

It's as though he's found another bridge to the North Side, Chuanyue (Cary) Wu says, explaining the pathway for cellular communication he found. The protein (migfilin) shown right, which helps cells know whether to divide, live, or die, is part of that pathway.

CELLULAR TRAFFIC COPS

SIGNAL PATHWAY FOUND THAT'S RELEVANT TO NEARLY EVERY DISEASE STATE | BY DOTTIE HORN

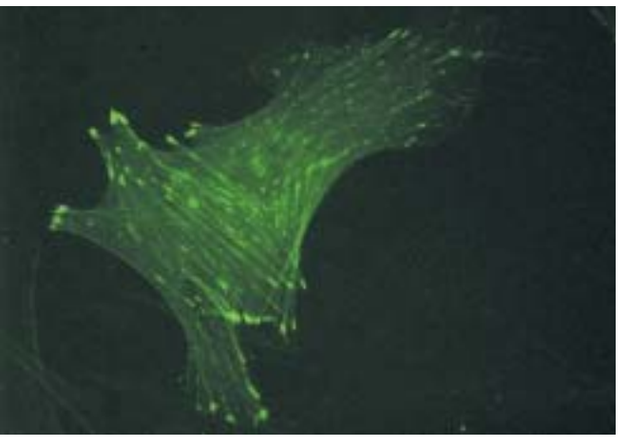
You accidentally cut your arm and begin to bleed. Cells rush to the spot and start to proliferate, stopping the flow of blood and eventually covering the wound over with new skin. But how did the cells know to go to the injured area and grow? It's almost as though a traffic cop directed them, helping them to function together in the crisis.

None of your cells lives in isolation. Each exists in constant communication with its environment. Sending vital signals to your cells—the so-called traffic cop—is the extracellular matrix, or ECM.

The ECM is made up of proteins secreted by cells and assumes different forms in different tissues. In skin, for example, the ECM forms a flat membrane beneath the bottom layer of skin—

a platform on which all the many layers of skin cells rest. In solid organs, like the liver, the ECM is like glue: It surrounds and lies between cells, holding them together in a mass. Scientists once thought that the ECM's function was primarily structural, because it physically organizes cells into cohered units. As it turns out, the ECM has another role, which is much more complex—and which is implicated in almost every disease imaginable.

In recent decades, researchers have found that the ECM and cells communicate back and forth—and that the ECM directs a cell to perform many of the cell's most basic functions. Whether a cell divides or doesn't divide, dies or continues living, is because of signals from the ECM. As an embryo grows, the ECM sends signals to each cell—saying things like, "You become a heart cell and move over there and divide."



The cell also sends messages back to the ECM. In effect, the ECM is an intermediary that allows cells to communicate with each other, to work in a coordinated fashion for the common good.

But when you're seriously ill, ECM-cell chatter can amount to cacophony. In cancerous cells, for example, the ECM's signal may be misinterpreted or go unheeded. Normal adult cells listen when the ECM says to stay put and not to travel. But despite a normal initial signal from the ECM, a cancer cell may take off and move to another part of the body. The cancer cell also does not respond if and when the ECM tells it to die.

In cancer, the two-way communication between the cell and the ECM becomes a negative feedback loop. As the cell becomes more deviant, it sends abnormal messages to the ECM, which then sends aberrant signals back to the cell as well as to nearby cells. As the cell and the ECM communicate back and forth, they both become more and more diseased.

One new strategy for treating cancer is to block key aspects of the ECM-cell communication. For example, if the ECM is telling the cancer cell to divide instead of die, why not simply cut off that signal? Without the signal, the cancer cell will eventually self-destruct.

To cut off such a signal, researchers would need to understand, at the detailed molecular level, how the ECM and cells communicate. Chuanyue (Cary) Wu, associate professor of pathology, and his lab are helping to delineate the intricacies of that communication. In a paper published on April 4 in *Cell,* they identified a new pathway through which signals travel between the ECM and the cell. (The pathway involves migfilin, a protein Wu discovered and named, and the proteins Mig-2 and filamin.) Wu likens the pathway to a bridge.

"From downtown Pittsburgh to the North Side there are five bridges. … It's almost like we've identified a new bridge which can connect downtown to the North Side," says Wu. "A lot of vehicles can move back and forth through this linkage."

Wu would like to identify the types of signals passing back and forth through the newly discovered pathway in future studies.

Understanding ECM-cell communication could be important for diseases other than cancer. Many kidney diseases, for example, are caused by fibrosis, an excessive and abnormal accumulation of ECM. Because the ECM controls such fundamental processes—like whether cells live, die, or reproduce—it is likely relevant to nearly every disease state, says Wu.

"Once we know the basic mechanisms controlling the communications, then we can develop a lot of new ways to treat those diseases," says Wu. "I always think that now is really the most exciting time because at this stage we can begin to understand [the communication] at the molecular level." ■

Trina Wood contributed to this article.

BRIDGES: CAMI MESA. MIGFILIN PROTEIN: COURTESY WU. CAKES: CORBIS.



HAVE YOUR LEPTIN AND CAKE, TOO?

CLUES TO WHY IT'S SO HARD TO LOSE WEIGHT

BY DOTTIE HORN

In 1994, the obesity research community held its breath: Had they found a cure for obesity? It was Jeff Friedman's tantalizing discovery that led to such hopes. For 10 years, the scientist at New York's Rockefeller University had studied ob/ob mice ("ob" stands for obesity),

a strain that eats voraciously and is obese, diabetic, and infertile. In 1994, Friedman discovered the mutation that leads to the mice's symptoms—they lack a hormone that was soon named leptin, after *leptos*, the ancient Greek word for lean. Researchers injected ob/ob mice with the newly discovered hormone; the animals ate less, lost weight, were no longer diabetic, and became fertile. Perhaps, obesity researchers thought, leptin could even lead to a cure for diabetes.

In 1996, Amgen spent $20 million on the patent for leptin. Soon after, scientists began raising red flags about the hormone's possibilities as an obesity cure. Unlike the ob/ob mice, obese humans did not lack leptin. Instead, researchers found, they had tons of it. In fact, the more obese one was, the more leptin one had. Despite these findings, Amgen began clinical trials: Would injections of leptin make people lose weight?

The answer was no. Only in extremely obese people did the hormone generate any weight loss at all—and the average loss was just six pounds.

Despite the disappointing results, researchers began to unravel the workings of the hormone. Leptin, they found, is secreted by fat tissue. When it reaches the brain, it suppresses hormones that stimulate people to eat. It also stimulates the release of hormones that inhibit appetite. In response to leptin, the brain sends messages to the body: Stop eating! Burn more calories by releasing more heat!

The more fat people have, the more leptin they have in their blood—so, on one level, it seemed that they should have less appetite and burn more calories than a person with less fat. But clearly that's not what happens. Somehow, in cases of obesity, the system for controlling how much food we eat breaks down.

"We have all these wonderful hormones such as leptin that are supposed to help us control appetite and body weight, but they don't work." says Allan Zhao, assistant professor of cell biology and physiology. He'd like to explain why, at the molecular level. He's already revealed what may be landmark findings on metabolism.

Researchers speculate that obese people's bodies become resistant to the effects of leptin. To study whether this is the case, Zhao used genetic manipulation to create a mouse model that is partially resistant to leptin. (The mouse has no receptors for leptin on its fat cells.) In Zhao's animals, the fat cells are totally immune to the effects of leptin, but the hormone affects cells elsewhere in the body, including the brain, as it would in normal mice.

He found that the partially leptin-resistant mouse has high levels of circulating leptin. Because the fat tissue cannot sense any leptin in the blood, it churns out more and more of the hormone. His mice eat the same amount as normal mice, but their body temperature is lower than normal (they burn fewer calories through heat release), and they gain weight—though they do not become as obese as the ob/ob mice. Because leptin affects the brain receptors of Zhao's mice as it would in normal mice, he surmised their *fat* tissue must be responsible for their decrease in body temperature. That proposition runs against convention, which says body temperature is controlled by the brain alone.

Zhao's mice are not diabetic, but they have resistance to insulin, which is a precursor to diabetes. If fed a high-fat diet, they become diabetic.

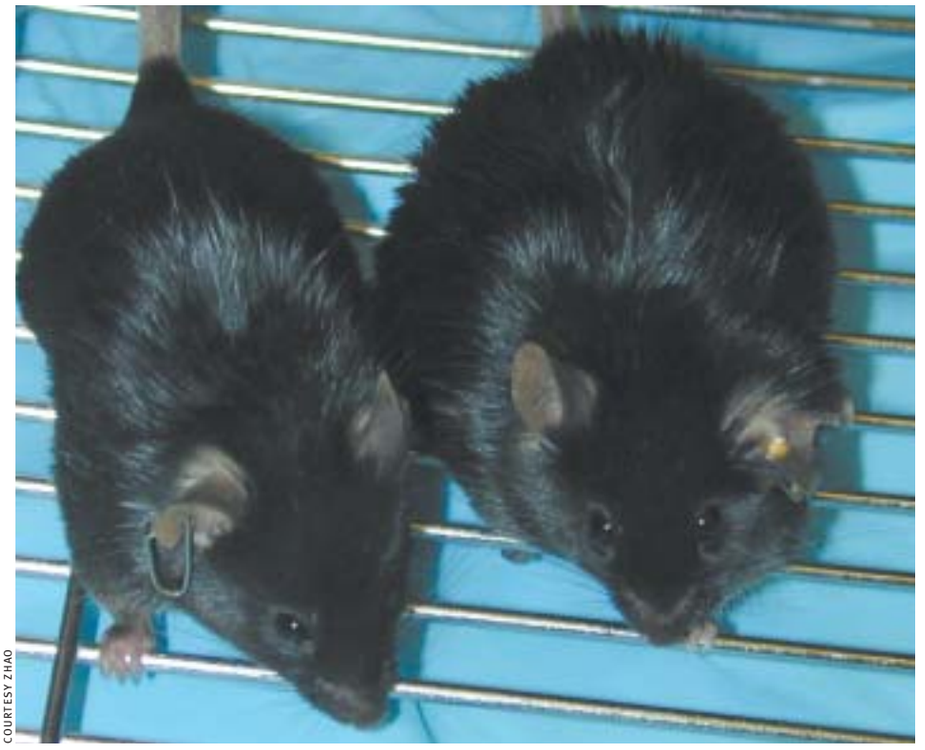
His mouse model lends support to the idea that leptin resistance is in fact associated with obesity. The model also shows that in cases of leptin resistance, fewer calories are burned through heat release—leading to weight gain despite normal food intake.

"Typically, we always blame obesity on overeating. Our model suggests that that's not necessarily true. You can still maintain the same food intake, but if you start having leptin resistance [in] fat tissue, you will still gain weight and become insulin resistant," says Zhao. Obesity researchers generally believe that obese people do eat more than lean people, so excess food intake and leptin resistance may both contribute to obesity.

In future studies, Zhao will study fat samples from human volunteers to see if leptin's actions on cells are reduced in obese people. Eventually, he hopes his work would lead to a drug to help leptin do its job, but he doesn't expect a pharmaceutical cure for obesity anytime soon.

"The more you appreciate this physiological system that helps us control food intake, the more you realize that probably our best hope is not to find the magic bullet, but to exercise and diet," he says. "Medical research can only do so much." ■

Jeff Friedman will be a featured speaker at Pitt's Science 2003 this September.



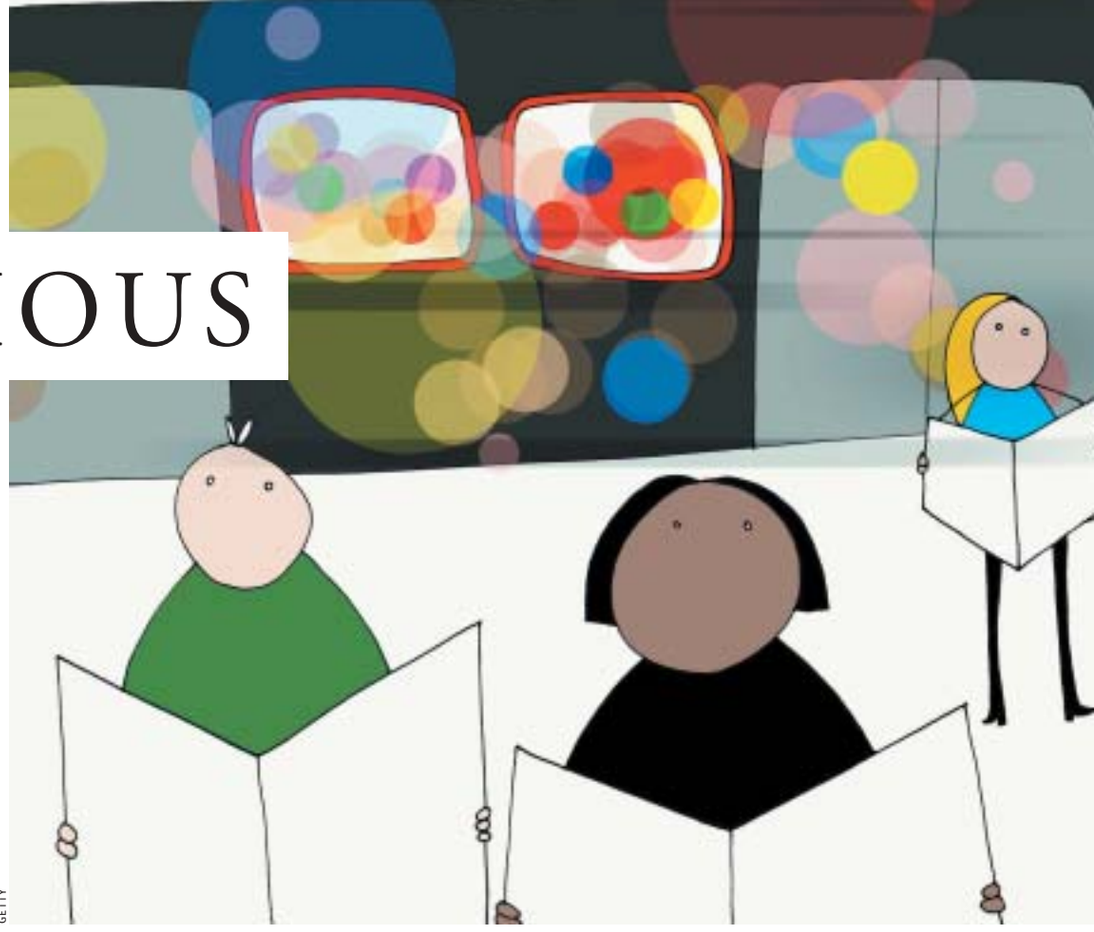
COURTESY ZHAO

These two mice ate the exact same diet—yet the animal on the right tips the scale at 1.5 ounces and his companion weighs only 1.1 ounces. Why the difference? The skinnier mouse burns more calories through heat release. His body temperature is a normal 98.6 degrees Fahrenheit—nearly two-and-a-half degrees warmer than the heftier mouse, whose temp is only 96.2 degrees. The mouse on the left is normal; Allan Zhao created the mutant on the right. Zhao's mouse is helping to show the world that fat tissue does more than just store energy.

IT'S CONTAGIOUS

A JOURNAL CLUB BY POPULAR DEMAND

BY CHUCK STARESINIC



GETTY

What are the odds that busy med students would sign up for extra work? What are the odds that they would not only sign up for extra work, but the program would be the academic equivalent to "sold out"?

Apparently, the odds are pretty good at Pitt.

Before the Journal Club for med students started in the fall of 2001, faculty organizers expected only a handful of students to join. Some 40 students signed up—so many that they had to split the group into two.

Then, for the 2002–03 academic year, the club expanded to include second-year students. Nobody camped out to get on the club list, but about 60 students participated this past academic year.

What makes the Journal Club so popular?

"Free food," quips Mark Gibbs while chewing a forkful of pasta salad at a recent meeting of second-year students. After swallowing, he admits the club provides a lot more than calories. Gibbs, who plans to work in a clinical setting, knows that physicians have to read and digest the literature "as soon as it's out there." Through the Journal Club, he is learning to read journal articles critically and to think about how physicians might apply what they glean to treating patients.

Across the conference table from Gibbs, Xinglei Shen finds the club equally nourishing to his interest in academic medicine and research. At club meetings, he and his classmates evaluate investigators' research techniques. "It's a good way to look at the process of going from research to medicine—how what we do in the lab gets into the medical textbooks and class lectures," he says.

According to its organizers, the club sheds light on the research practices that advance knowledge. It also prepares students for practicing medicine in a world in which rapid scientific advances quickly translate into treatment.

"We're not bringing students up to date on the literature. That's not what's going on," says Peter Drain, with a slightly conspiratorial air. Drain, an assistant professor of cell biology and physiology, is a founding codirector of the club along with associate professors of medicine Mary Choi and Amy Justice. "The club was designed to teach critical scientific thinking, to share an infectious enthusiasm for research, and to take young people from being students to being active participants in science and medicine," he says.

At the beginning of the term, the club's codirectors pair students with faculty mentors who display a certain "star quality." Some received glowing student evaluations as lecturers. Others are simply recognized by their colleagues as investigators whose excitement about science is contagious.

Mentors assign the articles—anything from a classic text to a more recent publication. Some articles explore clinical research. Some contain a daunting amount of science, or, as Mitchell Creinin, associate professor of obstetrics, gynecology, and reproductive sciences and current club codirector, puts it, "biochemistry that will make you pull your hair out." Mentors meet with their students informally and help them understand the article and prepare a presentation.

At the final meeting of the Journal Club in the spring, second-year student Charlotta Weaver stands and presents "Decline in Physical Activity in Black Girls and White Girls During Adolescence" (*New England Journal of Medicine,* Sept. 5, 2002), which was co-authored by her mentor, research assistant professor of family medicine Nancy Glynn.

After a lively discussion about how the study was designed and data were presented, Creinin presses the group to think about "the real meaning of this study."

Discussion turns to the factors that lead to inactivity in adolescent girls and how communities can foster healthy activity through organized sports and education. Creinin likes this direction, but he narrows the discussion again, as if the students are approaching a breakthrough and he refuses to let them walk away from it. He's looking for that moment when a student begins to, he explains later, "translate medical and social research into how you practice medicine in a community."

Creinin pointedly asks Weaver, "What do you do with this information?" She is quiet for a moment, then begins, "As a physician in my office with a patient, I would…"