One place DNA enzymes could not supplant ribozymes, however, is in gene therapy. A gene for a therapeutic ribozyme could be inserted into the body, which would then make the ribozyme continuously; a DNA enzyme, in contrast, has to be synthesized and given as a drug.

Santoro and Joyce published the 10-23 sequence in the April 1997 *Proceedings of the National Academy of Sciences*, putting RNA-cleaving DNA enzymes in the hands of any researchers who wanted to copy the catalytic sequence. Explains Breaker, "These would be the simplest enzymes anyone can make. Just send an e-mail to a company that makes DNA, and you can have it the next day."

In the last few months, researchers have reported promising test tube results with customized variants of the 10-23 DNA enzyme. Sun and colleagues, for example, designed a DNA enzyme to target the growth-stimulating gene *myc*, which effectively froze the growth of smooth muscle cells in a culture dish. And Kazunari Taira's group at the University of Tokyo and the National Institute of Advanced Interdisciplinary Research at Tsukuba Science City in Japan deployed a DNA enzyme against an abnormal gene message made in certain leukemic cells. The abnormal protein keeps the leukemic cells from self-destructing when normal cells do, leading to uncontrolled growth. The DNA enzyme destroyed the abnormal messenger RNA and triggered the self-destruct circuitry in the leukemic cells.

Khachigian's work with DNA enzymes is a first step toward the clinic. His group altered 10-23 so it would target the RNA from *Egr-1*, a wound-repair gene identified by Khachigian in Collins's lab at Harvard in 1996. *Egr-1* acts like a chief of disaster operations. Undetectable in healthy arteries, its protein appears on the scene within minutes of injury, recruits a crew of tissue repair factors, and disappears a few hours later. Because *Egr-1* acts early in wound repair, Khachigian thought it might be a strategic target. "It's a case of shooting the messenger," he says.

Six hours before ballooning and during the procedure, the researchers applied the DNA to the outer surface of a rat's carotid artery, relying on chemical carriers to ferry it into the smooth muscle cells in the vessel wall. After 2 weeks, the new layer of cells lining the artery was twice as thick in untreated rats as it was in rats that had been treated with the DNA enzyme. Next, Khachigian plans to try this approach in pigs and then, if all goes well, in human patients.

But DNA enzymes modeled on the RNA-cleaving 10-23 molecule are just the beginning. In laboratory evolution experiments like the one that spawned 10-23, catalytic DNA molecules sporting bizarre new structures have emerged, some with four strands rather than the usual one or two, others co-opting amino acids—the building blocks of proteins—for extra catalytic power. Over the last year, these modified DNA variants have proved able to catalyze a whole new array of reactions in the test tube—for example, cutting, rejoining, and chemically modifying DNA strands. And Breaker thinks new DNA enzymes as potentially powerful as 10-23 could target proteins as well as RNA and DNA. "We must now consider the possibility that other enzymes like 10-23 are out there, with even greater catalytic power, just waiting to be discovered."

Says Breaker, "My goal is to develop the therapeutic warheads of the future."

—ELIZABETH FINKEL

Elizabeth Finkel is a writer in Melbourne, Australia.

MEETING MATERIALS RESEARCH SOCIETY

Building the Small World Of the Future

BOSTON, MASSACHUSETTS—Nearly 4400 researchers gathered here from 29 November to 3 December to speed the way to future materials for everything from electronics to medicine. Highlights included new schemes for wiring molecular electronic devices and genetically engineered proteins that assemble materials.

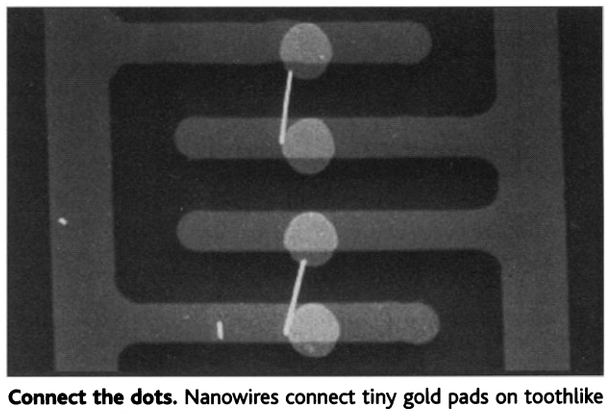
Wiring Up the Nanoworld

In computer technology, if not in space flight, smaller almost always means faster, cheaper, and better. But researchers at the frontiers of miniaturization, who are fashioning experimental switches and storage devices from single molecules, have outrun their ability to wire these devices together into working systems. At the MRS meeting, scientists described several schemes—including one that uses DNA and another involving electric fields—that could help them link molecular circuitry with nanoscale wires. Although no working molecular devices have been rigged up yet, experts say the approaches could help make dreams of molecular electronics a reality.

"This was really nice work," says Zhenan Bao, an advanced electronics specialist at Lucent Technologies' Bell Laboratories in Murray Hill, New Jersey. "It's the future direction the field [of molecular electronics] will take."

On today's computer chips, the smallest features are 250 billionths of a meter, or nanometers, across. Although that's vanishingly small, the devices can still be made and wired up with photolithography, the industry's workhorse patterning technology, which shines light through stencils to direct the etching of fine features on silicon chips. Molecular-scale devices, however, can measure just a few nanometers in some dimensions, and light simply can't be focused tightly enough to lay out the patterns for the fine wiring needed to connect them. Researchers have to take another tack, such as first making the minuscule wires, and then positioning and connecting them. But although they can already make sufficiently small wires—one technique condenses metal atoms in the pores of membranes to form tiny metal rods—achieving the connections is another matter.

Working with nanorods that have platinum shafts and gold tips, a team of researchers at Pennsylvania State University in University Park led by electrical engineers Theresa Mayer and Thomas Jackson, along with chemists Thomas Mallouk and Michael Natan, has now come up with two speedy ways to solve this problem. One as-



Connect the dots. Nanowires connect tiny gold pads on toothlike electrodes, 25 micrometers long from base to tip.

CREDIT: T. MAYER/PENNSYLVANIA STATE UNIVERSITY

sembly strategy exploits the ability of DNA strands to seek out and bind to strands with matching sequences. The researchers first used small organic molecules called thiols to link single-stranded DNA to the rods' gold tips. Next, they decorated a separate gold surface with single-stranded DNA whose sequences were complementary to those attached to the rods. When the team mixed the rods with a solution containing the DNA-coated gold, the complementary strands bound to one another, linking the rods to the gold surface.

In a second strategy for assembling nanorods, the Penn State team turned to electrical attraction. Here they were linking a pair of electrodes resembling combs, positioned so their teeth interlaced. The researchers insulated these electrodes with a layer of silicon dioxide and placed a tiny gold pad halfway down each tooth, so that the pads on the adjacent teeth lined up in a row. They then immersed the apparatus in a solution containing their tiny metal rods and applied a voltage between the electrodes.

The voltage created an electric field that triggered two very different electrical effects to first attract and then bind the metal nanorods between adjacent gold pads. Initially, the field created a long-range electrical attraction that reeled in the nanorods from afar. The rods then bridged adjacent gold pads, as the full electrode assembly tried to maximize its capacitance, or its ability to store charge. Capacitors store charge as an electric field between two separated conductors harboring opposite charges. In this case, the overall electrode assembly contained two types of capacitors: The first consisted of the large electrodes and the gold pads separated by the insulating silicon dioxide, and the second of adjacent gold pads, separated by the solution.

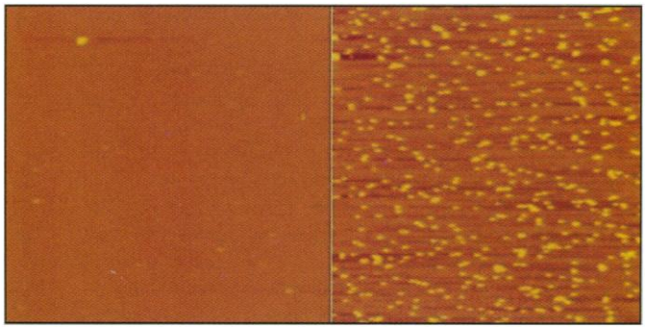
The small size of the gold pads limited the capacitance of the overall device, which can only store as much charge as its smallest capacitors. But nanowiring lifted this restriction. By linking the gold pads, the nanowires opened a continuous electrical connection between the pads. That disrupted their ability to store charge, allowing the larger capacitors to take over. The bottom line, says Mayer, is that "we can use the field to drive the wires where we want them to be."

That's not all. When the rods were shorter than the gap between the gold pads, the system's tendency to maximize capacitance caused several rods to line up end to end to form a bridge. The researchers then "welded" these rods into continuous wires by enriching the solution with gold ions. The ions filled in the gaps, producing longer rods that could conduct current, as the researchers confirmed.

"It's still somewhat unclear" how these techniques could be adapted for building molecular computers, says Mayer. "These are just baby steps," adds Jackson. But it's the first steps that are the hardest to take.

Protein Patterns for Electronic Devices?

Biological organisms aren't just master builders of soft and squishy organic materials. They also do a pretty decent job of assembling rocklike inorganics—witness the strength of the everyday clam shell or your own bones and teeth. Of course, the secret behind such synthetic feats is the soft, squishy proteins that both clams and people have evolved to help organize inorganic molecules into intricate and useful patterns. Now materials researchers are trying to use the same trick as well.



Spot of gold. The bright dots (right) consist of gold drawn from solution to a surface by a modified bacterial protein.

CREDIT: M. SARIKAYA

At the Boston meeting two independent research teams, one led by materials scientist Mehmet Sarikaya of the University of Washington, Seattle, and the other by Angela Belcher, a chemist at the University of Texas, Austin, reported that they had used a laboratory version of evolution to create genetically engineered proteins that could bind to tiny semiconductor and metal particles and assemble them into larger clusters. If the same protein-engineering techniques can generate molecules capable of organizing and patterning a wide variety of materials, proteins could become invaluable tools for crafting transistors, wires, and other electronic devices with components hundreds of times smaller than those on current computer chips.

"The whole idea of merging biology with materials synthesis is very important," says Chad Mirkin, a materials researcher at Northwestern University in Evanston, Illinois. "Organic systems have molecular recognition abilities that have had a long time to evolve. [They] far surpass what we can do readily in the lab."

Both Sarikaya and Belcher hoped to exploit the abilities that the proteins critical to forming bones, shell, and teeth display: They have the selectivity to bind only certain inorganics, seeding and organizing their growth into desired patterns. Abalone, for example, use separate proteins to organize calcium carbonate into different mineral phases: iridescent mother-of-pearl, or aragonite, for the shell's inner layers and rock-hard calcite for the shell's outer surface. Such naturally occurring proteins don't work well with many industrially important materials such as metals and semiconductors, however. So the Washington and Texas researchers decided to see if they could improve matters.

For their part, Sarikaya and his Washington colleagues set out to coax bacterial proteins into binding to gold, which is used widely in the electronics industry. They started with multiporin, a cell membrane protein from the bacterium *Escherichia coli* that does not bind gold in its natural form. They then cloned the multiporin gene to make millions of copies. From each copy, they snipped out a section coding for a segment of the protein that forms a loop projecting from the *E. coli* membrane. That's where the protein would bind gold if its chemical makeup allowed it to do so.

To alter the makeup of the loop, the researchers replaced the snipped-out gene segment with random DNA sequences produced by an automated DNA synthesizer. They then introduced the mutated genes back into bacteria, grew the bacteria, exposed them to gold particles, and—in a set of steps analogous to natural selection—they washed off poor binders and regrew the better ones, eventually identifying the colony that did the best job of binding gold. Finally, they purified multiporin from these bacteria and attached the protein to the outer surface of both tiny plastic spheres and flat surfaces in solution. When they then spiked their mixture with a small amount of gold, the protein picked up the flecks, decorating either the outside of the spheres or dotting the surface.

Belcher's group, meanwhile, took a different approach to evolving proteins that could bind to semiconductors, such as zinc selenide and gallium arsenide, which are also widely used in electronics. The team used an off-the-shelf kit containing 10^9 random DNA sequences, which they inserted into copies of a gene that codes for the outer coat of a bacterial virus called a phage. They then infected bacteria with the modified phages, allowed the phages to multiply, and exposed the viruses to a solution containing semiconductor particles to select the viruses best able to

bind the semiconductor.

Thus far, Belcher reported, the technique has worked beautifully. Her team has identified proteins that can discriminate between similar semiconductor alloys, such as gallium-arsenide versus aluminum-gallium-arsenide, and can even discriminate between different faces of the same semiconductor crystal, which have different arrangements of the atoms on the crystal surface. Down the road, she says, her team is planning to pattern the semiconductor-binding proteins on surfaces and use them to nucleate the growth of tiny semiconductor crystals in controlled arrangements. That's just what researchers around the globe are trying to do, in an effort to create ultrasmall transistors and other computing devices. And if Belcher and Sarikaya have their way, proteins may be just the handle they need to get there.

–ROBERT F. SERVICE

TAIWAN

Science Staggers Along After Deadly Earthquake

Chung Hsing University sustained heavy damage in the 21 September earthquake that left 100,000 homeless and caused massive disruptions to Taiwan's economy

TAICHUNG, TAIWAN—Working in the Food Science Building at Taiwan's National Chung Hsing University here is not for the faint of heart. The cracks and spalls in the building's concrete beams and columns are a constant reminder of the devastating earthquake that struck on 21 September, claiming 2300 lives and leaving more than 100,000 homeless. The toll included two students at Chung Hsing, one of Taiwan's major research universities. But 3 months later science goes on, as researchers and grad students step around scaffolds and reach over braces as they struggle to make up for the deadly interruption. "I don't feel safe," says grad student Lai Li-An. But with her master's thesis due this spring, she says, "we have to keep working."

Chung Hsing has so far received from the government only about one-fourth of the estimated $12.5 million needed for emergency repairs, and its request for another $34 million to replace the most heavily damaged buildings is pending. And it is far from the only supplicant. The quake wreaked havoc on educational facilities of all types, and drove students and faculty at National Chi Nan University, a small, relatively new university in Nantou, into borrowed classrooms in Taipei. The Ministry of Education estimates that it will cost $800 million to replace and repair more than 800 school buildings throughout the damaged area.

The toll on university equipment and instruments has not even been calculated. Some things may be impossible to replace, such as biological culture collections. Yet it could have been worse. The campus, 40 kilometers from the epicenter, was spared the full brunt of the magnitude 7.6 earthquake that struck near the central mountain town of Puli, 160 kilometers south of Taipei. More than 50,000 structures in the region were destroyed, and downed power lines led to outages and rationing that lasted for several weeks. Total economic losses have been estimated at $9 billion, or about 3.3% of gross domestic product.

At Chung Hsing, the 30-year-old Food Science Building and the library, now closed for repairs, sustained the most damage. But most buildings "performed as expected," says Lin Chi-Chang, chair of the Department of Civil Engineering, despite the fact that the lateral seismic loads imposed on the buildings were much greater than they were designed to withstand. The cracks that run through interior walls in many buildings, he adds, do not threaten their structural integrity.

Equipment is another matter, however. The quake destroyed the magnet in the chemistry department's prized 400-megahertz nuclear magnetic resonance (NMR) spectrometer, and the department doesn't have the $100,000 it would cost to buy a replacement. Instead, researchers are using older NMRs, which are less powerful and therefore slower. "People are having to wait for machine time," says department chair Gau Han-Mou. A key component in a high-performance liquid chromatograph was also knocked out of kilter in the quake and sent off for repairs. "We keep calling, but they haven't yet figured out what's wrong," says Gau, who was using it to study the chirality, or handedness, of molecules. That work has been suspended until the instrument can be fixed.

Settling down. Chung Hsing's Tseng Yi-Hsiung, left, and Chen Liang-Jwu have learned to live with the cracks in the Life Sciences Building.

CREDIT: D. NORMILE

The Institute of Molecular Biology's entire collection of culture samples was lost when a weeklong power outage shut down freezers. "We had emergency generators, but they were thrown off their supports in the earthquake," says Tseng Yi-Hsiung, an institute professor. The lost samples represent years of efforts to identify and isolate agriculturally important strains of bacteria and enzymes. "I can't even estimate the loss," Tseng says. Fortunately, his own work on a bacterium that damages vegetable crops has continued thanks to samples from other labs.

Officials have also tried to ease the pain of those who suffered the greatest losses. The parents of one of the fallen students, a popular senior in the horticulture department, added their own funds to a collection taken up for their daughter and gave it back to the school for repairs. But university officials instead have combined it with other contributions and created a scholarship fund for students from families that lost a breadwinner in the earthquake.

Some of those survivors say it has been hard to return to work. "The experts are more optimistic than we are," says Tseng. Nights are particularly bad. "People used to work here until very late," Tseng says. "Now we're all afraid to be in the building after dark." For a long time, however, going home wasn't much comfort, either. Tsen Hau-Yang, a professor of food science, says that he and his family worried for weeks about the safety of their two-story house. "So I slept in my car for the first month after the quake," he says.

Although Tsen is back to sleeping in his bed, many faculty members expect repercussions from the quake for years. Tseng is particularly worried that the uncertain state of repairs will drive away top-quality applicants to the university and its graduate schools. "That could be the most serious problem of all," he says.

–DENNIS NORMILE