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.

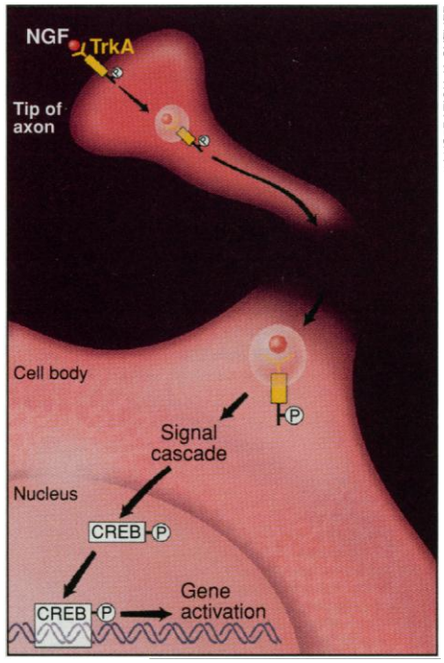

ILLUSTRATION: K. SUTLIFF

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