, until researchers learn to construct complex nanostructures from the ground up, they have little choice but to become small-time thieves. "Instead of trying to build [nanostructures] from scratch, let's just steal them from biology," says Jacob Schmidt, a bioengineer at the University of California, Los Angeles. A handful of nanotech research groups has been perpetrating such theft in recent years, Mirkin and others say, but now the nano field is in the midst of a kleptomania epidemic.

Bioelectronic assembly

At the meeting, for example, Williams described an emerging effort to harness the selective binding capabilities of a chemical relative of DNA called peptide nucleic acid (PNA) to assemble carbon nanotubes into molecular-scale electronic devices. Williams is a postdoc in the lab of Cees Dekker, whose team reported making the first nanotube-based transistor in 1998. To construct that device, Dekker's team scattered nanotubes across a surface patterned with tiny gold electrodes and then used an atomic-resolution microscope to find a lone nanotube draped across two electrodes. The team then measured how much current flowed through the nanotube when a voltage applied to the material beneath it made the nanotube more conductive—the essence of a transistor.

But randomly scattered nanotubes can't be the scaffold for more-complex molecular-scale circuitry. So Dekker and Williams have turned to PNA, a molecule that, like DNA, is made up of a series of nucleotide bases (A's, T's, G's, and C's) that bind selectively to one another. The difference is that PNAs replace DNA's backbone of sugar and phosphate groups with more stable links

CREDITS: KEITH WILLIAMS AND CEES DEKKER/DELFT UNIVERSITY OF TECHNOLOGY

* 2002 Fall Meeting, 2 to 6 December.

based on peptides. That substitution enables PNAs to withstand higher temperatures and solvents often used to process nanotubes.

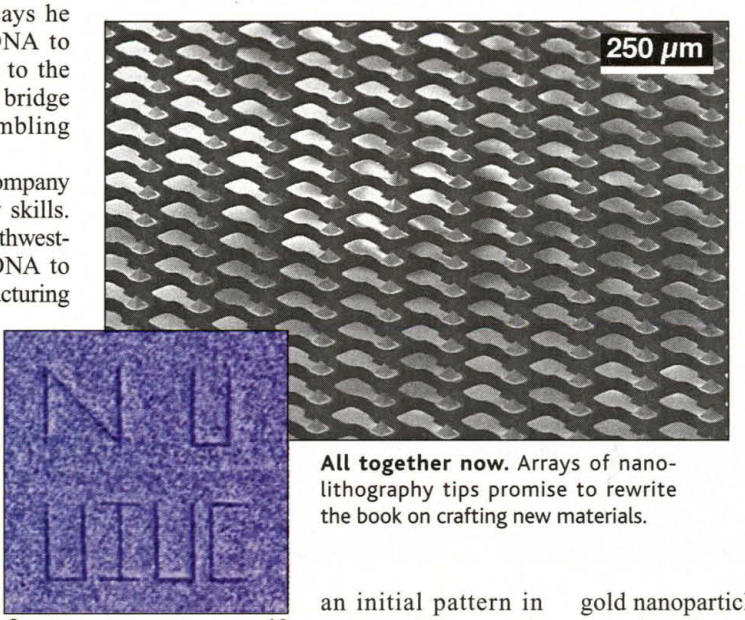
Williams started with bundles of nanotubes that he placed in a bath of nitric acid. The acid slowly ate away at the nanotubes, digesting them from the ends in toward the center. After a few hours, Williams removed the acid and was left with short tubes, each studded with carboxylic acid groups at both ends. These groups readily react with amide groups on the ends of the PNA molecules, making it possible for Williams to link PNAs to the tips of each nanotube. Williams then spiked the nanotube-PNA mixture with DNA strands harboring nucleotide sequences complementary to those in the PNAs and confirmed that the partners found their mates, a result published in this week's issue of *Nature*. Next, Williams says he plans to attach single-stranded DNA to electrodes. The DNA should bind to the PNAs and direct the nanotubes to bridge electrodes, the first step in assembling nanoscale circuitry.

The Delft group has plenty of company in turning to DNA for its assembly skills. Mirkin reported that his team at Northwestern is making progress on using DNA to make sensors and a new nanomanufacturing platform. In 1997, Mirkin's group showed that it could detect free-floating target DNA strands with complementary DNA linked to tiny gold nanoparticles. When the target strands bind to the gold-bound complementary strands, they pack the gold particles close together. That changes the color the particles reflect, creating a simple color-based detector for specific DNA sequences.

Mirkin's DNA detection scheme is already finding applications. At the meeting, James Storhoff, a chemist at Nanosphere—a Northbrook, Illinois–based start-up founded by Mirkin and his Northwestern colleague Robert Letsinger—reported that the company has turned it into a bench-top tool for rapid diagnoses of infectious diseases and detection of tiny genetic mutations called single-nucleotide polymorphisms. Storhoff says the diagnostic scheme can readily distinguish antibiotic-resistant bacteria, such as *Staphylococcus aureus*, from nonresistant strains, a development that could cut in half the time needed to alert doctors to the status of a patient's infection. Storhoff noted that the detection scheme is so sensitive that it can pick up DNA from a target bacterium without first amplifying the DNA by the now-standard polymerase chain reaction, a shortcut that could speed up detection rates even more. Eventually, the advances might enable doctors to diagnose infections in hours rather than waiting for days as samples are processed in a lab. It could also speed the detection of smallpox and other potential bioweapons and give emergency workers a leg up in containing an outbreak before it becomes widespread.

Biomechanics

Mirkin's group is also marrying DNA with tiny mechanical devices in hopes of revolutionizing nanomanufacturing. In 1999, the researchers reported developing a technique called dip pen nanolithography, in which they use the tip of an atomic-force microscope to write nanosized letters or other features on a surface (*Science*, 15 October 1999, p. 389). Later, they showed that by using a DNA-based "ink," they could write an initial pattern in DNA and then use it to bind complementary DNA sequences toting nanoparticles. The technique carried the promise of patterning materials at fantastic resolution. But it was painfully slow, because features had to be written out one by one.



All together now. Arrays of nanolithography tips promise to rewrite the book on crafting new materials.

No longer. At the Materials Research Society meeting, Mirkin reported that his team had constructed an array of 10,000 microscope tips, each capable of acting independently from the others. Team members reported that by using 10 tips in concert they can draw essentially any desired shape. "The goal is to use dip pen nanolithography to generate [DNA-based] templates on surfaces that guide the assembly of nanoscale building blocks," Mirkin says. "It opens the door to placing electronic particles right where you want them. We think it's ultimately going to be a production tool." What's more, Mirkin says there's still room to grow: "This is not going to stop at 10,000. We can make arrays of arrays."

Like Mirkin, MIT's Jacobson has linked gold nanoparticles to DNA and other biomolecules. His aim, though, is to disrupt the capabilities of biomolecules to recognize targets. Earlier this year, Jacobson's team reported that by guiding the nanoparticles with a simple radio-frequency (RF) transmitter, they can control whether DNA fragments exist as two separate single strands or as bound pairs. With the RF field turned on, the gold nanoparticles spin, heating the associated DNA enough to melt the bonds between complementary strands. Turn the RF field off, and the strands knit themselves back together. Although still in its early stages, the technique promises to provide researchers with an electronic switch that they can use to turn genes on and off.

At the Boston meeting, Jacobson announced that his team had extended its electrical control over biomolecules to proteins as well. The researchers started with an RNA-chopping protein called ribonuclease (RNAase), which they cut into two pieces: a large protein segment made up of 104 amino acids, and a small 18-amino-acid strand called the S-peptide. The RNA-chewing machine couldn't do its job unless the small strand sat in the mouth of the protein. Jacobson's team linked gold nanoparticles to the end of S-peptide strands and used the particles as a switch to turn the enzyme on and off. In the absence of an RF field, the nanoparticle-toting S-peptides adopt their usual conformation, allowing RNAase to do its job. But when the team switched on an external RF field, the field set the nanoparticles twirling, which prevented them from assembling with the larger protein.

Down the road, Jacobson says he hopes that electronically controlled proteins and DNAs will enable molecular biologists to cut and splice genetic information electronically and eventually program computers to engineer new organisms. "It's [the] early days," says Jacobson. "But we're trying to feel our way to see how complex systems we can build and to see if we can get biology to build these systems for us." Many other groups are starting to feel their way along as well. Where they succeed, expect the marriage of nanotech and biology to provide big payoffs.

–ROBERT F. SERVICE

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