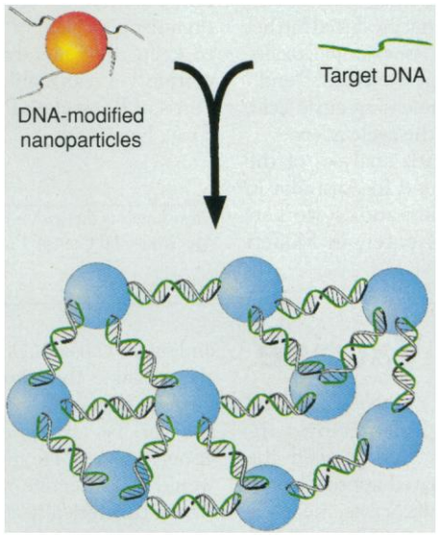
MATERIALS SCIENCE

DNA Ventures into the World Of Designer Materials

Organic molecules have an unparalleled ability to seek out and latch onto particular partners. Just witness antibodies' proficiency at homing in on precise molecular targets. Inorganic materials, meanwhile, have their own fortes, such as strength and electrical conductivity. Over the past year, chemists in the United States and Ireland have taken initial steps at forging a new link between these two chemical families by creating designer materials in which DNA and other organic molecules help connect tiny inorganic particles to create exquisitely organized structures with surprising new properties.

Now, on page 1078, researchers at Northwestern University in Evanston, Illinois, present the first large-scale device embodying this strategy: a sensor, made from a web of DNA and gold particles, that changes color when it detects a precise strand of DNA. The sensor showcases the talents of both components: DNA's ability to recognize and bind matching sequences stitches the web together, while the electronic properties of the inorganic gold are responsible for the color shift. This easy-to-read color change could lead to simple and cheap detectors of pathogens for use everywhere from doctors' offices to the battlefield, says Northwestern University chemist Chad Mirkin, who along with colleague Robert Letsinger led the research project. "It's really marvelous," says Paul Alivisatos, a University of California, Berkeley, chemist. Alivisatos is co-leading a related effort in this field with colleague Peter Schultz.

Moreover, Alivisatos, Mirkin, and others say this approach is destined to yield more than just sensors: The new work represents an early step in transferring DNA from the biological to the material world. Researchers have long exploited electrical interactions and other mechanisms to help them guide nanoparticles into forming structures, says Christopher Murray, a chemist at IBM's T.J. Watson Research Center in Yorktown Heights, New York. But such interactions are not selective, and therefore cannot place individual particles exactly where they're wanted. The highly specific interactions of DNA and other organic molecules, however, makes combining them with nanoparticles "a good approach to controlling the architecture of materials," says Murray. Already several teams are racing to use that specificity to organize metal and semiconductor nanocrystals into ultra-small electronic devices that essentially assemble and repair themselves in solution.



R.C. MUCIC, J.J. STORHOFF/NORTHWESTERN UNIVERSITY

Hybrid web. DNA strands on nanoparticles seek out target DNA, forming a network.

"It's a very exciting time right now," says Donald Fitzmaurice, a chemist at University College Dublin in Ireland who is leading one of these hybrid efforts. "There's been a huge amount of activity in the last few months in this area." Ed Chandross, a chemist at Lucent Technologies' Bell Labs in Murray Hill, New Jersey, agrees. "It's an area with a tremendous amount of promise. People are making structures that could not readily be made before." But he and others acknowledge that the research has a long way to go before such complex structures can be made with ease.

The Northwestern researchers started simple, building their DNA sensors from three different fragments of single-stranded DNA and a slew of tiny gold particles just 13 or so nanometers in diameter. One set of DNA strands acts as the "target" strand—the sequence that the sensor is designed to detect. The other two are probe strands, each of which has a sequence complementary to half of the sequence of the target.

The researchers glued the probe strands to the gold nanoparticles. They attached sulfur containing organic groups called thiols onto one end of their probe strands. Next, they added the gold particles to two separate reaction baths, each containing one of the families of DNA probe strands. Sulfur's affinity for gold then caused the DNA probes to bind to the particles, resulting in fuzzy gold nanoparticles coated with dozens of DNA strands each.

To create the sensor, the researchers then combined the two sets of DNA-coated particles into a single bath. They tested it by mixing in the target DNA. The result: the first probe linked to half of the target DNA strand, and the second probe linked to the other half, causing the target strand to bridge the two probes. Repeated millions of times, the process glued the nanoparticles together in a three-dimensional web.

The formation of this web changes the electronic behavior of the particles. When the particles are separate, the electrons in any one particle are more or less free to move independently. But as the particles approach one another, electrons spontaneously moving around one particle induce movements in the electrons of neighboring particles. This choreographed movement influences which wavelengths of light the material absorbs. As a result, the formation of the network prompts a color change, which is the key to the network's sensor application. Unlinked, the probe-coated nanoparticles appear red in color when dried on a special glass plate. When the "right" target links the coated particles into a web, the dried spot turns blue. Because the probe sequences can be tailor-made, the sensor can be designed to detect any DNA sequence.

Mirkin believes that since such a DNA detection system is easy to read—just look for the color change—and cheap to make, it could serve as a rapid screen for pathogens, which could prove useful for everyone from doctors quickly testing patients for infections at the bedside to soldiers scanning for biological warfare agents on the battlefield, where current lab-based diagnostics cannot be used. However, he acknowledges that the sensitivity of the current sensors is only "moderate." Making the color change visible to the naked eye requires millions of copies of the target DNA, so it may not show up if the target DNA is present in minute quantities.

Equally important, Mirkin and others say, the nanoparticle sensor is a proof-of-principle for a strategy to make nanoparticles arrange themselves into tiny devices. In the 15 August 1996 issue of *Nature*, where the Northwestern team first laid out its strategy for festooning nanoparticles with dozens of DNA strands, Alivisatos, Schultz, and their Berkeley colleagues reported linking single DNA strands to particles. The strands assembled the particles into nanoparticle "molecules" containing two or three nanoparticles each. And now, says Alivisatos, the research-

ers are working to use the DNA to precisely order a series of nanoparticles into a wire.

Fitzmaurice and his Dublin colleagues, meanwhile, have already made progress towards a similar goal, using semiconducting titanium dioxide particles linked to a modified RNA building block called uracil, which is in turn linked to an electron-hungry group known as viologen. In a February 1997 paper published in *Chemistry, A European Journal*, Fitzmaurice and his team described preparing titanium dioxide particles so that they automatically bind to the uracil-viologen combo in solution, forming an organic-inorganic molecule. Exposing the particles to light boosted the conductance of electrons in the particles, which then jumped to the viologens.

That electron flow, says Fitzmaurice, demonstrates that it may be possible to coax these particle-biomolecule hybrids into assembling themselves into ultra-small electronic circuits. Such circuits would be many times smaller than those housed by the millions on semiconductor chips, which are reaching a practical limit of miniaturization. If bioparticle-based circuits do prove possible, this lab-grown marriage between organic molecules and inorganic nanoparticles could prove to be a happy one indeed.

–Robert F. Service

NEUROBIOLOGY

NGF Signals Ride a Trolley to Nucleus

Neurons have a special communication problem: The length of a nerve cell, from the tip of its axon to its main cell body, can be many centimeters or even a meter—"an amazing distance" for a molecular signal to travel, says Johns Hopkins neuroscientist David Ginty. Yet that's the distance that nerve growth factor (NGF), a nurturing elixir that bathes the axon tips of some neurons, must send its signal to regulate genes in the nucleus. New work by Ginty and his colleagues suggests that NGF delivers its long-range message by boarding a subcellular trolley that shuttles it to the cell body.

Researchers have known for decades that NGF is swallowed up and packaged in vesicles that travel up the axon, and that this "retrograde transport" is important for NGF signaling. But no one knew just what role it played. On page 1097, however, Ginty's team shows that the transport system is apparently necessary for NGF to activate CREB, a protein that regulates the genes that respond to NGF.

"It is a really elegant set of experiments," says neuroscientist Story Landis, of the National Institute of Neurological Disorders and Stroke. "The big hole in the NGF field has been what is the nature of the signal. This makes it clear that NGF itself has to be transported retrogradely to get the response." The finding could have medical significance, notes neurologist William Mobley of the University of California, San Francisco (UCSF). His group recently showed that mice with Down syndrome have a failure in retrograde transport. If that leads to defective NGF signaling, it might help explain the neuronal abnormalities of the syndrome.

Researchers have been intrigued with retrograde transport since its discovery in the 1970s, because neurons clearly need a specialized way to get signals from axon tip to cell body. In ordinary cells, when a protein binds to a receptor, its message is relayed by a short biochemical signaling cascade that traverses the cytoplasm from membrane to nucleus. That works fine in a round compact cell, but such a cascade, triggered in a neuron's axon tip, would be way out of striking range of the nucleus. Retrograde transport could help by shuttling NGF or other growth factors directly to the cell body, where they can trigger a signal cascade that would easily reach the nucleus.

To see if retrograde transport indeed works that way, Ginty's team cultured rat neurons in chambers that allow the neurons' cell bodies and axons to grow in different fluid environments, so that each could be exposed to particular treatments. To detect the effects those treatments had on TrkA, the main membrane receptor for NGF, and on CREB, they stained the neurons with antibodies that recognize only the active forms of the two molecules.

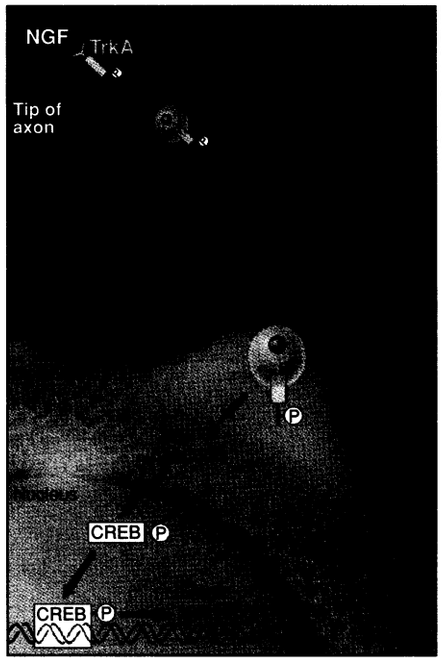


ILLUSTRATION: K. SUTLIFF

On track. NGF and TrkA may ride together in vesicles to the cell body to turn on genes.

The speed with which CREB was activated depended on where the researchers applied the NGF. When they put it on the cell bodies, they saw active TrkA and CREB in the cell bodies within 5 minutes. But NGF applied to the axon took 20 to 40 minutes, depending on the length of the axons, to produce active TrkA and CREB in the cell bodies. That, Ginty says, resembles the time it takes for NGF to travel up the axon, suggesting that its transport is needed for CREB activation.

To test that idea, they treated the axons with NGF bound to plastic beads, which allow the molecule to activate TrkA receptors but prevent it from being taken into the cells and transported. They saw activation of TrkA in the axons but no TrkA or CREB activity in the cell bodies—further evidence that transport and CREB activation are linked.

To confirm that activated TrkA must be in the cell body to trigger the events that turn on CREB, the team flooded the cell bodies with an inhibitor of TrkA activity. As expected, it prevented CREB activation by NGF added to the axons. That finding meshes with work by Bob Campenot's group at the University of Alberta in Edmonton and Rosalind Segal's at Harvard Medical School in Boston. Both found active TrkA in cell bodies after NGF was given to the tips of axons. (Campenot's results appear in the 26 July issue of the *Journal of Cell Biology*, and Segal's are in press at the *Journal of Neuroscience*.)

Ginty's explanation for the appearance of activated TrkA in the cell body is that it rides in from the axon with NGF. Although no one has directly shown TrkA to make that trip, Mobley's group at UCSF discovered that NGF-containing vesicles also contain TrkA. But Campenot sees a bit of TrkA activation in the cell body too soon after NGF exposure for retrograde transport to explain it. He thinks this fast signal travels by another method, perhaps a chain of TrkA molecules phosphorylating—and thereby activating—other TrkA molecules all the way up the axon. And both researchers may be right. "It may be that there is more than one signaling pathway," says Segal, a view held by others in the field.

Researchers can now investigate these possibilities by, for example, blocking the movement of vesicles up the axon, or by blocking the phosphorylation reaction that Campenot proposes. And so the answers to long-held questions about how signals span vast molecular distances may itself be just around the corner.

–Marcia Barinaga