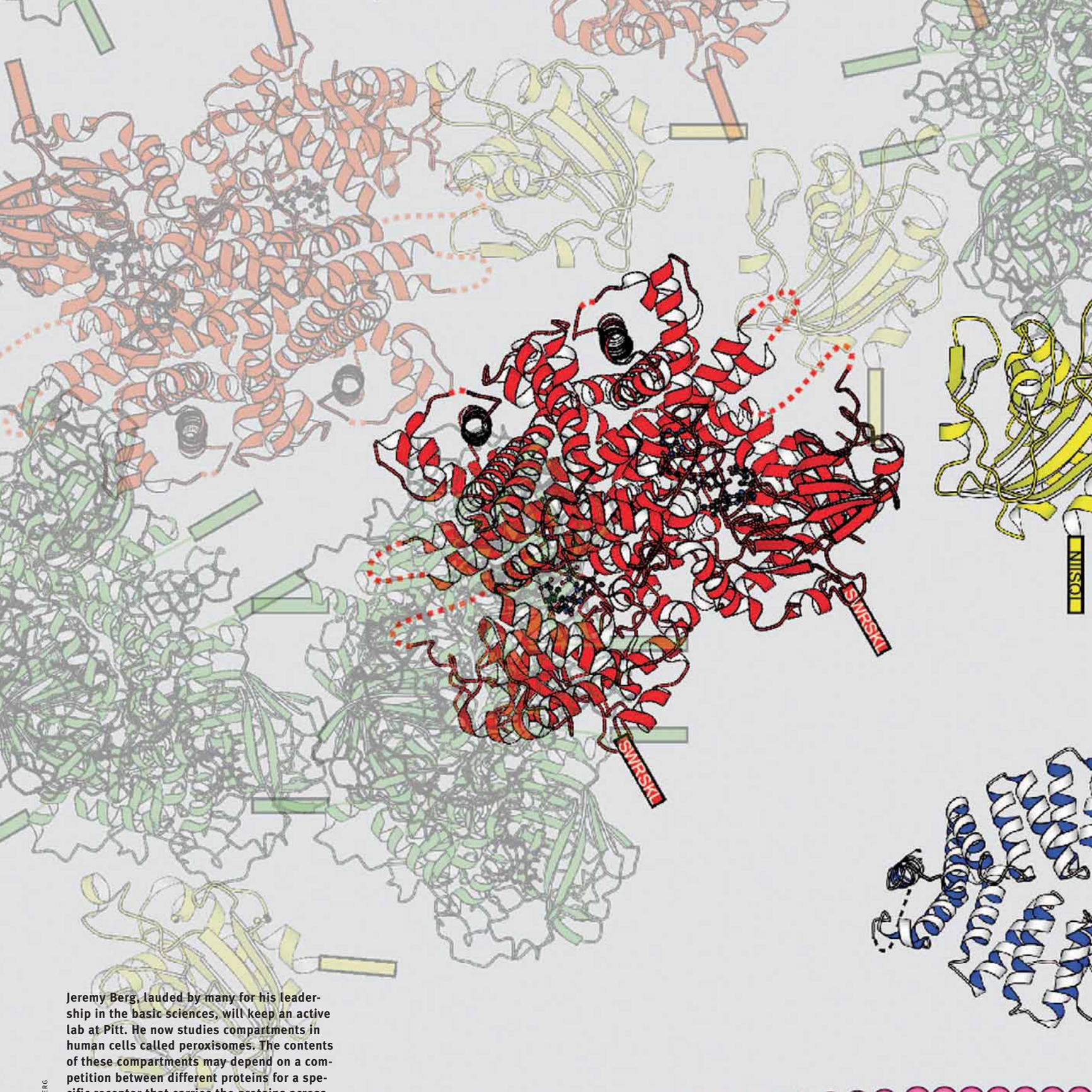
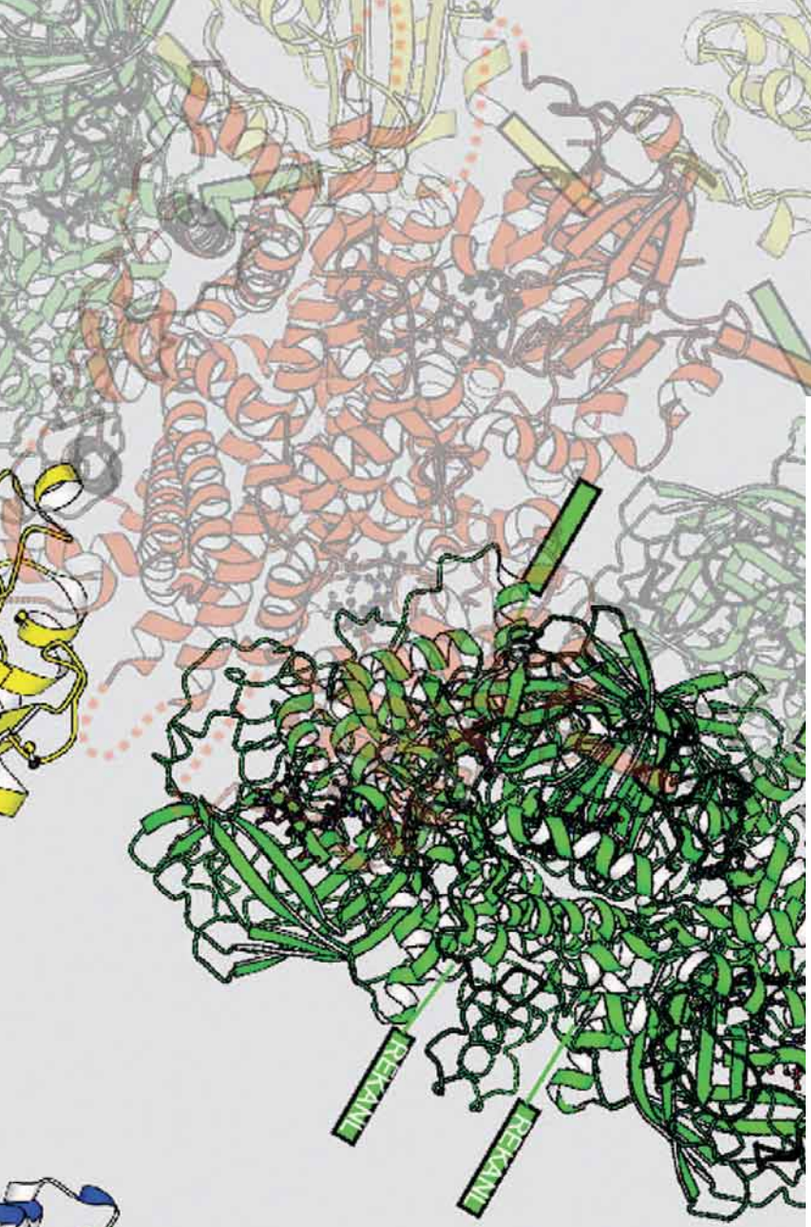


Jeremy Berg, lauded by many for his leadership in the basic sciences, will keep an active lab at Pitt. He now studies compartments in human cells called peroxisomes. The contents of these compartments may depend on a competition between different proteins for a specific receptor that carries the proteins across a membrane (shown here as pink-and-green-layered ribbon) into the interior of the peroxisome.

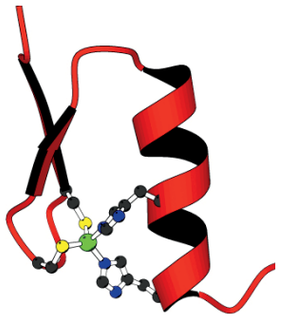
COURTESY J. BERG



JEREMY BERG, A RISING STAR AT NIH, COMES TO PITT | BY REID R. FRAZIER

THE NATURAL

When he was a young assistant professor at Johns Hopkins University, Jeremy Berg's grad students could hear him coming before he walked in the door. So eager was he to start the next activity, the scientist made a habit of running between meetings. John Desjarlais, a PhD student in Berg's lab, remembers hearing the elevator door open and the sound of the 6'2", wide-shouldered scientist bounding toward him. "You'd hear this freight train coming down the hall. He would literally sprint down the hallway," says Desjarlais, now vice president of research at Xencor, a California biotech company that engineers proteins. "We all knew not to open any doors when we heard this."



COURTESY J. BERG

Berg predicted the structure of zinc fingers, which are now customized by scientists to "knock out" DNA sequences.

Berg's haste could be forgiven. He was busy making eye-popping discoveries about the structures of transcription factors, proteins that activate DNA. Berg pioneered the study of zinc fingers, molecular tools used by transcription factors to identify binding sites on DNA. He was extremely curious. He was enthusiastic. He'd spend hours in his office bending a wire model of a protein structure to get the shape just right. He'd do experiments with proteins just to see what happened. (He once asked Desjarlais to add cobalt to an insoluble zinc-finger analog—just to confirm that it would turn blue. It did.)

What propelled him down the halls of Johns Hopkins sustained him during a run to the upper ranks at the National Institutes of Health (NIH). At the age of 45, he was named director of the National Institute of General Medical Sciences.

In his eight years as head of NIGMS, Berg became a leading thinker in how to fund scientific research, spread grant money to more labs, and encourage creativity in science. He championed high-risk research, young investigators, and diversity. "He was one of the best hires I ever made," says the man who brought him to the agency, former NIH director Elias Zerhouni.

This year, Berg made a quick turn in his run as he came to Pitt to become the University's first associate senior vice chancellor for science strategy and planning for the health sciences. Berg will continue his research as professor of computational and systems biology. In general terms, Berg's job will be to think deeply about biomedical science at Pitt. How to do it better, how to do it creatively, and how to get young scientists the training and resources they need.

"I see his role being very similar to the role that he had at NIH, which is to participate with me in the planning and strategizing inherent in science," says Arthur S. Levine, Pitt's senior vice chancellor for the schools of the health sciences and dean of the School of Medicine. "He'll help me make our institution as competitive as it can possibly be."

Levine first learned of Berg's interest in Pitt in late 2010, when he got a letter from him. *Was there any work for him in Pittsburgh?* Berg wanted to know.

"I would have to admit I was surprised," Levine says. "Dr. Berg is a terrific scientist and a terrific scientific leader. He is seen almost heroically by the national scientific community."

It is rare for an NIH director to knock at your door. But Berg's situation was unique. His wife, the influential radiologist Wendie Berg, was being recruited at a number of different universities around the country. Could any of them find a job for her trailing spouse? "A lot of other places were kind of not sure what to do with me," Berg says.

Levine's answer to Berg's query? "Of course."

Who wouldn't want Berg's help? A quick scan of his CV reveals a stellar career. But really the proof is in the respectful tone former colleagues, bosses, and students get when speaking of Berg.

Zerhouni first met Berg when the two men worked at Johns Hopkins, where Zerhouni was vice dean for research. The two men worked together when Berg headed Johns Hopkins' Institute for Basic Biomedical Sciences, which coordinated scientists from across disciplines.

"In that position, he really was a leader—you could tell," says Zerhouni.

"He was open to understanding the dynamics of research outside his own field."

At NIH, Berg drew attention for his frank and open discussions about the agency's challenges. He started its first blog. Earlier this year, he made waves as the lone dissenter on a vote that, among other implications, would likely close NIH's National Center for Research Resources, a home for basic and translational science for decades. Berg thought NIH hadn't thought the decision through enough and said so. The vote was 12-to-1 in favor.

Berg nonetheless gained respect from scientists for speaking his mind. "He has great integrity to stand up for his convictions," says Stanford's Suzanne Pfeffer, president of the American Society for Biochemistry and Molecular Biology.

GOING UP, IN A HURRY

Berg began this life of curiosity as a Stanford faculty brat. His father, Paul Berg, was a mathematician, and his mom, Judy Nadell, a hematologist. For his 12th birthday, Berg's father gave him *The Architecture of Molecules*, an illustrated book coauthored by Nobel laureate Linus Pauling and artist Roger Hayward. The book portrayed molecules in pastel ball-and-stick drawings. It was chemistry made visible, and the young Jeremy Berg understood just enough of it to get hooked.

As an undergraduate at Stanford, he migrated toward chemistry. Among his teachers there were structural chemist Keith Hodgson, biochemist Lubert Stryer, and inorganic chemist Richard Holm. He learned X-ray crystallography from Hodgson. Holm was interested in modeling the active sites of metal-containing enzymes, particularly those containing molybdenum. (This element allows enzymes to promote key reactions such as the conversion of nitrogen gas to ammonia and the conversion of xanthine to uric acid.)

"He was extremely skilled in determining 3-D structures of molecules using X-ray defraction," Holm says. "Mind you, this guy was a freshman or sophomore; and this is the kind of technique that graduate students, some of them, don't learn very well, ever.

"He was a brilliant student, one of the most outstanding undergraduates I've ever seen, anywhere," says Holm, now a professor of chemistry at Harvard. Working with Hodgson and Stryer, Berg, at 21, coauthored a paper in *Nature*.

Berg got a PhD in chemistry at Harvard, working with his old Stanford professor after Holm moved his lab to Cambridge, Mass. Holm asked Berg to create molecules that would simulate the reactivity in addition to the structural properties of the catalytic sites of some molybdenum-containing enzymes. Berg developed such a system, one of the first reactivity models in bioinorganic chemistry.

Pure chemistry wasn't Berg's primary interest—he wanted to work in biology, too. So he chose a postdoctoral fellowship in the department of biophysics at Johns Hopkins, where his soon-to-be wife, Wendie, was getting her MD/PhD. (They met in quantitative analysis class

Berg asked a colleague at Hopkins how many times someone had predicted a protein structure. "If yours is correct," his friend told him, "that would be one."

at Stanford. His parents also met in college, in quantitative analysis class.) At Hopkins he worked in the lab of Carl Pabo, a young scientist studying the structures of DNA-binding proteins.

Berg landed a faculty position in Hopkins' chemistry department. As he was preparing to start his own laboratory, a group of scientists led by Nobel laureate Aaron Klug of the MRC Laboratory of Molecular Biology in Cambridge, England, discovered "zinc fingers," small domains organized around bound zinc ions within a protein that binds to specific sequences of DNA. They proposed that the zinc fingers determined the DNA sequences to which the protein binds.

This discovery got Berg wondering: What did those zinc fingers look like? If scientists could understand how zinc fingers were made, they could conceivably make their own. "I had time to stare at the sequence and think about what it might mean," says Berg. "It was sort of like Tinkertoys. Once you had the building blocks, then it was a question of how can you put these together in a way that made sense to the overall structure."

Berg proposed a structure in which the zinc ion organized each zinc finger into a unit well-suited to bind DNA. This model would allow the fingers to slide inside the double-helical tube of DNA at precise positions. This would explain the structures' ability to bind with such specificity and affinity.

Berg asked a colleague at Hopkins how many times someone had predicted a protein structure. "If yours is correct," his friend told him, "that would be one."

He published his prediction in 1988. Berg waited. A year later, a group of scientists at Scripps used nuclear magnetic resonance spectroscopy to determine the structure of the zinc finger. There it was; just as he'd predicted. (Pabo's lab, where Berg had done his postdoc, later became the first to develop the crystal structure of a bound zinc-finger protein.)

In tandem with other technologies, zinc fingers are now used in the creation of "knockout" rats and mice—scientists now design fingers that recognize a sequence on the genome they want to exchange.

Berg's zinc-finger prediction got the young scientist noticed at Hopkins. Among those impressed was Thomas Pollard, chair of cell biology. He saw Berg give a presentation. "He'd done something brilliant, and the way he conveyed it really gave you confidence that he was on top of things," Pollard says.

MARTHA RIAL

Berg at his new home, the University of Pittsburgh. To learn about his thoughts on building an inspiring research climate, see his conversation with George Whitesides (p. 15.)

Pollard was on the search committee for a chair in the biophysics department, where Berg had been a postdoc. Berg was 32, almost preposterously young for the position, but Pollard put his name up for the post anyway. (Pollard was 34 when he became chair of his department.)

"I think I literally said, 'Why would I want to ruin my career at such an early stage by getting into administration so early?'" Berg says now, with a chuckle. Berg thought it might slow down his research career. But every morning, heads of other departments would stop by his office, nudging him to take the job. He did. He was among the youngest department chairs in the history of the university.

ASKING HARD QUESTIONS

Jeremy Berg met Elias Zerhouni through Wendie, Zerhouni's colleague in radiology. He worked closely with Zerhouni on various intramural committees, and Zerhouni was impressed by the "ecumenical" way Berg treated other disciplines. When Zerhouni was named director of NIH in 2002, he had to fill several leadership positions. A search committee forwarded him several names for the NIGMS job. One of them was Berg's.

NIGMS holds a special place in the hearts and minds of basic scientists around the world. "It's probably one of the most critical institutes, because it funds science at the edge," says Zerhouni, who is now president of global research and development for Sanofi. "It's where the frontier of knowledge is created." Unlike most NIH institutes, NIGMS has no disease focus. Along the continuum of bench to bedside, it is the most "bench" of all institutes.

For the position, Zerhouni wanted someone who was committed to what he called "transformational" research—high-risk, high-reward science. When he interviewed Berg, he got an earful about some of the agency's shortcomings in this regard. NIH didn't invest heavily enough in risky science or lesser-known

and younger scientists, Berg told him. "He felt the NIH peer review was somewhat conservative and that it should truly encourage breakthrough research," says Zerhouni. On this the two men agreed, and Zerhouni eventually convinced Berg to take the job in 2003.

It didn't take Berg long to make his mark on the agency. In 2004, NIH launched the Pioneer Award, a pet project of Zerhouni's. Zerhouni had wanted to fund innovative research, especially from scientists who may not score as highly along traditional NIH guidelines. When the first batch of awardees was unveiled, Berg was disappointed.

"I was really looking forward to Googling a bunch of people I'd never heard of and trying to figure out what they were doing and why they were chosen," Berg says.

The nine awardees were all excellent scientists, Berg says. But they were also well-established, and almost all were older, white men.

"I was mouthing off to the deputy director [Raynard Kington, now president of Grinnell College] that I thought this was a lost opportunity," Berg remembers. Kington told him to, essentially, go tell it on the mountain. Berg wrote a long e-mail to Zerhouni spelling out why he thought NIH could take bigger chances with the Pioneer program.

"A day or two later," Berg recalls, "I walked into a meeting, they pointed over to me and said, 'How would you like to run the Pioneer program?'"

Berg accepted the challenge and asked colleague Judith Greenberg to help administer the award. The following cycle, NIH did more to advertise its intention to award high-risk projects and a diverse pool of applicants. Among the next year's recipients was Nathan Wolfe, a young public health scientist at Hopkins who was interested in tracking down novel animal viruses in Asia and Africa before they "made the jump" to human populations. (Wolfe's work has since been featured in *The New Yorker* and *Time*; he founded and directs the Global Viral Forecasting Initiative.) Approximately half the recipients were women, and several were from underrepresented groups.

There was another problem with NIH, Berg had told Zerhouni. Many weren't sure why it supported some investigations but not others. "I said, 'What will you do about it?'" Zerhouni says. "He said, 'I'll be more transparent. I'll tell people, *Here's the funding we have; here's what we're funding and why.*'"

Berg then became the first blogger in the NIH administration. The Feedback Loop, begun in 2009, is a blog that Berg and others in his institute used to communicate their methods to scientists. Berg has blogged about how the institute rates and debates grant applications. He published his own studies on the correlation between peer-review scores and the likelihood a grant gets funded.

"None of the rest of us do that," says Story Landis, director of the National Institute for Neurological Disorders and Stroke. "How big should a lab be to get the maximum productivity, per person or per dollar? We all talk about that, but Jeremy actually did the analysis."

In the spirit of transparency, Berg has studied how well the peer-review process correlates to quality, as measured in publications, citations, and patents. And he's illustrated the results with Lorenz curves, Gini coefficients, and histograms.

"These are things that people at NIH hadn't been doing or sharing," says Greenberg, now director of NIGMS. "After he started doing it, more and more of these kinds of analyses are coming out from other parts of NIH."

Pollard, Berg's champion at Hopkins and now dean of the graduate school of arts and sciences at Yale University, wasn't surprised about Berg's innovations at NIGMS.

"He's absolutely curious about how things work, whether it's zinc fingers or whether it's teaching or whether it's how the NIGMS runs. And if you're curious about how they work, you can try to figure out how to make them work better."

WHAT CAN BERG DO FOR YOU?

The next chapter in Berg's career began this summer, when he moved into his office at Pitt's Scaife Hall. Berg will continue his own research, which in recent years has turned toward the targeting of proteins to peroxisomes. These are organelles that have several vital functions, including breaking down long-chain fatty acids and synthesizing certain lipids. Berg is attempting to decode the system that determines the appropriate composition of proteins within peroxisomes that leads to proper function.

Wendie Berg, meanwhile, will continue her work on techniques to improve breast cancer screening. She has led multicenter investigations into the efficacy of the techniques. (See "Lessons in Survival" in the Summer 2011 *Pitt Med*.)

In his science strategy and planning position, Levine envisions Berg working on some of the same topics that interested him most at NIH—looking for ways to improve diversity, encourage breakthrough research, and help refine bioscience graduate training.

Berg's experience at NIH will also be of use at a time of economic uncertainty in science funding. His arrival at NIH coincided with the end of its "doubling" period, in which the budget increased from $15 billion in 1998 to $28 billion in 2002. Since then, the budget—currently at $31 billion—has been held essentially flat.

How do you get the most bang for the research dollar? How much funding is too much? These are the kinds of questions Berg asked at NIH.

How do you get the most bang for the research dollar? How much funding is too much? These are the kinds of questions Berg asked at NIH, and they are very relevant in the current funding climate, says Pfeffer, president of the biochemistry and molecular biology society. (Berg was elected to succeed her as president in 2012.) "It's probably time to ask, 'Are we spending that money as wisely as we should be?'" Pfeffer says. "Berg has some really good ideas about that."

Berg is also putting thought into how to foster bold, high-risk science at the University.

"That's one of the things that's attractive about Pitt," he says. "There seems to be a fairly strong culture of that boldness.

"There's still so much we don't understand," he says.

"There's still a lot more to be discovered. There are just many, many examples over time of people who are working on one problem who then make an observation that didn't make any sense at all at the time, and then had the good judgment to decide it was potentially something really important."

If these types of observations and researchers aren't supported, he says, "you're going to end up not knowing about whole areas of science that are going to be more relevant in the long run." ■