Junior investigators count on the National Institutes of Health to finance their research. Pitt found a way to fuel discovery during the times when political discord leaves scientists unfunded and dangling in the balance.





HOW PITT SPANS THE FUNDING CHASM

BY JENELLE PIFER

In the winter of 2009, Lisa Borghesi was primed to decipher a fundamental question of longevity. She wanted to know how immune cells develop—in particular a variety called hematopoietic stem cells. Accounting for just 1 in 100,000 blood cells, they are solely responsible for regenerating blood throughout life.

"Part of our longevity is determined by how long these stem cells can continue to repopulate," says Borghesi. "This is a question about life, about vitality."

Borghesi was still relatively new at the University of Pittsburgh, having joined the faculty as a PhD assistant professor of immunology in 2004. With start-up money—which the University provides to new hires—and several small federal and private grants, her five-person lab team had studied cells in the immune system that produce antibodies, working to understand how they fight infection. It was only in 2009 that their interests began to swim "upstream," Borghesi says, from the function of mature cells to the complex ways in which they develop. "How are these cells replenished every day?" they wondered.

ILLUSTRATION | MICHAEL LOTENERO

The team was eager to investigate. Specifically, they wanted to understand an underlying transcription factor in hematopoietic stem cells called E47, essential to the regulation of immune cell formation and function. The work had special promise to help patients with compromised immune systems, including those who'd undergone transplants or chemotherapy, says Borghesi. But the project was big. "And we couldn't begin without knowing we had stable funding," she says. At that point, they didn't.

"The idea that the school offers bridge funding says that it cares enough to keep its faculty, even when they're down on their luck a little bit."

That winter, Borghesi had narrowly failed to attain an R01, a five-year grant from the National Institutes of Health that she calls "the benchmark for promotion and tenure at most U.S. universities." She was keenly aware that she needed the award—to benefit her research, her lab, and her career. Without it, the salaries of her staff were on the line. She had scored highly, within the top 14 percent. But she was still denied the resources she needed, largely because the U.S. Congress was in the midst of a budget standstill that had left the resources of the NIH undefined, and dwindling. She watched her students' enthusiasm deflate.

"When they see their mentors who are just a few years ahead of them struggling, it is a disincentive for our brightest young people to continue," says Borghesi. Some of the graduate students in her classroom—as well as the postdocs in her lab—began to wonder whether a career in academic research was realistic, she says, or whether the bar was set just a little too high.

"To that point I had only understood the significance of budget impasse in theoretical terms," she says. "It was the first time a congressional situation became very personal." That winter *Nature* published her op-ed on the subject. "What makes the crucial difference for me," she wrote, "is tremendous support from my department and colleagues."

In those early months of 2009, Borghesi, now associate professor of immunology at Pitt, was among a handful of researchers chosen to receive bridge funding—a short-term grant from Pitt meant to "bridge" lapses in funding from external sources. Half of each award is allocated by Arthur S. Levine, an MD senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the School of Medicine. The other half is allocated by the investigator's department. Funding is based on availability and totals an average of between $1.5 and $2 million per year.

"[The program] was created in response to increased difficulty in acquiring external funding," says Michelle Broido, a PhD and associate vice chancellor for biomedical research for the health sciences. "In particular, applications that did very well in peer review, that in previous years would likely have been funded, were not being funded."

Here's how it works: NIH money goes to applicants who score within a certain top percentile after peer review. The exact percentage of funded applications—called "the payline"—is determined by budget. When the budget dips, the payline gets lower. In the 2013 fiscal year, the payline at many of the institutes hovered just above or in the single digits. In this way, budgetary decision making at the federal level always affects the greater scientific community. But current politics are unprecedented, forcing a funding scarcity and leaving the careers of both junior and established researchers victims of bad timing.

For the past decade, the NIH's budget has been shrinking. Since it peaked in 2004, small increases in funding have failed to meet the pace of inflation. This alone shriveled the agency's spending power by some 20 percent. Then the 2013 sequester took hold, slashing an additional $1.55 billion—or 5 percent at each of the 27 institutes. The NIH turned away patients from its own clinical trials and shelved projects exploring ways to use stem cells to cure Parkinson's disease, manage pain in sickle cell disease, and diagnose autism sooner.

In such a funding climate, bridge funding is popping up at more research universities across the country as one of the best, if most temporary, options for helping investigators make do. In 2013, the Association of American Medical Colleges surveyed 123 medical schools nationwide. Of the 74 institutions that responded, 91 percent had formal bridge funding policies in place, according to an analysis published by the AAMC in February.

The Pitt program, then, isn't novel. But it is one of the longest running, administrators having been quick to recognize the power of such a mechanism to help researchers. "Ours was one of the first if not *the* first," says Broido of the program, which began in 2006. Already, nearly $8 million in bridge funding has supported Pitt investigators in maintaining the groundwork that sometimes takes years of labor and significant funding to develop, even before the innovative work can be begin. Costs might involve keeping trained staff on the payroll, making sure selectively bred mice stay alive, and procuring the necessary supplies for day-to-day lab work.

For researchers interested in applying, Broido is the gatekeeper. She is the first person prospective applicants speak with about whether or not they are a good fit and likely to qualify. She also oversees the review committee, made up of faculty within the schools of the health sciences. In three application periods per year, this anonymous group of established investigators considers which researchers deserve bridge funding and how much they should receive. Applicants are considered in five separate categories, each with distinct criteria. There's no set minimum or maximum monetary amount for the award, Broido says, but rather a constant consideration of the question: "Are these the monies really needed to prevent things from falling apart?"

Derek Molliver, a PhD and assistant professor of medicine, joined Pitt as a research associate in 2002 and was able to secure his first R01 relatively quickly. The young scientist led a small team studying the role of the peripheral nervous system in chronic pain. Early on, they discovered a new class of receptors in sensory neurons—called the P2Y family—that Molliver felt could be important in sensing and transmitting pain. The team wanted to characterize the receptors' function. If they could figure out how the receptors were involved, perhaps they could disrupt function and ease pain. But there was a great deal of digging to be done.

Throughout the course of a multiyear grant, the team amassed data, published papers, and

succeeded in expanding the basic knowledge of the subject. "But then my renewal didn't go through," says Molliver. In 2012, he had a lapse in funding. "The application got a fairly low impact score, which is sort of the kiss of death," he says.

One of the key discussions Broido has with researchers interested in bridge funding explores why the application wasn't funded in the first place. "Consider this," says Broido. "Somebody proposes something. It's a good question. The person has the expertise to do it and the facilities to do it, but one experimental component is fatally flawed. The reviewer is going to think, *No*, and the score will not be good." Contrast this with the case in which reviewers judge the potential impact of the work to be low. The study is sound experimentally, but is it really the best use of money? The reviewer is going to think, *No*, and the score will not be good.

"You can have the same poor score with two different meanings," says Broido. "In determining whether or not to apply for bridge funding, the difference between the two is important." Bridge funding is only awarded to those projects that have a reasonable expectation of receiving external funding within two years. "Otherwise there's no point," says Broido, "because you'd be building a bridge to nowhere."

Molliver's application, with its low impact score, was not eligible for bridge funds.

But he bounced back quickly. "Once we got those criticisms, we retooled," he says. During the course of their previous research, Molliver and his team had uncovered something exciting. "There was a related family of receptors that were potentially analgesic," he says. The receptors they studied initially were helping to transmit pain signals, but this related subset actually seemed to be blocking them. "So we started looking at how we could harness those potentially analgesic receptors to treat persistent pain."

He resubmitted a brand new R01—"a much stronger application," he says—and though the application still fell outside the payline on first attempt, the impact score was higher. This time, he qualified for bridge funding and received $32,000 to support the lab while he revised the application to include additional preliminary data. He subsequently garnered a $750,000 R01 to fund his lab through 2017.

Young researchers, historically, compete not only with one another but also against long-standing labs and investigators with established track records. In her op-ed in *Nature*, Borghesi wrote about "the trend that has raised the average age of first funding from 37 in 1980 to 42 in 2007." To combat the numbers, the NIH in recent years began funding a slightly wider payline for "new investigators"—those who have not previously achieved federal funding as principal investigator or program director on a project—and asked that review committees put less emphasis on their track records and preliminary data in favor of their overall approaches. Consequently, from 2006 to 2010, the number of new investigators receiving competing R01s increased. Still, the average age at first award has not lowered. In 2009, just before receiving her first R01, Borghesi wrote, "My age? 39. My optimism? High, reflecting a supportive university environment."

Both Borghesi's and Molliver's cases involved awards that helped preserve the career paths for tenure-track investigators who experience a delay or lapse in funding.

Although bridge funding has surely been a strong source of support for young researchers at Pitt, this was never the sole intention of the program. "No, in many ways the original focus of bridge funding was for people who had funded projects, who applied for renewal funding and, as they say, came close but didn't get the cigar," says Broido. "People who have had 20 years of continuous funding are having problems, and that's a direct function of money being cut."

Enter Pitt's Category Two, wherein established tenured or tenure-track investigators can apply for funding to continue projects that have been ongoing for years, or even decades. Near the close of one funding period, several applicants' renewals were unexpectedly denied.

Janet Lee, an MD associate professor of medicine, was among them. She uses an animal model to study mechanisms related to injury and repair in the lungs.

"We actually don't know a lot about lung injury. We know when it happens to patients, but we don't exactly understand the process," she says, noting that the work is important for treating a number of conditions, including pneumonia, pancreatitis, sepsis from aspiration, and even fibrosis.

In 2011 she was several years into a five-year R01. "I remember trying to prepare for the worst," she says of the period before her renewal was due. She watched the NIH payline tick up and down, dipping as low as 6 percent at her funding organization, the National Heart, Lung, and Blood Institute. She looked at what she was spending and proactively made adjustments, creating for herself what's called a "no-cost extension," which essentially allowed her additional time to use the funding she saved by operating frugally. She bred fewer lines of mice, purchased only essential reagents, and left a lab staff position unfilled.

"I wanted to calibrate my spending so that I knew I had enough money to keep going for a while. Not forever."

It was a prescient move. Lee's renewal fell below the NIH payline, yet her score was close enough to qualify for $50,000 in bridge funding from Dean Levine and an equal amount from her department. Combined with her own frugality, it was enough to support key personnel and maintain animals until her R01 was successfully renewed in the following cycle.

While Lee's effort to calibrate spending is perhaps a useful exercise, it's also emblematic of a time-consuming—and some might say all-consuming—new pressure that diverts scientists' attention away from their work and toward the bottom line.

"It's a second job to look for research money," says Bruce Rollman, a tenured MD professor of medicine and 2011 bridge fund recipient. Rollman has conducted NIH-funded clinical trials for treating mood and anxiety disorders in primary care and cardiac settings for more than two decades. Yet in

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2010, while successfully completing two trials—including one published in the *Journal of the American Medical Association* in 2009—he found himself suddenly unable to secure new NIH grants.

As a result, Rollman had to lay off most of his staff, some of whom had worked with him for a decade or longer. "I was able to network with colleagues to find everyone new positions," he says. Nobody was left unemployed, but Rollman found himself "in a near-death experience as a clinical investigator." Since then, he has won nearly $10 million for two new R01 trials—one testing the effectiveness of an Internet support group to treat depression and anxiety in primary care and another testing the efficacy of a "blended" model for treating depression and heart failure together. Yet climbing out of the deep hole wasn't easy.

What really helped Rollman continue—he insists—was a small but critical boost he received through Pitt's bridge funding program. Those funds allowed him to retain his project coordinator (who had been with him for 11 years) as well as a statistician and a graduate student data analyst. This small team continued to write and publish data from completed trials while Rollman focused on new grant applications.

His clinical research team is now eight people strong, he says, and will double in 2014.

Perhaps the most basic idea underlying the power of bridge funding is that a small investment today can lead to a bigger award in the future. At Pitt, it's estimated that at least 70 percent of bridge awards lead to subsequent funding, says Broido, who notes that this figure doesn't include funds received through private foundations and other non-NIH sources and is likely low. The AAMC analysis also underscores the amplification effect. For the several schools that made data available, bridge funding led, on average, to nearly 12 times the amount in external funding.

Take, for instance, the experience of Pitt's Gregg Homanics, PhD professor of anesthesiology, who in the winter of 2009 was getting the sinking feeling that he was living a researcher's version of *Groundhog Day*.

"I was really frustrated," he says, "I had a grant that we made a lot of progress on a few years prior. It was a long-standing grant, it didn't get renewed, and I had to give up the work. I was afraid the same thing was going to happen with this project." In 2009 he failed to renew a second R01 on a project he'd pursued for 14 years.

The work sought to study the molecular effects of alcohol in the brain. Despite alcohol being the most widely used and abused drug, the mechanisms underlying alcohol-induced behavioral changes remain largely unknown, says Homanics. His project uses two approaches in genetically altered mice. One investigates the role of a common type of brain receptor called GABAA in affecting behavioral change through alcohol use. The other explores epigenetic effects—those that are genetically inheritable that affect gene expression—in the presence of alcohol in the brain.

Through a total of $20,000 in Category Two bridge funding—"a small drop in the bucket," says Homanics—he leveraged approximately $4.7 million in research dollars over 10 years in the form of a prestigious NIH MERIT (Method to Extend Research in Time) Award. "We asked for five years of funding, but they said, 'We like this so much, we're going to give you ten years of funding,'" says Homanics, who is funded through the National Institute on Alcohol Abuse and Alcoholism.

In a passage on its Web site, the NIH characterizes the MERIT Award for researchers as intended "to foster their continued creativity" and "spare them some of the administrative burdens" of grant applications.

For the bulk of his career, Greg Siegle, a PhD associate professor of psychiatry, accepted that when people get depressed or anxious, they become very reactive. "Their brains react strongly to emotional information, and they keep reacting," he says.

But three years ago, he and collaborator Wendy D'Andrea at the New School in New York City began wondering about the opposite end of the spectrum—whether people with various psychiatric disorders might shut down or stop processing emotional information altogether. Once they opened their eyes to the possibility, it was everywhere they looked.

"It was like realizing I was looking at only half an elephant for the past 20 years," Siegle says. "It was not just a slightly broader perspective as much as an entire retrenching of my theoretical, methodological, and analytical platform."

While the other bridge-funding groupings support scientists at career stages either early or advanced, Category Three bolsters investigators who, in some way, find themselves at the nexus of both. "We recognized that there were established investigators who wanted to change their research direction," says Broido.

Siegle and D'Andrea launched an R01 project to scan the brains of people in various diagnostic categories—including PTSD, anxiety, depression, and borderline personality disorder—and characterize the results. When the grant was not funded initially, strong support from his department—including chair David Lewis and assistant director of research Hermi Woodward—helped Siegle secure $60,000 in bridge funding and ultimately find R01 funding success.

Departmental support and a letter from the chair are must-haves in any bridge application, as the department funds half of any award that is made. For Siegle, it underscored the idea that being a medical researcher is not at all like having a job without a net. "The idea that the school offers bridge funding says that it cares enough to keep its faculty, even when they're down on their luck a little bit," he says. "And that conceptual support is huge."

Bridge funding is a support system that continues to evolve. Broido and her colleagues create new categories as they watch needs arise. There is a fourth grouping for scientists who officially earned funding but experience delays getting the money. And a fifth that's investigator-based and awarded, albeit rarely, on the basis of track record.

This fall, Broido and her team explored how Pitt scientists were affected by the 16-day government shutdown, asking, *How might bridge awards accommodate them?* Happily, they found that Pitt scientists had survived the shutdown—which occurred just after the September application period closed—unscathed, though they remain on the lookout for less positive scenarios.

Borghesi herself is unsure how things will go for her lab this time.

She has a second grant in the works—a smaller R21 that received promising initial scores from reviewers. But no matter where the payline falls, she knows how she'll react.

"The difference is I don't take it personally. Before, I took it as a reflection on my scientific competence. Now, I understand that this is the status quo." It's happening to everyone, she says. And the best thing investigators can do for themselves, their students, and their universities is to maintain enthusiasm for the work itself, to "keep focus and try to drive good science." ■