INNOVATIVE TECHNOLOGY DEVELOPMENT

Thinking Outside the Box: Fostering Innovation and Non–Hypothesis-Driven Research at NIH

Richard Aragon

The National Institutes of Health (NIH) has long been known as an institution that supports biomedical advances through hypothesis-driven research. Another aspect of NIH, however, has received comparatively little attention and may be critical to advancing translational science beyond its current limitations. Specifically, this aspect of NIH focuses on supporting innovation through the development of high-risk technologies that have the potential to empower research.

A NEW FUNDING PARADIGM EMERGES: NON–HYPOTHESIS-DRIVEN RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH

In 1998, the National Cancer Institute (NCI) established the groundwork for what was to become a highly successful, cooperative program to meet the specific needs of cancer researchers and clinicians by stimulating the next generation of research-enabling, multidisciplinary technologies for studying cancer. Rather than being averse to the type of risk that is often viewed as potentially detrimental to scientific funding, the Innovative Molecular Analysis Technologies (IMAT) program solicited only the most cutting-edge ideas despite their risk, thus restricting its application pool to those projects that were risky but that also had the potential to be truly transformative if successful. Unlike other programs at the National Institutes of Health (NIH) during the time of its establishment, IMAT did not support traditional hypothesis-driven research but rather the development of technologies that could potentially catalyze and empower the type of research usually supported by R01 research project grants. In supporting such projects, IMAT provided a "home" to applications containing ideas that might not have fared well in traditional study sections because of the inherent risks associated with the lack of preliminary or feasibility data that usually accompany high-risk applications. For an institution such as NIH, this type of support might seem rather surprising and perhaps even out of place. Yet, such programs form an important part of a comprehensive national portfolio designed to support all aspects of translational science, including the type of creative thinking and calculated risk-taking that is necessary to advance translational research. Further, in establishing IMAT the NCI maintained the most integral aspect of R01 research: support for the individual investigator. By using two investigator-initiated support mechanisms (the R21 and R33 research project grants), IMAT hybridized investigator-initiated funding with a focus on innovation and high-risk technology development, thus filling a void that no other program at NCI or NIH addressed (Fig. 1).

Recognizing the need for an appropriate review process that took into consideration the high-risk but also potential high-payoff nature associated with most highly innovative ideas, the NCI established special review bodies known as Special Emphasis Panels (SEPs), composed of individuals from both academia and industry, to thoroughly review all applications submitted to each IMAT Request For Applications (RFA). Unlike traditional review panels, SEPs were synthesized on somewhat of an ad hoc basis according to the nature, type, and subject matter of applications received for any given cycle of review. It was thus not unusual to have engineers, mathematicians, statisticians, biologists, chemists, industrial experts, and clinicians all sitting across from one another as they individually and collectively evaluated non–hypothesis-driven, technology-centric applications submitted to the NCI under the auspices of the IMAT program. Taking into consideration the rapid pace and momentum with which

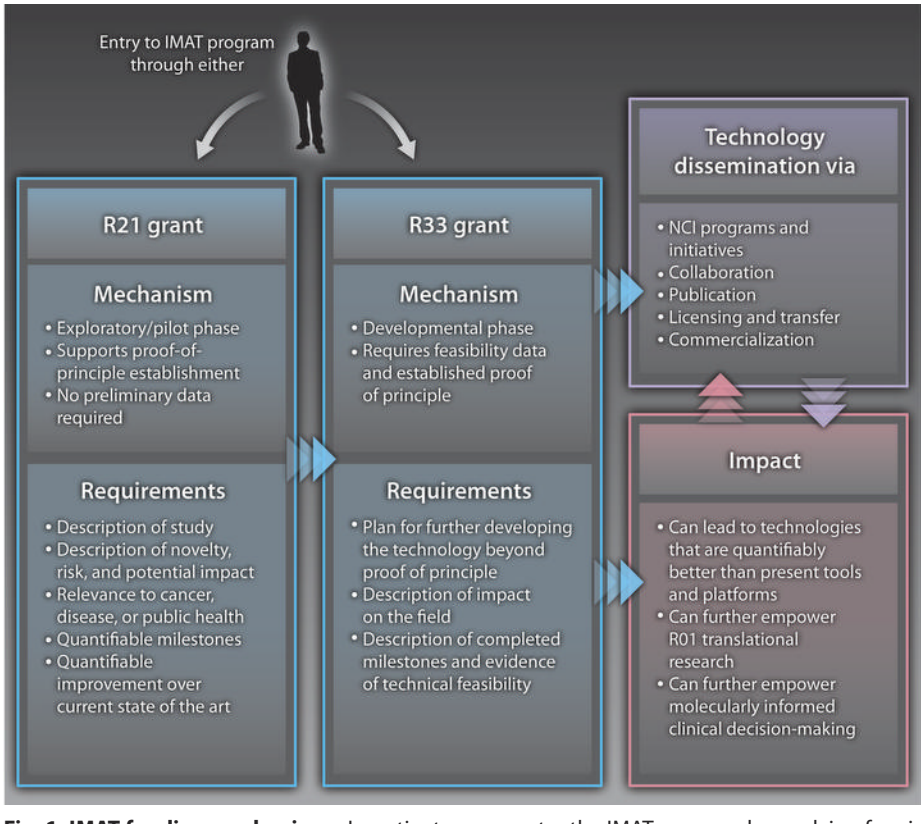

Fig. 1. IMAT funding mechanisms. Investigators can enter the IMAT program by applying for either an R21 or an R33 grant.

Office of Biorepositories and Biospecimen Research, Center for Strategic Scientific Initiatives, Office of the Director, National Cancer Institute, Bethesda, MD 20892, USA. Corresponding author. E-mail: Richard.Aragon@hhs.gov

technology progresses, the NCI structured three receipt dates per year into each of its IMAT RFAs, thus allowing no more than 4 months to elapse before soliciting the next round of proposals containing highly innovative ideas.

The establishment of the IMAT program represented a milestone for NIH because it reflected a new way of thinking and conducting science that is at least as important today—if not more so—than it was in 1998. It represented a shift away from the traditional paradigm of hypothesis-driven research but kept the individual investigator-initiated focus that NIH has historically and traditionally supported. It brought together individuals from multiple and historically disparate communities, institutions, and organizations in order to focus their collective efforts on the most pressing and common technical barriers that impede biomedical research. In an attempt to support solutions to these common technical barriers, it supported the development and subsequent dissemination of quantitatively better tools, devices, and technologies that represented a substantial improvement over the current state of the art and that were applicable to multiple fields of science rather than just a single field, discipline, or disease. In the evaluation of applications for a program of this sort, NIH created a review process that was flexible enough to adapt to the changing landscape of translational science and technology while also providing a venue for dialogue and communication between individuals of historically disparate disciplines.

FUNDING INNOVATIVE TECHNOLOGY RESEARCH: WHAT HAVE WE LEARNED AND WHAT HAVE WE GOTTEN BACK?

Einstein was once thought to have observed that "the significant problems we face cannot be solved at the same level of thinking we were at when we created them" (*1*). The approach used by the NCI in the establishment of programs like IMAT highlights the continuing need for new, creative, and out-of-the-box ways of thinking and problem solving that are cooperative, geared toward tackling common technical barriers to translational progress, and centered on the belief that the ultimate source of innovation and invention lies not with organizations or infrastructure but rather with the people that compose them, with individual investigators, clinicians, technologists, and engineers.

Throughout its 12-year history, IMAT has not only funded creative ideas but in so doing has also created the means by which to effectively translate ever-increasing and seemingly diverse bodies of knowledge into better instruments, tools, platforms, technologies, and the physical means by which cancer research and treatment can be demonstrably and quantifiably improved. The accumulation of knowledge alone, although important, is relatively meaningless without the accompanying support mechanisms by which to translate that knowledge into new, more effective implements that have the capability of both contributing to and capitalizing on newly acquired insights and ultimately improving individual health outcomes. To this end, the amount of investment made in new, first-time (noncontinuing) awards by IMAT has increased from $7 million per year in 2004 to $10.5 million per year in 2010. The average award size has ranged from approximately $275,000 in direct costs for smaller, proof-of-principle establishment awards to well over $500,000 in direct costs for more advanced projects. Success rates for the acquisition of such awards have, on average, paralleled the success rates for the acquisition of traditional R01 research project grants for any given year, a not-at-all surprising statistic in light of the fact that one of the stated aims of programs like IMAT is to catalyze R01 research through the development and dissemination of quantifiably better research tools and technologies. Further, the program supports an average of 75 to 100 individual investigators at any given time, with approximately one-third of the program's portfolio traditionally consisting of new or first-time investigators.

What proof exists that this type of approach works? One metric by which to answer such a question involves examining specific and quantifiable outputs. By taking risks on potentially transformative technologies, IMAT has contributed to many of the technologies that are now in almost ubiquitous use across the cancer research and clinical communities. Successfully commercialized products such as RNALater, Affymetrix gene chips, Illumina bead platforms, and Quantum dot labeling technology were all considered high-risk ideas at the time of their inception and initial funding. Yet, their current widespread use and applicability to multiple clinical and basic sciences settings are a testament to the high pay-off (both financially and biomedically) and impact that such transformative technologies have had on the field of cancer research. By soliciting and supporting these otherwise risky ideas and technologies through programs like IMAT, the NCI and NIH have not only supported the development of these new transformative technologies per se but also supported them in a manner consistent with investigator-initiated funding and with providing the research community rapid access to such platforms through appropriate commercialization and dissemination. NIH has thus taken risks to substantiate the ultimate value and utility of such technologies even in cases in which venture capital firms might have been reluctant to do so because of the inherent risks associated with highly innovative technology development, particularly in light of the current economic climate. It should be noted that funding of non–hypothesis-driven research does not equate to the diminishment of support for hypothesis-driven research but rather an empowerment thereof, particularly if such research is supported by investigator-initiated means.

IS INNOVATION STILL NECESSARY?

Currently, there are new challenges facing cancer researchers and clinicians and, as such, the need for innovative thinking has never been greater. Challenges represented by the need to comprehensively assess all of the epigenetic changes in single cells, collecting rare cells from the blood of patients with chronic disease, optimizing the use of clinical biospecimens for fit-for-purpose analysis, and understanding the physical mechanics associated with disease progression all require creative thinking and calculated risk-taking to enable and empower research in a manner similar to the way in which gene expression profiling is currently enabled. Through programs like IMAT, NIH seeks to meet this challenge by the following means:

(i) Empowering individual investigators and small commercial entities to think creatively,

(ii) Encouraging technologists and engineers to partner with biologists and clinicians who face similar or common technical challenges, and

(iii) Taking the risks necessary to overcome common and pressing technical barriers that currently impede translational progress, effective research, and informed clinical decision-making.

By meeting these specific goals, NIH seeks to stimulate progress in the field of translational research at a pace that is revo-

lutionary rather than evolutionary or incremental and to ensure the adequate, fair, and equal dissemination of knowledge and resources that stem from such an approach.

Two recent examples that illustrate the efficacy of this type of approach are reflective of areas that are often left comparatively unaddressed by conventional funding paradigms: the commercialization of university technologies and the provision of seed capital to small start-ups.

Microfluidic Genetic Analysis (MGA) Technology, developed by James Landers, a 2006 R33 IMAT grantee from the University of Virginia, is a prime example of how funding for innovative, non–hypothesis-driven, university-based research can stimulate rapid progress in the field of cancer diagnostics. The Association for Laboratory Automation presented Landers with its 2008 Innovation of the Year Award for his new MGA technology. This unique lab-on-a-chip device resembles a common microscope slide but nonetheless houses the analytical tools of an entire laboratory. Vastly complex and distinct procedures take place within millimeters of one another in tiny troughs that are etched into the chip. Minute tissue or blood samples are placed into the chip, and an electric charge is applied to the samples—for electrophoresis—to separate out particular sections of DNA according to what type of diagnosis is needed. Once the DNA of interest is separated, it is replicated on one portion of the chip and then pushed to yet another area to be screened for irregularities. This unique technology may enable the rapid detection of cancer and other infectious diseases in a fraction of the time and cost of current tests, as reflected in the ability of the prototype to detect bacteria-based infections in mice and humans within only 30 min, thus reducing the analysis time by nearly two orders of magnitude (*2*). Landers's MGA work has led to several filed patents on chip-based analysis for both clinical and forensic applications (*3*, *4*). Some of the intellectual property rights associated with this technology have been licensed by MicroLab Diagnostics in Charlottesville, Virginia, which, in partnership with Lockheed Martin Corporation, has begun to scale this technology for more widespread use in the forensic DNA analysis sector, illustrating its applicability to not only cancer but multiple other fields of research as well (*5*).

Microfluidic oil droplet technology is another promising analytical modality and was commercially released by RainDance Technologies in 2009. RainDance, a former start-up company now based in Lexington, Massachusetts, developed a technology that produces uniform picoliter-scale aqueous microdroplets at rates of up to 10 million per hour. Because each droplet is the functional equivalent of an individual test tube containing a single molecule, reaction, or cell, this technology has the capability of substantially improving established cell and molecular assays through quantifiable gains in efficiency, reaction kinetics, and a minimum of process-induced errors. The initial application of the technology provides targeted sequence enrichment to prepare samples for next-generation sequencing. The sequencing depth and reduced amplification bias provided by microdroplet technology enable accurate detection of sequence variants within a heterogeneous mix of sample DNA (*6*). In addition, RainDance has recently extended this approach to enable targeted sequencing of a sample's methylome by using bisulfite-treated templates, providing base-pair resolution of the methylated cytosines that have been associated with aberrant transcription in cancer (*7*). Single-cell droplet technology is thus an exciting and versatile new tool that should allow for more targeted interrogation of specific factors that influence disease pathology, including cellular responses to drugs and other therapeutics. The NCI funded proof-of-concept for this technology by awarding a research project grant to a principal investigator who himself was both a nonbiologist and new investigator at the time of the award. For small start-up concerns having innovative ideas, NIH thus offers a "value proposition" in addition to potential funding opportunities by virtue of its established peer review structure. Scientific validity can be evaluated and obtained by having proposals reviewed under an appropriate NIH system, thus providing additional means by which to recruit supplemental capital for a bright, innovative idea.

INVESTING IN INNOVATION MEANS INVESTING IN PEOPLE

As the above examples illustrate, the successes of programs like IMAT are due in large part to the recognition and belief that the ultimate source of innovation and invention is the individual researcher. Although large, infrastructure-based programs and initiatives have their place, a truly balanced approach to supporting innovative science must, by necessity, include support for individual investigator-initiated research. This by definition includes support for the next generation of scientists and clinicians. This latter group forms not only the historical backbone of translational science in the United States but also its very future. One cannot adequately speak of or address innovation without also addressing the very means by which innovation occurs: the education and training of future and early-career investigators. Investing in innovation thus equates to investing in both research and training because these provide the means through which both critical and creative thinking are stimulated and promoted.

Institutions and organizations have an active and equal role to play in establishing and encouraging the type of environment that promotes, supports, and contributes to innovative science by creating programs and initiatives that reinvest in people and that encourage both meaningful dialogue and collaborative partnerships. This latter function is particularly important in instances in which such partnerships might occur via nontraditional means, that is, internationally and perhaps even between scientists, business leaders, knowledge brokers, and policy-makers. Under its new leadership, NIH has established a number of initiatives and opportunities that have taken concrete steps toward supporting this type of innovative, multidisciplinary paradigm. Some of these initiatives (both within and outside of NIH) and their associated funding opportunities are listed in Table 1. This list is meant to be illustrative rather than all-inclusive.

MOVING FORWARD: THE NEED FOR MORE CONVERGENT APPROACHES TO SCIENCE AND TECHNOLOGY RESEARCH AND DEVELOPMENT

As an institution renowned for its support of investigator-initiated research, NIH has taken concrete steps to bridge the gap between engineers, technologists, clinicians, and biologists and to allow for the integration of highly innovative technologies into the mainstream biomedical community. In doing so, NIH has taken a further step forward toward fulfilling its mission of alleviating disease burden and improving individual health outcomes. Although institutions such as NIH can cultivate the type of environment and mechanisms necessary for the potential of translational medicine to be fully realized, it will still ultimately fall to the individual researcher

Table 1. Cross-section of initiatives and associated funding opportunities to support innovative, multidisciplinary, and nontraditional research.

Bioengineering Research Partnerships In recognizing the importance of bioengineering in public health, NIH developed the Bioengineering Research Partnerships (*8*), Bioengineering Research Grants (*9*), and Exploratory/Developmental Bioenginnering Research Grants (*10*) program announcements. The primary objectives of these programs are to encourage basic, applied, and translational or clinical bioengineering research that could make an important contribution to improving human health. Bioengineering integrates physical, engineering, and computational science principles for the study of biology, medicine, behavior, or health, with the aim of developing innovative biologicals, materials, processes, implants, devices, and informatics approaches for the prevention, diagnosis, and treatment of disease, for patient rehabilitation, and for improving health.
Transformative R01 Awards The Common Fund's NIH Director's Transformative Research Projects Program (*11*) was specifically created to support exceptionally innovative, high-risk, original, and/or unconventional research projects that have the potential to create or overturn fundamental paradigms. These projects tend to be inherently risky but if successful can profoundly affect a broad area of biomedical research. As compared with the other NIH Director's Programs, the Pioneer and New Innovator Awards, the primary emphasis of the Transformative Research Projects Program is on funding creative ideas—providing adequate support for projects that have the potential to transform a field of science—rather than funding creative individuals who have proven themselves to be innovative researchers to go in a new pioneering direction.
NIH Director's Pioneer and New Innovator Awards NIH Director's Pioneer Awards (*12*) are designed to support individual scientists of exceptional creativity who propose pioneering—and possibly transforming—approaches to major challenges in biomedical and behavioral research. The term "pioneering" is used to describe highly innovative approaches that have the potential to produce an unusually high impact on a broad area of biomedical or behavioral research. Biomedical and behavioral research is defined broadly by this initiative as encompassing scientific investigations into the biological, behavioral, clinical, social, physical, chemical, computational, engineering, and mathematical sciences that have the greatest potential to improve the public health. The NIH Director's New Innovator Award Program (*13*) is a high-risk research (*14*) initiative of the larger NIH Common Fund. The research proposed for a New Innovator Award may be in any scientific area relevant to NIH's mission (biological, behavioral, clinical, social, physical, chemical, computational, engineering, and mathematical sciences) and thus need not be in a conventional biomedical or behavioral discipline. The focus is on innovation and potential impact.
EUREKA Awards The EUREKA program funds exceptionally innovative research that if successful will have an unusually high impact. EUREKA targets investigators who are testing new, unconventional hypotheses or are pursuing major methodological or technical challenges. The potential impact of the proposed research must be substantial in terms of both the size of the scientific community affected and the magnitude of its impact on the community. A specific feature of the EUREKA program includes a specialized R01 application focusing on importance and innovation (*15*).
Global Health Initiatives The Fogarty International Center at NIH recently launched the Global Infectious Disease Research Training Program. This collaborative research training program is aimed at strengthening the capacity of institutions in low- and middle-income countries, as defined by the World Bank classification system (*16*), to conduct infectious-disease research training programs focused on major endemic or life-threatening emerging infectious diseases, neglected tropical diseases, widespread co-infections of HIV/AIDS patients, or infections associated with noncommunicable disease conditions of poverty in developing countries (*17*).
Stand Up To Cancer (SU2C) Innovation Awards Although not an NIH-affiliated initiative, SU2C (*18*) awarded its first 13 Innovative Research Grants in December of 2009 to support cutting-edge cancer research that might not receive funding through traditional channels. These Innovative Research Grants support early-career scientists with new ideas characterized by a strong potential to affect patient care, projects that are thus high-risk but that could also potentially be high-impact. In this manner, SU2C supports research similar to that supported by some of the NIH programs described above.
ARPA-E Recognizing the need to reevaluate the way the United States spurs innovation, the National Academies released a 2006 report titled "Rising Above the Gathering Storm" that included the recommendation to establish an Advanced Research Projects Agency (ARPA-E) within the U.S. Department of Energy (*19, 20*). This agency was charged with attracting many of the United States' best and brightest minds—those of experienced scientists and engineers and especially those of students and young researchers, including persons in the entrepreneurial world—to focus on creative "out-of-the-box" transformational energy research that industry by itself cannot or will not support because of its high risk but where success would provide dramatic benefits for the nation, thus creating a new tool to bridge the gap between basic energy research and development and industrial innovation. The current director of the ARPA-E program is in fact a former NCI/NIH IMAT program grantee (*21, 22*).

to put forth the necessary effort to create new perspectives, build new bridges between disciplines, develop new methods of thought and inquiry, and, yes, take the calculated risks when necessary. Future progress in translational science will depend on creating and sustaining a convergent approach to science and technology research and development that draws from multiple disciplines, communities, and institutions within an atmosphere of open communication, collaboration, creativity, and accountability. Tackling such a challenge will by necessity involve a great deal of out-of-the-box thinking.

REFERENCES AND NOTES

1. A. Calaprice, Ed., *The New Quotable Einstein* (Princeton University Press, Princeton, NJ, 2005).
2. C. J. Easley, J. M. Karlinsey, J. M. Bienvenue, L. A. Legendre, M. G. Roper, S. H. Feldman, M. A. Hughes, E. L. Hewlett, T. J. Merkel, J. P. Ferrance, J. P. Landers, A fully integrated microfluidic genetic analysis system with sample-in-answer-out capability. *Proc. Natl. Acad. Sci. U.S.A.* **103**, 19272–19277 (2006).
3. J. M. Bienvenue, N. Duncalf, D. Marchiarullo, J. P. Ferrance, J. P. Landers, Microchip-based cell lysis and DNA extraction from sperm cells for application to forensic analysis. *J. Forensic Sci.* **51**, 266–273 (2006).
4. K. M. Horsman, J. M. Bienvenue, K. R. Blasier, J. P. Landers, Forensic DNA analysis on microfluidic devices: A review. *J. Forensic Sci.* **52**, 784–799 (2007).
5. C. R. Reedy, K. A. Hagan, B. C. Strachan, J. J. Higginson, J. M. Bienvenue, S. A. Greenspoon, J. P. Ferrance, J. P. Landers, Dual-domain microchip-based process for volume reduction solid phase extraction of nucleic acids from

dilute, large volume biological samples. *Anal. Chem.* **82**, 5669–5678 (2010).
6. R. Tewhey, J. B. Warner, M. Nakano, B. Libby, M. Medkova, P. H. David, S. K. Kotsopoulos, M. L. Samuels, J. B. Hutchison, J. W. Larson, E. J. Topol, M. P. Weiner, O. Harismendy, J. Olson, D. R. Link, K. A. Frazer, Microdroplet-based PCR enrichment for large-scale targeted sequencing. *Nat. Biotechnol.* **27**, 1025–1031 (2009).
7. M. Medkova, E. Brouzes, E. Dahan, S. Kotsopoulos, J. Warner, J. Larson, J. Olson, D. Link, M. Samuels, Analyzing cancer at single cell resolution with droplet technology. Poster at the annual meeting of the American Association for Cancer Research, Washington, DC, 17 to 21 April 2010.
8. Bioengineering Research Partnerships (NIH), http://grants.nih.gov/grants/guide/pa-files/PAR-10-234.html.
9. Bioengineering Research Grants (NIH), http://grants.nih.gov/grants/guide/pa-files/PA-07-279.html.
10. Exploratory/Developmental Bioenginnering Research Grants (NIH), http://grants.nih.gov/grants/guide/pa-files/PA-06-418.html.
11. The Common Fund's NIH Director's Transformative Research Projects Program, http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-10-010.html.
12. NIH Director's Pioneer Awards, http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-10-008.html.
13. NIH Director's New Innovator Award Program, http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-10-009.html.
14. http://nihroadmap.nih.gov/highrisk/.
15. EUREKA program (NIH), http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-11-003.html.
16. http://data.worldbank.org/about/country-classifications/country-and-lending-groups.
17. Global Infectious Disease Research Training Program (Fogarty International Center, NIH), http://grants.nih.gov/grants/guide/pa-files/PAR-10-260.html.
18. Stand Up To Cancer, http://www.standup2cancer.org.
19. Advanced Research Projects Agency (Department of Energy), http://arpa-e.energy.gov/.
20. Committee on Science, Engineering, and Public Policy, *Rising Above the Gathering Storm: Energizing and Employing America for a Brighter Economic Future* (National Academies Press, Washington, DC, 2006).
21. A. Majumdar, MEMS as a platform for nanoexploration and nanointegration. *Int. J. Comput. Eng. Sci.* **4**, 189–194 (2003).
22. J. C. Stachowiak, M. Yue, K. Castelino, A. Chakraborty, A. Majumdar, Chemomechanics of surface stresses induced by DNA hybridization. *Langmuir* **22**, 263–268 (2006).
23. **Competing interests:** The author declares that he has no competing interests.

10.1126/scitranslmed.3001742

Citation: R. Aragon, Thinking outside the box: Fostering innovation and non–hypothesis-driven research at NIH. *Sci. Transl. Med.* **3**, 70cm5 (2011).

Science Translational Medicine

Thinking Outside the Box: Fostering Innovation and Non–Hypothesis-Driven Research at NIH

Richard Aragon

Sci Transl Med **3**, 70cm570cm5.
DOI: 10.1126/scitranslmed.3001742

Science Translational Medicine (ISSN 1946-6242) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title *Science Translational Medicine* is a registered trademark of AAAS.