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[Home](#) » [December 14, 2009 Issue](#) » [Government & Policy](#) » Spurring Innovation

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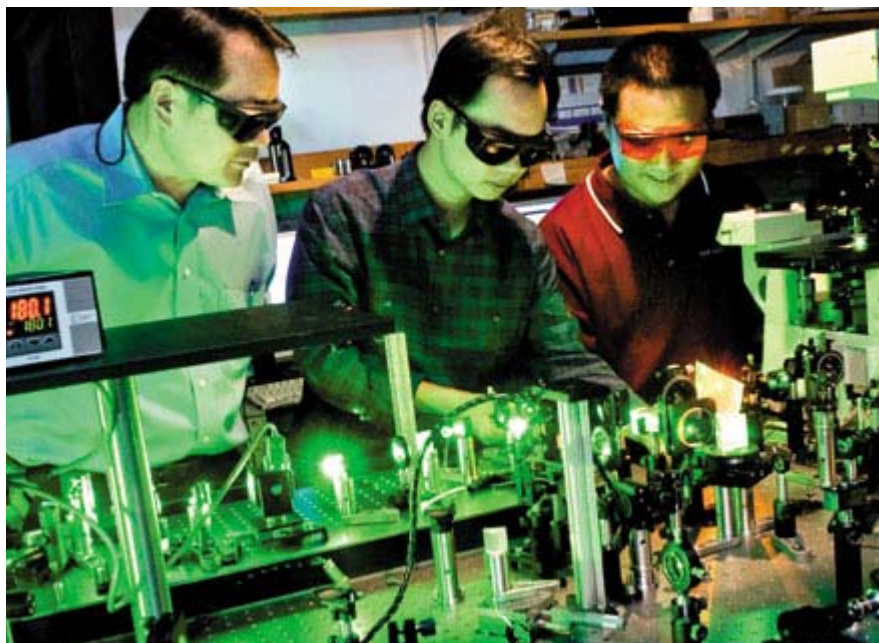
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Spurring Innovation

Federal agencies try new ways to encourage transformative research, but funding remains scarce

[Britt E. Erickson](#)



Marcus Halevi

TAKING RISKS Xie (from left), postdoc Wei Min, and graduate student Sijia Lu explore imaging of single molecules with undetectable fluorescence using stimulated emission microscopy.



Newscom

SPEAKING OUT Lane (left) emphasizes the need for more federal funds to support high-risk, high-reward research during an October hearing of a subcommittee of the House Science & Technology Committee.



Berg



Echegoyen

Peter Cutts Photography (Both)

Harvard University biophysical chemist and spectroscopist [X. Sunney Xie](#) was really worried last year, knowing that his prestigious five-year Pioneer Award from the [National Institutes of Health](#) was set to run out this fall. The award gave him the freedom to be creative and probe gene expression in a living cell one molecule at a time—an idea that would not have been funded by traditional grants. “This experience has changed the way I do science,” he says.

Xie and other scientists who work on high-risk, high-impact research often have ideas that are too “outside the box” for traditional funding mechanisms. As a result, potentially transformative projects that could help solve some of society’s biggest challenges never get explored.

Fortunately, Xie doesn’t have to figure out how to make his cutting-edge work fit into traditional grant programs, at least for the time being. In late October, he was selected to receive a grant from NIH’s new Transformative Research Projects Program (T-R01). The funding will allow his group to pursue ultrasensitive and label-free nonlinear optical imaging of living cells in real time—work that seemed impossible just a few years ago.

But awards such as the ones Xie received are highly competitive and in short supply. And although federal agencies, including NIH and the [National Science Foundation](#), have recently ramped up efforts to encourage more innovative or high-risk research, such investments represent just a tiny fraction of each agency’s research budget.

In fiscal 2009, NIH spent about \$201 million on a combination of high-risk research programs. That amount represents just 0.7% of NIH’s total research budget. Likewise, NSF spent less than 1% of its research budget on high-risk research.

Those numbers are expected to slightly rise in 2010, in part because of the American Reinvestment & Recovery Act (ARRA). NSF Director Arden L. Bement Jr. has pledged to give increased priority to high-risk, high-payoff research when awarding ARRA funds. In addition, the proposed NSF fiscal 2010 budget provides \$92 million (a minimum of \$2 million for each division) to help support potentially transformative research.

Some of NIH’s high-risk research programs have already received a boost thanks to ARRA funds. For example, \$23 million was added to the agency’s New Innovator Award Program, bringing its total funding to \$131 million for 2009. The program targets highly innovative, early-stage investigators. But these increases still fall short of what many experts say is needed.

Each agency has a different approach to funding high-risk research, and there is no agreement on what exactly high-risk means. As a result, some programs are highly competitive, but others lack participation.

All of the NIH high-risk research programs have received strong responses, says Jeremy M. Berg, director of the [National Institute of General Medical Sciences](#) (NIGMS). NIH's portfolio in this area includes the T-R01s, the New Innovator Awards, and the Pioneer Awards. The New Innovator and Pioneer Awards support exceptionally creative scientists who propose pioneering or transforming approaches to major challenges in biomedical research. These awards focus more on funding people, whereas the T-R01s focus more on their ideas.

Each year, there are about 400–500 applications for about 15 Pioneer Awards, notes Berg, who currently oversees the selection process for those awards. The New Innovator Awards and the T-R01s are also very competitive, he says. For example, in the first year of the New Innovator Awards, NIH received about 2,300 applications for only 29 awards.

In contrast, NSF isn't getting large numbers of high-risk, potentially transformative proposals, according to Luis Echegoyen, head of the NSF Chemistry Division. "The success rates are actually quite high," he says, referring to NSF's Small Grants for Exploratory Research (SGER). The program was created more than a decade ago as NSF's primary vehicle for funding high-risk research. But it did not have a lot of participation.

In fiscal 2008, NSF awarded 389 SGER grants from a pool of 438 applicants, resulting in an 89% success rate. That year, NSF spent about \$34.2 million on SGER grants, or 0.6% of its research budget.

SGER was split into two programs in January: the [Early-Concept Grants for Exploratory Research](#) (EAGER) and the Grants for Rapid Response Research (RAPID). The change was intended to draw more attention to NSF's high-risk research program and to reflect that the grants are bigger than they used to be. EAGER grants can be up to \$300,000 over one or two years. RAPID grants can be up to \$200,000 for one year and are awarded for urgent research, such as that needed immediately after a natural disaster.

But NSF's awards for potentially transformative research are still small compared with those from NIH. For example, NIH's Pioneers receive \$500,000 per year for five years, and New Innovators get \$300,000 per year for five years. NIH's T-R01 grants are completely open-ended, meaning applicants can ask for however much money they think they will need to address the problem, Berg notes.

In 2009, NIH invested approximately 30% of its Common Fund, or about \$159 million, on its three flagship high-risk research programs—the Pioneer, New Innovator, and T-R01 Awards, according to Elizabeth L. Wilder, deputy director of NIH's Office of Strategic Coordination.

Wilder works within the office of the NIH director to coordinate activities that relate to the Common Fund, a pool of money that is used to support programs that cut across the missions of the various NIH institutes and centers. In 2009, the Common Fund was approximately \$530 million, 1.7% of the NIH budget.

In addition to its flagship programs, NIH also has some smaller high-risk research efforts, such as the Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA) programs, developed by NIGMS and launched in 2007.

EUREKA awardees receive about \$200,000 per year for up to four years. The program was developed because of concerns about another mechanism for funding high-risk research called the Exploratory/Development Research Grant Program (R21), Berg says.

The level of funding for an R21 grant was about \$150,000 over two years, Berg says. "It wasn't enough money to do something that was really hard. It was a little bit too small," he notes, adding that "it was the low-risk approach to high-risk" research.

The situation changed this year when NIH awarded \$42.2 million in EUREKA grants and boosted EUREKA funding to \$67.4 million for 2010. The gain was in part due to \$10.6 million in stimulus money. Nine institutes across NIH, including NIGMS, now participate in the program, Berg says.

Another difference between NIH and NSF is their approach to peer review for high-risk research. At NIH, reviewers are picked for their ability to show judgment over a broad range of scientific areas. "The matching of

expertise is much, much looser” than with a normal NIH peer review, Berg notes. “The intent is really to have something that’s sufficiently compelling as a problem that somebody outside your field could appreciate it.”

At NSF, grant proposals to the EAGER program, like its predecessor SGER, are reviewed in-house by NSF staff. The decision not to use outside peer review was in response “to some people in the community not wanting to share their most significant and potentially transformative ideas with reviewers,” Echegoyen tells C&EN.

Neither NIH nor NSF requires preliminary data for high-risk research proposals. Applicants, however, do have to show the intellectual feasibility of their ideas, the agencies say.

“High-risk, high-reward research is needed to maintain the U.S. position of leadership in science and technology.”

The lack of NSF funding for high-risk research has caught the attention of Congress and the scientific community. In response to the concerns that NSF is too conservative in its funding decisions, NSF began encouraging each division to use up to 5% of its budget to fund potentially transformative research. “Consistently we don’t even make it to 0.5%,” Echegoyen says, referring to the Chemistry Division. “It’s a great mechanism, and it’s underused tremendously.”

The reason why NSF’s Chemistry Division doesn’t fund more in this area is because it isn’t receiving enough proposals, Echegoyen emphasizes. “NSF is very interested in identifying and funding high-risk and potentially transformative research.”

Many researchers, however, have the perception that it is very difficult to get proposals funded, particularly by NSF, if they are not in the mainstream. “We’ve had projects like ubiquitous sensors for safety monitoring of bridges, buildings, and water infrastructure. Every proposal to NSF has been returned as too high risk,” says [Richard D. McCullough](#), vice president for research and a professor of chemistry at Carnegie Mellon University.

At a hearing in October of a subcommittee of the [House of Representatives Science & Technology Committee](#), McCullough encouraged Congress to increase federal funding for high-risk, high-reward research. He provided numerous examples of innovative projects at Carnegie Mellon that have not been able to get federal funds, including work in green chemistry. He pointed out that he and other investigators have had to turn to private foundations and the university to get some projects funded.

Congress held the hearing to address how much money federal agencies should spend on high-risk research as it prepares to reauthorize the America Competes Act in 2010. That bill grew out of a 2006 National Academies report called “Rising Above the Gathering Storm: Energizing and Employing America for a Brighter Economic Future.” The America Competes Act addressed nearly all of the recommendations in the report, except the recommendation that each federal research agency set aside 8% of its budget for high-risk, high-payoff research.

That recommendation came up again in 2008 in a report called “ARISE: Advancing Research In Science & Engineering” by the [American Academy of Arts & Sciences](#) ([C&EN, June 16, 2008, page 44](#)). “High-risk, high-reward research is needed to maintain the U.S. position of leadership in science and technology and to ensure the nation’s future economic competitiveness,” [Neal F. Lane](#), a professor and senior fellow of the James A. Baker III Institute for Public Policy at Rice University, testified at the October hearing on behalf of the academy.

Other investigators don’t think more investment in this area is needed, particularly because some of the grants have been awarded for controversial projects ([see page 32](#)). “I think we need to fund what we already have out there,” says [Alan P. Kozikowski](#), a medicinal chemist at the University of Illinois, Chicago. Kozikowski is trying to find cures for Alzheimer’s disease and other neurodegenerative diseases. “I have compounds in the clinic,” he tells C&EN, adding that to him this clinical research is high risk, even though it isn’t funded that way.

Part of the problem is that there is no definition for high-risk, high-reward research. McCullough and others have suggested that federal agencies clarify the difference between high-risk, high-reward research and basic research. But McCullough notes two caveats: Scientists and engineers “rarely think of their ideas initially as high reward or transformative, and many scientific discoveries occur in basic science and are even accidental and then become transformative.”

One area that tends to do better than average in acquiring funding from high-risk research programs is technology development, Berg tells C&EN. And that's because new technologies often impact multiple fields. Part of the criteria for selecting high-risk research projects is whether they are likely to have a big impact, he says.

[Shohei Koide](#), a biochemistry and molecular biophysics professor at the University of Chicago, received a T-R01 this year to develop technology for generating reagents to detect and capture protein targets in complex biological samples. He emphasizes that he is "very encouraged by NIH's recognition of the importance of technology development." All too often, biomedical research is technology limited, he says. "The development of powerful technology can enable unprecedented research that leads to new knowledge and new medical strategies."

In many cases, awards for technology development are considered high risk because it is not clear that the applicants understand the biological problems as well as they need to in order to pass a normal NIH peer review, Berg says. "On the other hand, they are smart, accomplished people in strong places, and if they build the technologies that they are planning to, they can make measurements and develop collaborations that can have a huge impact."

Pioneers such as Xie know about that problem firsthand. When Xie moved from Pacific Northwest National Laboratory (PNNL) to Harvard 10 years ago, one of the first things he had to do was learn molecular biology.

At PNNL, Xie helped develop room-temperature, single-molecule imaging and spectroscopy and pioneered the field of single-molecule enzymology. When he moved to Harvard, he wanted to apply the technique to living cells to study fundamental biological processes such as transcription and translation in real time on a single-molecule basis. To get up to speed on the biology, he audited a molecular biology course with his students.

In general, chemists such as Xie have done quite well in getting high-risk research awards, Berg notes. Out of 42 T-R01 recipients this year, about a dozen are members of the American Chemical Society. C&EN contacted them to learn more about what they plan to do with the money.

All of those who responded tell C&EN that it would have been difficult to get funding for their projects through a traditional grant mechanism because they lack preliminary data to show proof of concept.

[Loren D. Walensky](#) of Dana-Farber Cancer Institute says he plans to use his T-R01 grant "to support the development of a new high-throughput technology to expand our ability to identify protein targets and their sites of interaction relevant in human disease." Identifying protein interactions is important for discovering biological pathways, disease mechanisms, and opportunities for new therapeutics, he notes. It is challenging, however, because "protein interactions mediate innumerable cellular activities in health and disease," he says.

Along the same lines, [Julio Camarero](#) of the University of Southern California School of Pharmacy says he will use his T-R01 grant to develop a "new generation of specific protein-capture reagents for diagnostic or therapeutic purposes." Camarero's group plans to use cell-based libraries of cyclotides (microproteins that have unique properties) to select specific cyclotide sequences against particular protein targets, "somehow mimicking what our immune system does with antibodies," he says.

Xie plans to pursue an equally challenging project with his T-R01: label-free optical imaging of living cells in real time. He admits that he's always been fond of taking risks. But the real gratification for him is seeing the success of his students who take risks with him, he says. "For students, this is a very special experience."

More On This Story

- [Spurring Innovation](#)
- [Watering Down Science?](#)

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