working, and be in the business of counting neutrinos, which we clearly are not going to be able to do until April."

Nor has AMANDA's ice-bound strategy been immune to problems. All of the 20 photomultiplier tube modules on the first string were working and recording the detection of Cherenkov radiation when the string was lowered into the hole in December. Three days later, the hole had successfully frozen around the equipment. But one photomultiplier tube broke and was lost for good while one more, said Bob Morse, a University of Wisconsin physicist who had just returned from the Antarctic, "was coaxed to come alive" and another was still doubtful.

Once the physicists have multiple strings in place, they will be able to start looking in the slowly accumulating data for evidence of point sources of neutrinos, perhaps from astrophysical sources. They're expecting discoveries to be hard to come by, however. When physicists started writing papers on neutrino observatories two decades ago, says Holtzen, they assumed that to observe enough neutrinos to detect anything of interest they would need a detector at least 10 times the size of DUMAND if not 100 times larger. "Unless we get lucky," says Holtzen, "these [first] detectors are too small."

What he and his colleagues hope to show with the first round of detectors is that they can distinguish neutrinos from the various background sources and record the directions from which the particles came. If the first detectors provide this proof-of-principle for neutrino astronomy, he says, "it's no big deal to build one 10 or 100 times bigger for on the order of $50 million, which is something the world should be able to afford."

If the world decides it can indeed afford such a detector, physicists will then turn their attention to potential neutrino sources such as AGNs. Astrophysicists believe that at the heart of these objects are massive black holes. Because of neutrinos' ability to pass through matter, says Salamon, detecting neutrinos from AGNs "is probably the only way to get direct information about what's happening at the very central engine of these objects. We're talking about getting practically to the edge of the black hole itself." Researchers are also interested in identifying neutrinos from binary pulsars and from the center of the galaxy, which might also be home to a massive black hole.

The bottom line, however, says Learned, is that "we're groping into terra incognito. We really don't know what the hell we're going to see." Or how hard it will really be to see it.

–Gary Taubes

Additional Reading

Learned, J.G. "Neutrino Astronomy with Large Cherenkov Detectors," *Annals of the New York Academy of Sciences* **647**, Dec. (1991).

Cell Biologists Get the Message in New Orleans

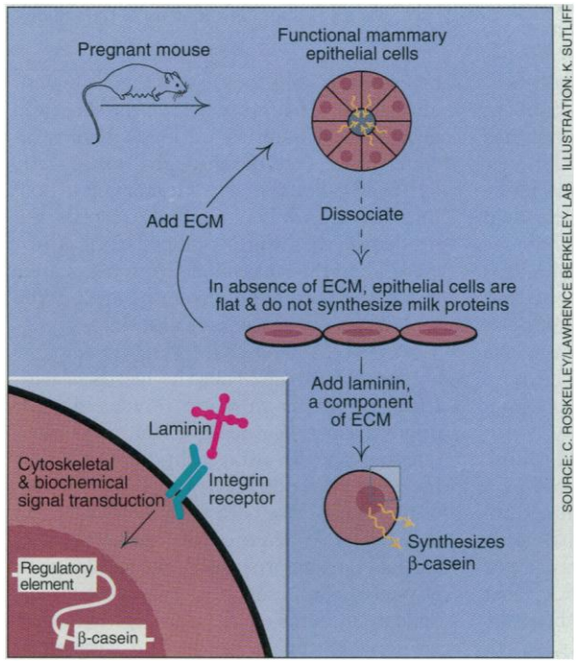
New Orleans–The 33rd Annual Meeting of the American Society for Cell Biology (ASCB), held here from 11 to 15 December, began on a triumphant note: In his opening address, Harold Varmus, the new director of the National Institutes of Health, proclaimed "that the scientific rabble [the bench scientists] has politely taken over the director's office." And he made clear, in what was his first policy speech since taking office, that he intended to fight for recognition for basic research. That message went down well with his ASCB audience–all keen supporters of basic research, as the samplings of the meeting below attest.

Matrix Work Wins Acclaim

Back in the premolecular days of cell biology, textbook writers assigned an unglamorous role to the extracellular matrix (ECM), the messy mix of giant fibrous proteins and globular glycoproteins that surrounds the cells. According to that early type-casting, the cells did all the interesting work, determining, for example, what shape an organ—or an animal—would take. The ECM merely provided an inert scaffold upon which the cells could grow. More recently, a small band of cell biologists has shown that the ECM, far from being a bit player, actually performs a dynamic role in dictating a tissue's shape and function.

One prime shaker in the up-and-coming new science of the ECM has been Mina Bissell of the Lawrence Berkeley Laboratory (LBL) in California. And at the ASCB meeting, Bissell described her group's recent results, which help explain just how the ECM exerts its effects on cells. The LBL workers have directly demonstrated that the ECM can trip switches deep within the nucleus and spur the genes themselves into action. "It's really exciting," says Donald Ingber of Harvard Medical School, who's also studying the ECM. "[Bissell] has brought regulation of gene transcription into the realm of the ECM."

Bissell's research is grounded in a decades-old observation that specialized cells grown in lab culture in the absence of ECM molecules beget throwbacks. For example, mammary gland epithelial cells from a pregnant mouse growing in an ECM-free brew yield uncharacteristically flat cells that do not produce milk. Add ECM molecules, and the cells differentiate again, becoming plump and well-rounded and organizing themselves into sacs of cells that secrete milk into their interior and bear a remarkable resemblance to the milk-secreting alveoli of the breast. And researchers have evidence that the ECM is equally as important to cell growth and differentiation in living animals.



Outside in. Laminin, an extracellular matrix protein, activates gene regulatory elements.

But although it's become clear that the ECM is vitally important for cells to function, until recently researchers had little inkling of the ECM's modus operandi. And that's where the LBL group's recent work comes in.

ECM proteins such as fibronectin and laminin provide structural support for cells by interlocking with cell surface receptors called integrins. What Bissell and her colleagues have now shown is that when these proteins bind to the integrin receptors, they also activate specific regulatory elements in the nucleus and in so doing incite gene activity.

The LBL group did this by attaching a bacterial "reporter" gene to a regulatory sequence needed to turn on the gene for the milk protein β-casein. After inserting this hybrid gene into cultured

mouse mammary epithelial cells, they measured the reporter gene's activity in the presence and absence of laminin. The result: Laminin increased the gene activity by a massive 50-fold. Antibodies that plugged the integrin receptors blocked laminin's stimulating effect, showing, Bissell says, that laminin binding to an integrin receptor has a direct impact on what's happening in the cell nucleus.

Now, the researchers are trying to work out just how the giant ECM molecules trip switches in the nucleus. And that, according to Harvard's Björn Olsen, "is when it gets really exciting." At an ASCB symposium chaired by David Cheresh of Scripps Research Institute, ECM experts presented data demonstrating that ECM molecules operate much like conventional soluble growth factors, binding to their integrin receptors to trigger a cascade of biochemical reactions in the cell interior.

But Ingber has evidence for a far more radical means by which ECM molecules could affect a cell's growth. It turns out that chemical signals triggered by ECM binding to integrins are necessary, but not sufficient, for cell growth—the cells must be stretched as well. Ingber has also shown that the integrins, which straddle the cell membrane, can transfer mechanical forces to the cytoskeleton, a network of tiny protein fibers that extends from the membrane to the nucleus. Ingber suggests that the binding of ECM molecules to the integrin receptors may trigger gene transcription by exerting an actual mechanical force on the cytoskeleton and the nucleus. This model "provides a molecular basis for integrating chemical and mechanical signals at the cell surface," he says.

Bissell likes Ingber's hypothesis not least because it's compatible with her own working model. Perhaps "the ECM tickles the receptor," she says. "That tickles the cytoskeleton, and that tickles the nuclear matrix." And it's exactly that type of thinking that won Bissell the 1993 ASCB's Women in Cell Biology Senior Award.

Smoke in Hamster Oviducts

The cigarette has long been a prime suspect as a cause of ectopic pregnancies—a life-threatening condition in which a fetus implants outside the uterus, usually in the narrow confines of the oviduct, which it can rupture. Now a team led by reproductive biologist Prue Talbot of the University of California, Riverside, may have found the smoking gun that will strengthen the case against cigarettes. Their work suggests that cigarette smoke increases the chances of an embryo implanting in the oviduct by paralyzing the oviduct cilia—just as it paralyzes the cilia lining the windpipe and lungs. Says Susan Suarez of the University of Florida in Gainesville, "[Talbot's results] are a good indicator of how smoking may cause ectopic pregnancies."

Until now, only epidemiological evidence linked cigarettes to ectopic pregnancies. The incidence of ectopic pregnancy has quadrupled since 1970—following the rise in cigarette smoking among women—and women who smoke are two to three times more likely to suffer an ectopic pregnancy than those who don't. But epidemiological evidence is by its very nature circumstantial. To make a solid case that smoking causes ectopic pregnancies, researchers needed its mode of action.

Knowing that cigarette smoking inhibits the airway cilia, the Talbot team, which includes Michael Knoll, Rayan Shaoulian, and Tanya Magers, looked for a similar effect on oviduct cilia. Such an effect could explain the epidemiological findings because the beating of the oviduct cilia plays an important role in moving the zygote from the oviduct into the uterus after fertilization has occurred. The Talbot team's early results support that conjecture.

They found that when they washed a hamster oviduct in a solution containing dissolved cigarette smoke, the cilia slow down, or stop beating altogether. Moreover, the paralyzing effect is produced with solutions that have smoke concentrations similar to those in tissue after smoking a filtered cigarette.

Still, the evidence against cigarette smoke is not yet airtight. Talbot and her colleagues don't know which of the 4000 different chemicals that make up cigarette smoke cripple the cilia. And most important, says Talbot, "we need to determine if similar effects occur in live female hamsters exposed to mainstream smoke." Only then can they clinch the case.

Turning Over a New Leaf

There's not much about plants that stirs envy among humans, but their ability to regenerate their body parts has, on occasion, aroused covetous desires. It's also stirred a good deal of interest among developmental biologists. Because the growing shoot tip (called the apical meristem) is a sort of perpetual embryo, it provides a remarkably useful tissue in which to investigate early development. And recent studies from several labs show that at the molecular level the animal embryo and the plant meristem are more similar than they superficially appear to be.

At the New Orleans meeting, for example, a team led by Sarah Hake of the U.S. Department of Agriculture's Plant Gene Expression Center in Albany, California, reported that in maize meristems, just as in animal embryos, a bevy of blueprinting "homeobox" genes may help set in motion the cascade of events that change undifferentiated cells into cells with a mission. Homeobox refers to a short segment of DNA, first identified in genes that determine which cells of the early fruit fly embryo will form the antennae, legs, and other body parts. In the case of maize, says plant cell biologist Keith Roberts of the John Innes Centre in Norwich, England, the newly identified homeobox genes probably dictate which cells will form leaves or stems.

So far, the Hake team has identified three such developmental maize genes. Hake happened on the first one by accident a few years ago, while she was trying to understand a plant mutation in which affected plants have peculiar outgrowths or "knots" on their leaves. When, in 1989, she cloned the gene at fault—called *knotted-1* (*kn1*)—Hake got a surprise. The *kn1* gene's sequence turned out to contain a homeobox, which is often (but not always) associated with genes active in early embryonic development. What's more, she also found that the knotting is caused not by a defect in the *kn1* protein, but by activity of the gene in the wrong place. In the mutants it was expressed in the leaves, not just in the normal meristem. Those findings suggested to Hake that *kn1* might be a blueprinting homeobox gene, similar to those of animal embryos.

Bonsai tobacco. The maize gene *knotted-1* turns tobacco leaf cells into plant "embryos."

SARAH HAKE/USDA PLANT GENE EXPRESSION CENTER IN ALBANY, CALIFORNIA

Hake provided direct evidence for this idea in a recent experiment in which she expressed the maize *kn1* gene throughout a tobacco plant and found, she says, that the tobacco leaf cells changed from "a structure with a determined fate, back into an indeterminate structure." That is, the gene made the leaf cell behave like a meristem and sprout new stems and leaves.

Hake also described two more potential blueprinting maize genes: *Roughsheath-1* (*Rs1*) and *Gnarley-1* (*Gn1*). The Hake team, working with a team led by Michael Freeling of the University of California, Berkeley, found that these genes also contain homeoboxes and are normally active in the meristem. And they, too, create plants with peculiarly twisted leaves and stems when active in the wrong places. So it looks, says Hake, as if these genes are also involved in early plant development.

And that may be only the beginning, says Hake postdoc David Jackson. The team has identified 10 other maize homeobox genes that may be involved in development, too.

–Rachel Nowak