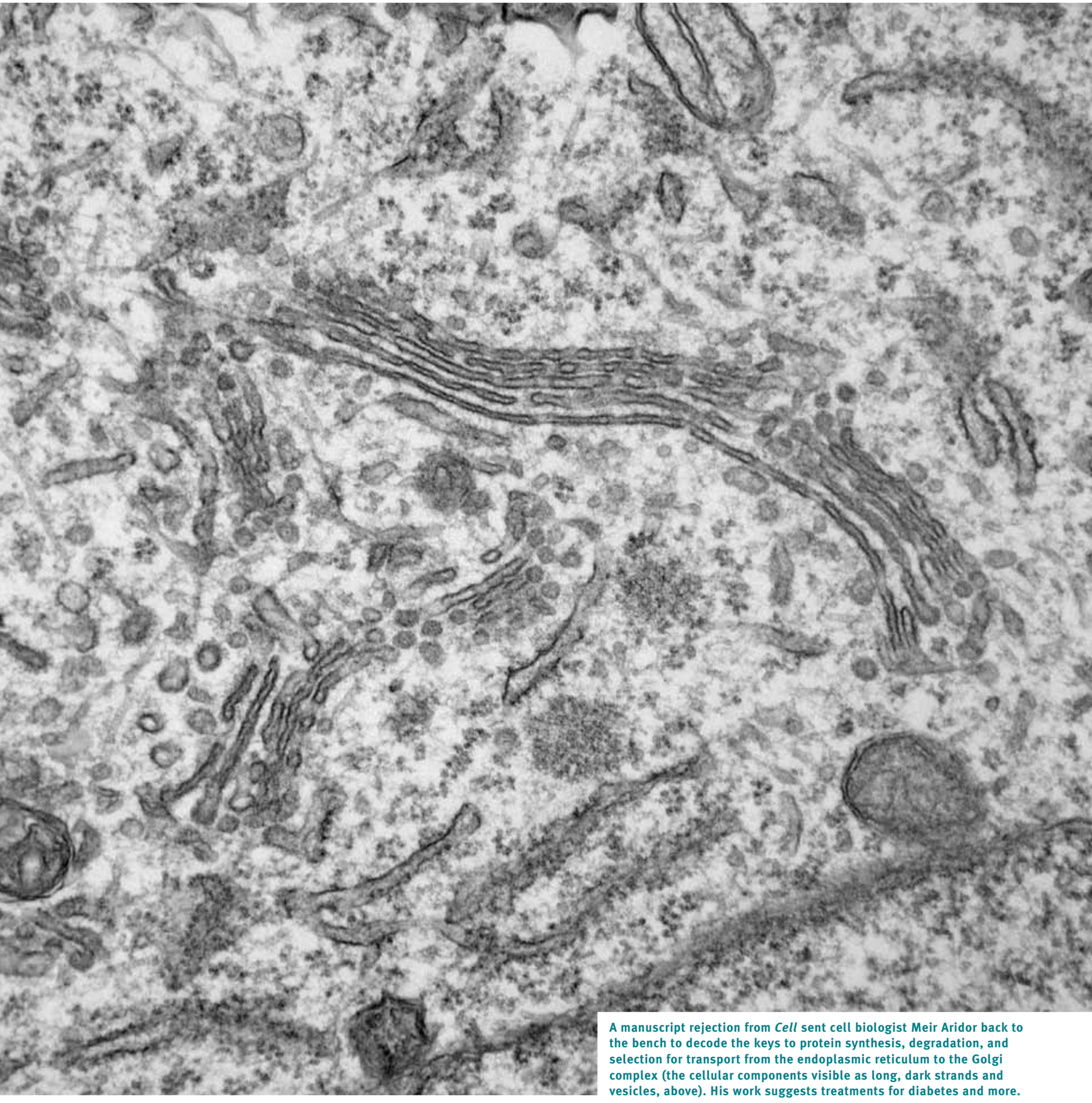

A manuscript rejection from *Cell* sent cell biologist Meir Aridor back to the bench to decode the keys to protein synthesis, degradation, and selection for transport from the endoplasmic reticulum to the Golgi complex (the cellular components visible as long, dark strands and vesicles, above). His work suggests treatments for diabetes and more.

SPECIAL DELIVERY

THE CELL'S SORTING MACHINE COULD BE KEY TO FUTURE THERAPIES | BY JOE MIKSCH

A cell is under a microscope. An organelle is seen sending out tiny vesicles, little budding bubbles. What's in them? What controls the packaging and, really, what is this thing—the endoplasmic reticulum, known as the "ER" to cell biologists—doing?

Meir Aridor has made real progress toward answering these questions and, in so doing, has made his mark on cell biology. His work helped change the prevailing view of the ER from an indiscriminate processor of proteins to a highly selective mechanism.

And this selective mechanism, he expects, will be key to developing more targeted therapies for a wide range of diseases.

Aridor is a PhD assistant professor of cell biology and physiology at the University of Pittsburgh. Prior to the early 1990s, he says, the ER—where the cell synthesizes, processes, assembles, sorts, and degrades proteins—was poorly understood. Investigators knew the "what" of the ER, but had little idea regarding the "how."

Scientists saw the ER as a passive mechanism, explains Aridor, one that allowed newly synthesized proteins to diffuse through the system.

"The assumption was that everything was free to diffuse ... that the ER and the secretory pathway worked like a distillation tower," he says.

That view began to change when Aridor and others noted that small vesicles budding from the ER contained specifically selected proteins. Further study showed that a coat protein complex, called COPII, resided on the vesicles' surface.

"In 1994, COPII was defined as a coat that can make vesicles in yeast," says Aridor. "We were the first, though, to show that it did the same thing in mammalian cells."

Aridor and colleagues demonstrated that COPII was responsible for protein movement out of the ER.

There was a small problem, though.

"We sent the paper to *Cell*, and it was a year in review," Aridor says. "The upshot is that they came back to us and said, 'This is interesting, but we don't believe it.'"

The problem, he concedes, is that the paper was based upon the analysis of visible phenomena, without explanation of the mechanisms involved. "I realized we had to determine the molecular basis of the process [to gain credibility]. Until we understood the interactions, we couldn't actually have these claims."

The rejection from *Cell* spurred years of lab work that pinned down the mechanisms and molecules responsible for selecting the protein cargo tucked into vesicles leaving the ER. Among the components Aridor and his lab mates characterized was a protein called Sar1 that is responsible for deforming the ER membrane to detach vesicles. It's also been Aridor's quest to unearth molecules responsible for cargo selection and for sending the protein-laden vesicles to particular destinations.

On a recent sunny and hot Pittsburgh afternoon, Aridor sat behind his desk and talked about the cell's protein packaging and sorting mechanism, which has been the focal point of his career since the early 1990s.

Describing his investigations into the ER's functioning, Aridor often seems on the verge of levitating above his chair. His hands wave, his bushy, graying hair sways, and his voice rises to punctuate the thrill of discovery.

Aridor's colleague Ora Weisz is a PhD associate professor of medicine in the renal electrolyte division. She has authored two papers with Aridor and describes him as "a big thinker. He has a really amazing ability to think big thoughts on a microscopic level. He's trying to unravel how, in the most basic way, proteins that are newly synthesized get out of the earliest step in the secretory pathway."

Recent work, on which Weisz collaborated, aimed to sort out the role lipids—functioning as signaling molecules—play in the ER. "Just in the past few weeks, we've identified proteins that bind the coat and specific lipids," Aridor says. "And we have preliminary data to suggest that this is how the ER exit site is organized."

Weisz says understanding the interaction between lipids and the COPII coat proteins is another step toward solving the mysteries of the ER. "Meir is beginning to develop a very mechanistic picture of how the cargo comes to one side, how the lipids remodel in order to change the curvature [of the membrane], and how the coat is recruited during this process to enable formation of vesicles," she says.

On a practical level, Aridor sees understanding the ER as a means to understanding a slew of diseases. He is in the process of updating a list of maladies—seven pages long in 2002—connected to malfunctions in intracellular transport: diabetes, Alzheimer's disease, and myeloma, to name just a few.

Understanding the ER will offer opportunities for new therapies in the near future, says Aridor. Take high cholesterol. Drugs now in use, such as statins, inhibit enzymes that participate in cholesterol synthesis.

"They also effectively disable export of viral proteins out of the ER," Aridor adds. This entirely blocks the synthesis of cholesterol, which is needed by cells. In an experimental system, cells die. In people, however, enough cholesterol is introduced through diet so the potential ill effects of the drug are limited.

One day, Aridor says, we may be able to control the traffic from the ER and thus the activation of just one transcription factor that regulates cholesterol level. This more specific targeting, made possible by understanding the individual components of the ER, would eliminate such possible adverse effects and allow for more effective drugs.

"The nice thing about this is you can study basic physical interactions and the insights, and you can learn a lot of stuff in terms of function and diseases," the scientist says. "I'm a little bit excited about this. Look at the possibilities." ■

COURTESY SIMON WATKINS

The monotone voices of children with autism helped orient Nancy Minshew's studies.

AUTISM:
A CASE OF MIXED SIGNALS?

PITTSBURGH RESEARCHERS FIND EVIDENCE FOR THEORY | BY REID R. FRAZIER

Every day, the children from the inpatient ward at Pitt's Western Psychiatric Institute and Clinic would whoop it up on their way to gym. Every day, Nancy Minshew could hear the voices in the hallway outside her office, even through her closed door.

"I could tell which children had autism based on their voices. They were often loud, and they spoke with a monotone."

This was during the mid-1980s, when Minshew had first come to the University of Pittsburgh as a pediatric neurologist. A colleague at the University of Texas had recently shown how stroke hindered prosody—the melody of a person's speech. Children with autism lack prosody. Minshew now says hearing those monotone voices helped orient her toward studying how autism works in the brain. Children with autism could do the essentials—like speak—but struggled with more complex aspects, such as modulating their speech.

Kids with autism have no trouble with the basics of mental function—they can see, hear, and remember facts. The problems come when many parts of the brain have to cooperate.

Autism remains a mystery to doctors and scientists of all stripes; yet Minshew, with other Pittsburgh researchers, is starting to make sense of it.

The disease impairs social interaction and communication. Children with autism often can't remember faces. They can't read facial expressions. They have few friends. They can become inconsolable if they experience a change in routine—a detour on the way to school, a substitute teacher, or the appearance of the moon during the day.

When Minshew started studying autism, most psychologists were looking for a single culprit—one region of the brain that caused the disease. Minshew thought the problem had to be in many parts of the brain. Kids with autism have no problem with the basics of mental function—they can see, hear, and remember facts. Many have normal IQs. The problems come when several parts of the brain have to work together, like when trying to understand a metaphor or play "make believe." Kids with autism don't do "make believe" very well.

"I had one kid tell me, 'Don't you understand? I don't play with things that aren't real,'" Minshew says.

She has long subscribed to a theory of disordered complex information processing and underdeveloped neural systems. That is, that autism affects the brain's connections, not just one of its regions. For a study Minshew coauthored last year, she gave 56 children with autism a series of neuropsychological tests, then compared their performance with that of their nonautistic peers. The results: Children with autism perform well on basic functional tests but fail on complicated ones. They could find Waldo in a "Where's Waldo?" picture. But they couldn't identify different people with similar faces. Minshew says this suggests that the brain's individual areas work fine, but they don't work together to perform complex operations.

Carnegie Mellon neuroscientist Marcel Just, one of Minshew's collaborators, used functional magnetic resonance imaging to watch the brains of 17 adults with autism and 17 without as they read and answered questions. In the brains of people with autism, the signals weren't as well synchronized among frontal regions and the other brain areas as they were in the control group. The results were the most convincing to date on underconnectivity, Minshew says.

Minshew directs Pitt's Center for Excellence in Autism Research, one of six such National Institutes of Health–funded centers in the country. She and her collaborators are seeking the biological and genetic causes of autism and, ultimately, new diagnosis and treatment methods. Beatriz Luna, one of the center's coinvestigators, is studying the brains of adolescents with autism to determine when intervention can be effective. (For more on Luna's studies, see article on p. 19.)

Minshew also helped turn Bernie Devlin's attention to autism. Devlin, a statistical geneticist (think big computers and incredibly long lines of genetic code), had been working on the genetics of schizophrenia and eating disorders. Minshew urged him to attend a conference in Italy a few years ago on the genetics of autism. (Since autism tends to run in families, many scientists believe it to be genetic.) A plant geneticist by training, Devlin devoured a stack of papers on the subject during the 12-hour trans-Atlantic flight. He got hooked. The allure of the problem was its complexity—there is probably no single gene for autism, but many that together convey risk.

Devlin later joined the Autism Genome Project, an international team of more than 150 geneticists trying to crack the disorder's genetic code. The group studied DNA samples from more than 1,000 people with autism in their families and found a series of genes that tend to correspond with autism. Of the body's 30,000 genes, some get duplicated or deleted ("knocked out," in geneticist parlance) when passed from parent to child. The scientists are looking at whether a series of genes related to the transmission of the chemical glutamate gets copied or knocked out in patients with autism. Glutamate is an important neurotransmitter that plays a role in memory and learning. A problem with glutamate transmission could be significant to understanding how the brain's signals become blurred in autism.

"We're sifting through a massive amount of data to figure out what's real and what's not," says Devlin, who is the group's lead computational geneticist. "We'll know a lot in about two years. But I predict we'll never know everything about it." ■

FOR MORE INFORMATION OR TO JOIN A STUDY:
1-866-647-3436
www.pittautismresearch.org

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