gling their way inside.

What's not yet known is whether the new dendrimer-bound catalysts are actually more efficient than their brethren. But Crooks says his team is looking into that now. If so, dendrimers could be in for a big future as tiny reaction chambers.

Single Electrons With a Chemical Sense

Single-electron transistors, which coax electrons to flow one at a time through nanometer-sized specks of material, could take electronic devices to extremes of tininess. Now, new work suggests that these devices could also find their way into ultrasmall, ultrasensitive chemical sensors.

At the meeting, a team led by chemist Dan Feldheim from North Carolina State University in Raleigh reported a new scheme in which the electrical current flowing through what amounts to a single-electron transistor (SET) varies depending on the chemical makeup in a solution surrounding the device, a phenomenon analogous to a nerve cell firing in response to specific neurotransmitters. By harnessing this ability to convert a tiny chemical signal into an electronic response, the new scheme could lead to a bevy of simple and sensitive chemical sensors, useful for detecting everything from chemical toxins to trace components in cells. "It's a very clever approach" to making chemical sensors, says Northwestern University chemist Chad Mirkin.

To make their sensors, the NC State team started with two electrodes, one a simple gold pad and the other the electrically conductive tip of a scanning tunneling microscope (STM). An STM maps the contours of conductive surfaces by nudging its tip up close and allowing electrons to leap across to the surface, in a flow that's proportional to the separation. Other researchers have shown that placing a metal or semiconductor nanocrystal between two electrodes can turn this setup into an SET.

Because electrons repel one another, only a limited number can reside on the tiny nanocrystal. As a result, additional electrons can hop from one electrode, the STM in this case, to the nanocrystal only as other electrons leave by jumping to the other electrode. As in a conventional transistor, a third "gate" electrode controls the tempo of the electron movements. Placed near the nanocrystal, the gate raises the electrical conductivity of the tiny island when it is charged, getting the electrons to hopscotch faster.

Feldheim and his colleagues wanted to see, he says, "if we could get that same [gating] effect chemically." Their idea was to coat gold nanocrystals with organic compounds that can alter their charge and thereby act like a gate electrode. In this case, the researchers coated gold nanocrystals with small ring-shaped molecules of an organic substance called galvinol. After attaching the coated nanocrystals to a gold electrode with the help of Velcro-like molecules called hexanethiols, they then dunked the assemblage in a water-based solution, maneuvered an STM tip close to the surface, and raised the solution's pH by adding a buffer. As the solution grew more basic, it pulled protons away from the galvinols, leaving the molecules negatively charged. This added charge makes it more difficult for an electron to hop onto the island and find its way to the gold electrode, creating a drop in the electrical current. The result, in short, was a SET-based pH sensor.

The NC State team's approach is still tied to a tabletop-sized STM, which restricts its possible applications. But the researchers are at work on a scheme to make arrays of tiny electrodes in pairs separated by just 5 nanometers or so, with a single nanocrystal perched between the paired electrodes. Because it's relatively easy to coat nanocrystals with a variety of compounds that are themselves sensitive to the presence of other chemicals, a single array could signal the presence of a range of molecules. Cells, which manage this type of sensitive chemical detection day in and day out, may be in for a little competition. **–ROBERT F. SERVICE**

CREDIT: J. THERIOT

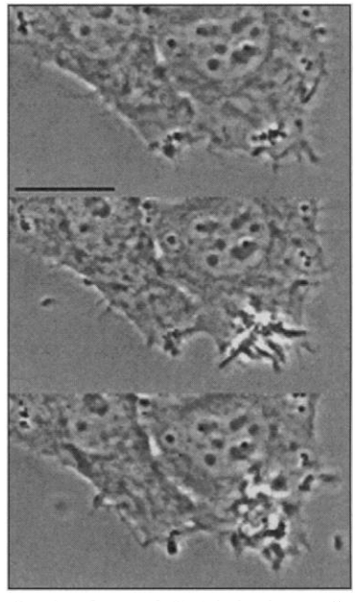
MEETING **AMERICAN SOCIETY FOR CELL BIOLOGY**

New Findings Point to an Abundance of Cellular Riches

SAN FRANCISCO—An air of optimism pervaded the annual meeting of the American Society for Cell Biology, held here last month. The $2 billion boost the National Institutes of Health budget got this year explained some of the good cheer. But the 8000 participants also found much excitement in the science, which ranged from new roles for the giant protein titin to the subtle tricks of the salmonella pathogen.

Bacteria Pull Cell Skeletons Out of the Closet

The ability of disease-causing bacteria to manipulate the cells they infect can make cell biologists drool with envy. Take the food-poisoning bacterium *Salmonella typhimurium*: When this pathogen encounters target cells, it stimulates a dramatic ruffling in the cellular membrane at the point of contact. The ruffled membrane then grabs the bacteria and pulls them inside. Biologists are now learning just how *S. typhimurium* tricks cells into aiding it.



Getting focused. SipA helps host cells form the bacteria-grabbing ruffles.

At the meeting, Daoguo Zhou, a postdoc in microbiologist Jorge Galán's lab at Yale University School of Medicine, reported that a bacterial protein called SipA appears to play a key role in this uptake. Injected into cells by the bacteria, it apparently binds to one of the main components of the cell's internal skeleton, a protein called actin. By modifying the properties of actin, SipA helps stabilize the fibers supporting the ruffles.

In addition to providing insight into how *S. typhimurium* coopts host cell molecules and causes disease, the result may lead to a better understanding of normal mammalian cell behavior. Actin rearrangements similar to those triggered by SipA also occur during the cell migrations needed for embryonic development and in cells responding to growth factors or becoming cancerous. The pathway that results in membrane ruffling "touches on almost every aspect of cell life," says Dafna Bar-Sagi, a cell biologist at the State University of New York, Stony Brook. Studies of bacterial mutants unable to stimulate events critical to ruffling could help scientists dissect the separate steps of the pathway and thus those of normal events.

The current finding is an outgrowth of a discovery made several years ago when researchers learned that many bacterial patho-

gens, including *S. typhimurium*, have a kind of molecular syringe that injects substances into target cells, stimulating them to take in the bacteria. To study this molecular subversion, the Galán group identified proteins that are delivered by the syringe. They then constructed *S. typhimurium* strains that lacked the genes for these proteins and probed how the mutations hamper the ability of the bacteria to infect cells.

One protein turned up by this screen, called SopE, is necessary for ruffling to occur. By forcing host cells to produce SopE or by injecting them with the protein, the Galán group showed that by itself SopE induces a rather weak and generalized ruffling of the whole cell membrane, rather than the strong ruffling seen at the sites of bacterial contact. Something else was apparently needed to localize the host cell reaction.

At the meeting, Zhou reported that SipA seems to fit the bill. Host cells in contact with bacterial mutants lacking SipA ruffled only loosely, even when all the other invasion genes were present. To find out how SipA works, the Yale team used genetic and biochemical techniques to look for proteins that SipA might team up with in the cell. The clues they gathered ultimately pointed to actin. Direct evidence that the two proteins interact came when the researchers mixed purified preparations of actin and SipA. When they centrifuged actin filaments, SipA ended up in the pellet too, indicating that the actin and SipA directly contact each other.

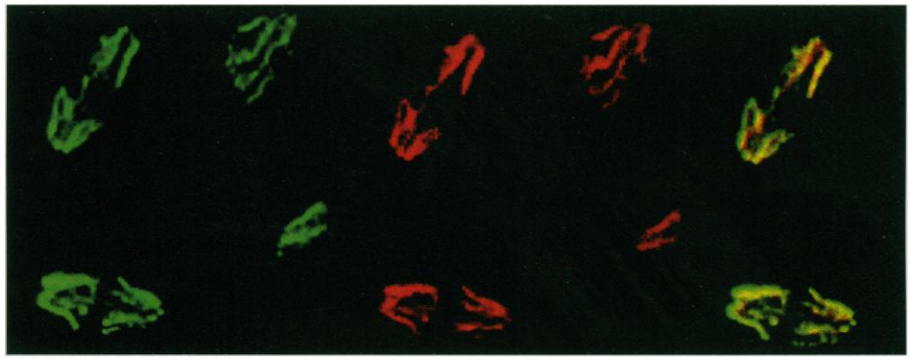
The team went on to probe exactly how SipA modifies actin behavior. Electron micrograph studies pointed to one difference. Actin filaments containing SipA appeared very straight instead of having the small kinks seen in actin strands without SipA. The researchers also found that SipA decreased the amount of actin required to form filaments and made the filaments more prone to form bundles with the help of another cell protein called T-fimbrin. Together, these findings suggest that SipA strengthens the actin filaments and that this fortifies the membrane protrusions, enabling them to stick out farther and envelop more bacteria.

As Julie Theriot, a cell biologist at Stanford University School of Medicine, describes the emerging picture, "SopE slaps the cell in the face and says, 'Wake up.' Then SipA takes the global response and physically focuses it, causing the cell to reach up to where the *Salmonella* are."

No one has yet found a eukaryotic counterpart of SipA, but experts say it's likely that at some point during evolution, a *Salmonella* predecessor captured a host protein and adopted it for its own purposes. "In the best case scenario, we'll find out that the same mechanisms *Salmonella* use to induce these activities will end up explaining what we see in other circumstances," says Bar-Sagi. If so, biologists' envy of bacteria will no doubt turn to gratitude. **–EVELYN STRAUSS**

An All-Purpose Protein Shock Absorber

These days, stretchy fabrics once fashionable only for runners, gymnasts, and speed skaters can be found in all kinds of clothing, even formal attire. A few threads of Lycra spandex fibers can help even the soberest outfits keep their shape. Now cell biologists are finding to their surprise that a giant stretchy protein called titin, which helps support the force-generating fibers in skeletal muscle, isn't limited to athletic duty either.



Unlikely liaison. The yellow color produced by merging micrographs of chromosomes stained for titin (green) with those stained for DNA (red) reveals that titin and DNA colocalize.

CREDIT: MACHADO *ET AL.*, *JOURNAL OF CELL BIOLOGY*, **141** (2), (1998)

At the meeting, Tom Keller of Florida State University in Tallahassee reported that his team found this accordion-like molecule in the structural fibers that help give human platelets their flexibility and in the smooth muscle of chicken gizzards. And in a much more surprising development, molecular biologist Cristina Machado from Johns Hopkins University in Baltimore described how she found titin in cell nuclei, where it may help the chromosomes shrink into compact structures prior to cell division.

"People have assumed that [titin] is just a muscle protein," says Ilia Ouspenski, a cell biologist at Baylor College of Medicine in Houston. Finding it in the nucleus, he adds, is "entirely unusual and new."

Early inklings of titin's versatility came in 1992 from Keller. While using electron microscopy to study another protein, myosin, in the smooth muscle cells of chick intestines, his team noticed that the cells contained micrometer-long threads, which looked like the giant protein. They later found the same protein in platelets and in the smooth muscle of chicken gizzard, and they have since been studying its function by labeling it with specific antibodies.

It's perhaps not surprising that titin is in smooth muscle cells and platelets, because all these cells undergo mechanical stresses that an elastic protein could help counteract. But Machado's findings were unexpected—even to her. Patients with the autoimmune disease scleroderma sometimes make antibodies that react to nuclear proteins, and to learn more about those proteins, Machado, a postdoc working with Deborah Andrew at Johns Hopkins, screened fruit fly embryonic tissue for proteins that react to those antibodies.

Once the team had a hit, they identified the protein by using the same antibody to search a "library" of bacteria expressing fruit fly genes. To their astonishment, the antibody picked up a protein whose gene proved to be the fruit fly equivalent of the *titin* gene. "I was looking for a chromosomal protein, and here I found a muscle gene," Machado recalls. (The results appeared in the 20 April *Journal of Cell Biology*.)

Since then, Machado has been studying fruit fly strains with mutations in the *titin* gene to get a better fix on what the protein does. As expected, the muscles of embryos with no titin at all "were all screwed up," and the embryos did not survive, Machado reported at the meeting. Fruit flies with milder mutations fared slightly better, but they had an unexpected handicap: Their DNA seemed to replicate poorly.

When Machado looked at larval brain cells that were preparing to divide, she saw that the chromosomes had not condensed, nor had they begun to pair off and line up properly. The few chromosomes that did pair up were three times more likely to separate prematurely than those in fruit flies with normal *titin*, she told the meeting participants. The researchers also saw chromosome breakage, an observation suggesting that in chromosomes, as in muscles and platelets, titin acts as a shock absorber that helps keep the structures intact. This may help explain, she says, how chromosomes can condense and expand 10,000-fold over the course of the cell cycle.

Because of titin's size—with a molecular weight of 3,000,000 it's the largest protein known—researchers are puzzled about

how it gets into the nucleus from the cytoplasm, where it is made. Nevertheless, "the data are absolutely compelling," Ouspenski says. "There can be no doubt that [the finding] is real." **–ELIZABETH PENNISI**

Homing In on a Sperm Receptor

From the U.S. president on down, it seems everyone is in a jam over sex. Sex causes problems for scientists, too, especially when it comes to understanding a key event: the union of mammalian eggs and sperm. But at the meeting, Nicole Sampson, a chemist at the State University of New York, Stony Brook, reported new findings that may help.

Although researchers have identified several sperm proteins that appear to bind to mammalian eggs, they have had less success at pinning down the receptors on the egg that grab onto those sperm molecules, mainly because eggs are scarce. Indirect evidence did suggest that an integrin, a type of protein known to be involved in cell-cell interactions, might be an egg receptor for sperm, but no one had detected physical contact between the integrin and any sperm proteins—until now, that is. Sampson and her colleagues have shown that the integrin binds to a small piece of sperm protein called fertilin already known to be critical for fertilization. (The results also appear in the January issue of *Chemistry and Biology*.) "This is the first evidence of direct binding [to fertilin]," says Paul Primakoff, a cell biologist at the University of California, Davis. The result might eventually lead to novel contraceptives that work by blocking fertilin binding to the integrin and perhaps also to a better understanding of human infertility.

Researchers had suspected that fertilin might attach to an integrin, because the sperm protein's amino acid sequence identified it as a member of a group of known integrin-binding proteins called disintegrins. Several teams had also found that peptides that correspond to fertilin's integrin-binding region bind to the egg membrane and inhibit sperm-egg fusion—presumably by blocking the sperm protein's attachment site. Antibody and other indirect evidence suggested that an integrin called α-6/β-1 might form that site, but Sampson and her colleagues decided to look directly for the receptor, using the putative integrin-binding domain of fertilin as bait. By narrowing their search to integrins, they exploited the limited number of available eggs to good advantage—and got very lucky.

To find possible fertilin-binding partners on the egg, the researchers synthesized a radiolabeled peptide containing 13 amino acids from the putative integrin-binding region of fertilin plus an amino acid that would attach to any nearby proteins in response to a flash of light. When they then incubated this peptide with mouse eggs and zapped the mixture with light, the researchers found that the peptide had attached to just one protein, which proved to be α-6/β-1 integrin. "The most remarkable thing to us was the specificity of labeling," says Sampson.

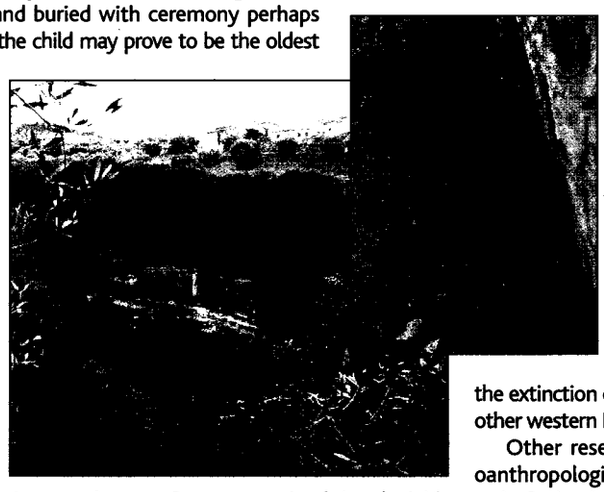
Even if further research proves that the egg integrin is a sperm receptor, the finding will not entirely explain the sperm-egg binding process. "While this interaction is important, there are likely to be other sperm and egg molecules that complement it," says Janice Evans, a reproductive cell biologist at the Johns Hopkins University School of Public Health in Baltimore. Still, the peptide the Sampson group used to fish out the α-6/β-1 integrin does inhibit in vitro fertilization, suggesting that the egg integrin could provide a new target for birth control. That could prove tricky, however, because the integrin is also on other cell types, posing challenges in drug delivery and raising the possibility of side effects.

Nevertheless, the finding is a sign that researchers are making headway in solving the puzzles of mammalian sex—at the molecular level, at least. "We didn't know the molecules on sperm and egg that were involved in [membrane] interactions just a few years ago," says Richard Schultz, a developmental biologist at the University of Pennsylvania, Philadelphia. "There's been a quantum leap in our understanding since then." **–E.S.**

Ancient Child Burial Uncovered in Portugal

In a rock-shelter in rural Portugal, archaeologists last month made a rare find: the complete skeleton of a young child of our own lineage, whose body was covered in red ochre and buried with ceremony perhaps 28,000 years ago. Researchers say the child may prove to be the oldest well-preserved early modern human on the Iberian peninsula. And in addition to the bones themselves, the burial may provide cultural clues to a pivotal era, when the last of the Neandertals co-existed with modern humans in southern Iberia.

Although the skull was shattered, the lower jawbone, complete with teeth, is almost intact, and the protruding chin clearly marks the child as an anatomically modern human, says Joao Zilhao of the University of Lisbon, Portugal's director of antiquities and leader of the excavation team. The find was made in early December when two of Zilhao's assistants were inspecting rock art in a valley about 140 kilometers north of Lisbon and spotted sediments containing charcoal and stone tools. Further probing yielded human arm bones and eventually a complete skeleton.



Ancestral grave. Portuguese site (*above*) yields Iberia's earliest known human (*above right*).

The body had apparently been wrapped in a blanket or animal skin drenched in red ochre, a practice thought to be related to ochre's resemblance to dried blood. A pierced marine shell, probably a pendant, lay near the throat, and animal bones were near the head and feet. Such features are typical of early modern human burials in central and eastern Europe, says Zilhao; the child's skeleton shows that early humans maintained common cultural practices over a vast area.

The bones were 2.5 meters below stone tools dated to about 21,000 years ago, suggesting that the bones could be as old as 28,000 years. If so, "it is really one of the first modern humans [in the region]—the ones that caused the extinction of the Neandertals," says Zilhao. Only two other western European burials are so old.

Other researchers are excited by the news. Paleoanthropologist Erik Trinkaus of Washington University in St. Louis rushed to Portugal this week to examine the bones. If the ages hold up, the find will be highly significant, says anthropologist Chris Stringer of the Natural History Museum in London. "We have very little material [from] this critical period" in Iberia, he says.

–CONSTANCE HOLDEN

CREDITS: J. ZILHAO