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Repaving the Road to Biomedical Innovation Through Academia

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Abstract

Biomedical innovation requires investigators to build on existing knowledge and achieve insights that are transformative. Innovation starts with incisive scientific discoveries, which are often made in academic research laboratories. Today, the financial model for supporting biomedical research in universities is threatened, and one victim is innovation. New models for public funding that support high-risk research in academia will spur innovation and ultimately advance clinical medicine.

The path to biomedical innovation requires a synthesis of seemingly unrelated observations; in rare instances, this process reveals previously obscure, fundamental truths. Much more commonly, engaging in biological research is like strolling through an art museum. Observation of the works of art on display enables us to acquire incremental bits of knowledge that also can be perceived by others. In contrast, innovation involves a different kind of insight that allows one to see around the corners, visualize connections, and conceive that which has not yet been imagined (Fig. 1). Theoretically, every-thing that exists in biology is knowable; the pieces of the puzzle—the truths—are out there. Innovation requires joining the pieces to solve the puzzle. This Commentary describes ways in which support of truly innovative academic science can enhance the discovery, sculpting, and assembly of these puzzle pieces to advance clinical medicine.

FEAR OF RISK IS RISKY

To paraphrase Justice Potter Stewart, it may be difficult to agree on a definition for innovation in the biological sciences, but we know it when we see it. Classic examples include the germ theory of human disease pioneered by Semmelweis, Lister, Koch, and Pasteur (1); the discovery of antibiotics exemplified by Fleming's work on penicillin (2); and elucidation of the structure of DNA by Watson and Crick using data from Franklin's x-ray diffraction images (3, 4). Many landmark innovations in biomedicine have emerged from academic laboratories. Today, however, the financial model for supporting biomedical research in universities is threatened by the crushing pressures of the increased costs of building the infrastructure to support science and recruit and retain the most talented faculty; by insufficient support from funding agencies such as the U.S. National Institutes of Health (NIH); by challenges and limitations to interactions with and support from the pharmaceutical industry; by prolonged postdoctoral training periods before an academic scientist becomes a principal investigator (5); and by limited opportunities for research careers in academic medical centers. The current situation is a perfect storm for academia,

and one victim is innovation, which often requires research that is deemed to be “too risky” by investors and other funding sources.

Ironically, NIH likely would not have funded proposals to test the germ-theory, antibiotic-action, or DNA double-helix hypotheses because these projects either would have been deemed too risky (that is, they have a low likelihood of success) or too speculative (lacking in sufficient “preliminary data”) or because the approach would have been criticized as being misguided (for example, varying the hydration of DNA in order to improve its x-ray diffraction). Yet each one of these innovations clearly caused a paradigm shift and ultimately was the basis for major subsequent innovations that benefited the care of patients. Today, each innovation would have been patented by the discovering scientists and their institutions and possibly licensed for development by the pharmaceutical industry. To some extent, academia and its essential partner, NIH, have failed to evolve. This failure has limited support for the truly innovative science required to meet the challenges of changing times. Today, the infrastructure for science has expanded dramatically at academic medical centers, and the access to technology that can enable cutting-edge science is greater than ever; but the problems that require solving are much more complex and elusive than ever before and demand creative solutions that were unimaginable just a decade or two ago. Indeed, academia and NIH have been guilty of a lack of innovation.

BALANCING THE INNOVATION ENVIRONMENT

Today’s challenge is how to preserve and stabilize robust biomedical research in academia without creating an environment that is toxic to innovation. What is needed is a new balance between risk and reward and between truly revolutionary research and the less innovative, but still important, incremental advances that are necessary to build the foundation of knowledge within a given discipline. This balance must be struck between high-risk innovative research, which is rare, and research that augments our knowledge base and provides opportunities for training. Both kinds of research are necessary, but the two should be funded by distinct mechanisms.

As part of the recent revision of the NIH peer review system, innovation—defined as research that “challenge[s] and seek[s] to shift current research or clinical practice paradigms”—has been singled out as one of the key criteria for scoring grant proposals. Yet everyone familiar with NIH operations knows that it is extremely difficult to obtain funding for groundbreaking, high-risk research. Indeed, the unwritten rule, often said tongue in cheek, is that when applying for NIH funding one should only propose experiments that one has already done and for which one can show convincing preliminary data. Indeed, these barriers to funding innovative proposals are so well established that recently several new funding opportunities—including the NIH Director’s Pioneer Awards—have been offered for “high-risk” science, implying perhaps that the standard funding mechanisms are not suitable for supporting risky research.

One solution to this paradox would be to restructure—and simplify—the NIH funding mechanisms. A restructured NIH Research Project Grant Program (which bestows RO1 grants) might provide funding to individual investigators for 10 years at ~\$500,000 per year with a fixed 30th-percentile pay line. These grants would be limited to one per investigator, and the criteria for these awards would be productivity, as measured by publication record. The rationale behind these awards is that they would provide stable funding for productive investigators, allowing for rational planning of research programs and laboratory staffing, and would eliminate the need to constantly write proposals rather than do science and teach. Stability would attract more of the best and brightest to careers in biological research instead of scaring them away, as the current system does, with single-digit pay lines and perpetual

grant writing. In order to maintain a 30th-percentile pay line, it would be necessary to postpone funding of large and expensive programs when sociopolitical pressures restrict discretionary funding. In better times, bigticket items could be funded, but never at the expense of the RO1 pay line.

In order to allow early-stage investigators to compete for these grants, NIH and other such funding agencies would need to offer institutional faculty recruitment grants that provide 5 years of laboratory start-up funding (instead of the current norm of 3 years). Academic institutions would have to compete for these recruitment grants and award them to the best candidates they can recruit. With 5 years of support, successful new faculty would have a sufficient track record of productivity to compete for subsequent RO1 funding.

A second distinct mechanism of funding would be for high-risk, innovative proposals. There would be no limit to the number of these grants that an investigator could have, and they would be based on productivity and past evidence of innovation as defined by truly paradigm-shifting research or the use of novel outside-the-box approaches and technologies. These proposals would be assigned to review groups that are composed of only senior investigators, distinct from the study sections that review RO1s, which also include young faculty. The two types of proposals would not compete for the same pool of funds. These innovation grants might be harder to obtain than the RO1s, but a reasonable pay line (for example, 20th percentile) should be stably maintained.

It could be argued that a focus on productivity and review by senior scientists would be unfair to young scientists. However, this should not be the case, because productivity is based on quality not quantity of publications and because scientists have a tendency to evaluate recent rather than cumulative productivity; thus, a young scientist should have a sufficient recent track record after 5 years of start-up funding. Requiring senior scientists (for example, tenured full professors) as reviewers would enhance the likelihood of obtaining grant reviews that focus on the “big picture” and the potential impact in a field rather than on largely irrelevant minutia, as so many current NIH reviewers are prone to do.

These mechanisms for federal funding should be focused on basic biomedical discovery research, defined as that which is hypothesis driven, directed toward elucidating biological and disease mechanisms, and conducted by using any model organism, including humans. Basic science is the pipeline that feeds translational and ultimately clinical science. Funding for expensive large-scale clinical trials should come largely from partnerships with industry, which is dedicated to clinical implementation and rapid translation. Diverting to industry most of the costs of those large clinical trials that are currently supported by NIH would enable the maintenance of stable pay lines at levels that are consistent with the powers of discrimination of the peer-review system. Making the distinction between highly productive but lowerrisk projects and high-risk science, and not forcing them to compete for the same pool of resources, would reward both kinds of science and foster innovation. Naturally, there will be clinical and translational studies that are not attractive to industry for commercial reasons yet are important for patient care, and these should be the purview of NIH-funded clinical research.

Partnerships between academia and industry are inevitable, as pharmaceutical companies continue to downsize their internal discovery programs and increasingly look to partnerships with academia and biotechnology (which for the most part are spinoffs from academic laboratories) for new targets and therapeutics. Academic clinical researchers should be recruited to design and direct clinical trials and to analyze the resulting data. Dramatic increases in the translation of new therapeutics that benefit patients could be realized via

increased academic-industry partnerships, particularly if the costs of clinical trials in the United States were reduced 10-fold and brought in line with those in the rest of the world.

RETURN ON INVESTMENT

It could be argued that the U.S. Congress and taxpayers likely will frown on scientific innovation that fails to be translated to practical applications (such as new therapeutics). Therefore, scientists must bear the responsibility to put in place mechanisms that facilitate the translation of innovative basic science discoveries into commercially successful and effective therapeutics and diagnostics that improve the lives of patients. By definition, high-risk innovative research yields more failures than successes. A focus on three criteria for moving innovative basic science forward to the translational stage can reduce the risk of failure: (i) identification of therapeutic targets and compounds with well-defined mechanisms of action in relevant biological systems; (ii) rigorous testing of the performance of drugs, therapeutic targets, and devices in model systems that test basic mechanisms of human disease; and (iii) a requirement that human genetic evidence provides validation that mutations in genes that encode therapeutic targets can cause the disease that is being targeted.

To help research meet these three criteria, investigators need increased access to reagents such as chemical and small interfering RNA (siRNA) libraries, collections of already-approved drugs, robust animal models of human disease, and genetic and genomic data; such resources often are developed with NIH funds but not shared because of competition among laboratories. Although the current NIH policies for sharing data and reagents are excellent, they are difficult to enforce. Centralizing these resources would eliminate dependence on the good will of individual scientists to share. For example, the National Institute on Aging maintains a colony of aged mice that is a terrific resource for studies of the aging process. Other cores should be established that provide access (for a modest fee) to animal models of human disease. Sharing via centralized facilities represents a cost-saving mechanism that would improve translational research by standardizing model systems and providing greater access to such reagents for testing the validity of novel therapeutic targets and efficacy of lead compounds. Cores for medicinal chemistry would provide investigators with compounds for probing signaling pathways to unveil novel therapeutic targets.

Ultimately, the success of translational biological research will depend on reducing barriers to testing of the physiological relevance of basic discoveries, perhaps by adopting some of the changes outlined above. Also needed are mechanisms by which investigators can share knowledge and be freed of restrictions imposed by intellectual property. Too often, concerns about sharing intellectual property limit interactions between academics or between academia and industry. To help overcome these bottlenecks, symposia should be held precisely for the purpose of bringing academic and pharmaceutical-industry scientists together, initially to share nonconfidential information. Such meetings could include platform presentations from academic and pharmaceutical-industry scientists and breakout sessions for more in-depth interactions. No doubt some of these meetings would lead to more detailed follow-up meetings under confidentiality agreements. In addition, to capitalize on innovation that arises from academic science pursuits, industry must provide support for conferences and retreats for academic scientists, and industry researchers should participate in these gatherings in order to forge diagnostics-, device-, and therapeutics-development partnerships. Conflict-of-interest issues would have to be addressed by oversight committees and institutional reviews. These issues are worth managing because the present system of putting up firewalls between academia and NIH on the one hand, and industry on the other, impairs the translation of innovative basic science.

The proposed changes to our current system of supporting basic, translational, and clinical research, designed to increase innovation, are achievable even in difficult financial times. The metrics for success would be stabilization of the academic biological research system; increased biomedical innovation; and, ultimately, novel medical products that benefit patients.

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Fig. 1. Seeing differently

Pablo Picasso and Georges Braque revolutionized painting and sculpture in the 20th century through innovation. Shown is the cubist painting *Three Musicians* by Pablo Picasso.