New Funding Frontiers: **Innovative Funding Models in Translational Research**

The Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics at Harvard Law School

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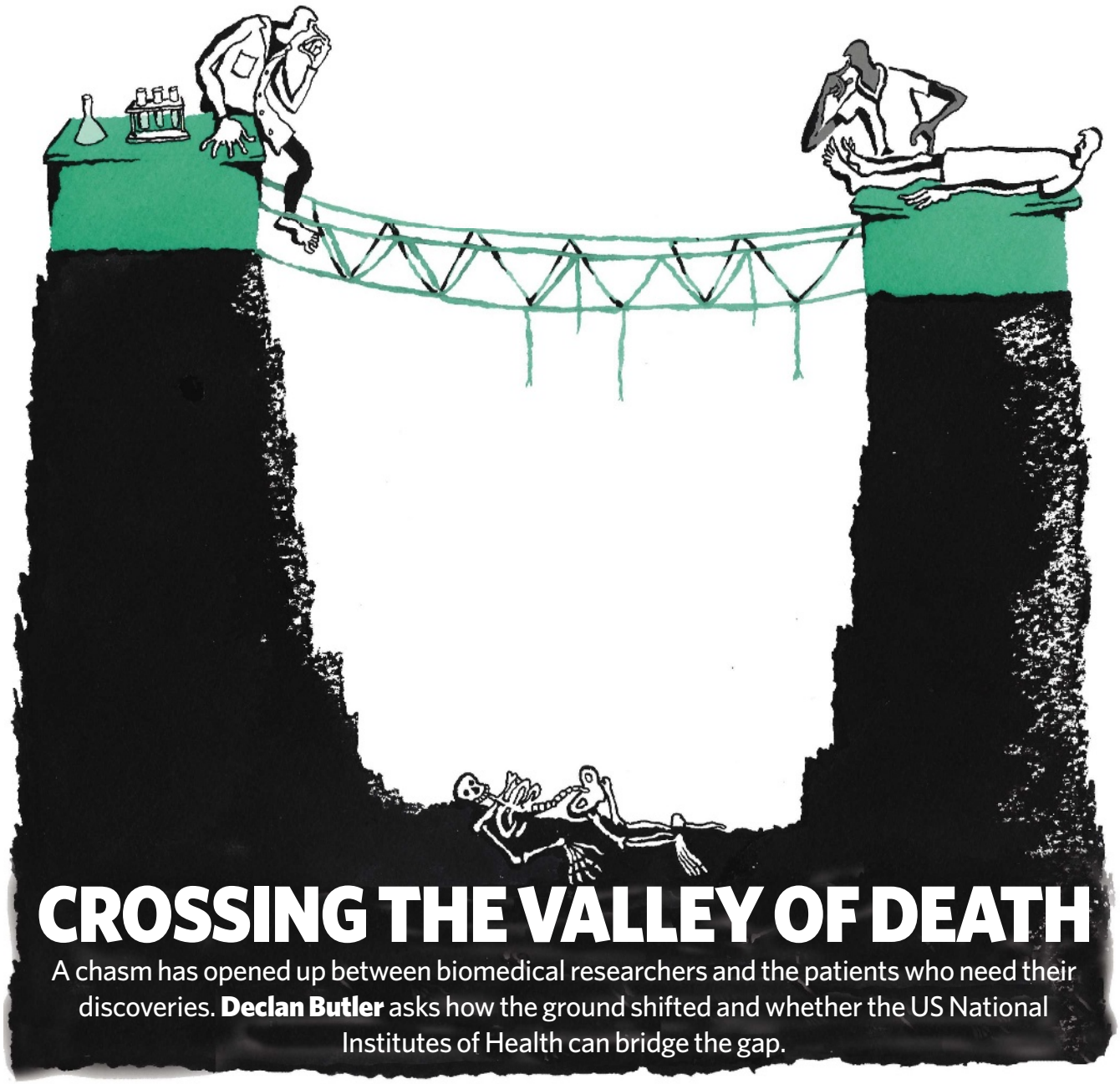
The Current Stage of Translational Research

Translational Research is a phrase that is used to describe a number of different activities, united by the common goal of turning the findings of basic research into medications and procedures that improve the lives of patients. Translational research is related to, but distinct from, basic research (which seeks to improve our understanding of natural phenomenon) and clinical research (which tests and improves upon a specific drug or therapy). Translational research is best thought of as the research that bridges the divide between basic and clinical research.

Translational research is vital, as targeted translation science can ensure that new treatments and research knowledge actually reach the patients or populations waiting for these breakthroughs. Nevertheless, in the age of frequent governmental budget crises and government spending cutbacks, relying on a government agency to promote such important developments may be problematic. An obvious solution to the funding gap that exists in current health care and biomedical research is the close investment and involvement of private, for-profit entities. The increased involvement of for-profit funding in early stage research is relatively new and, therefore, raises questions about the best practices for supporting research through these funding models.

The aim of this working group is to bring together a variety of experts and advocates interested in advancing translational research to explore the shifting dynamics, opportunities, and challenges that present when translational research increasingly turns to for-profit funding streams.

Declan Butler, *Translational Research: Crossing the Valley of Death,* 453 NATURE 840, 840–842 (2008)



CROSSING THE VALLEY OF DEATH

A chasm has opened up between biomedical researchers and the patients who need their discoveries. **Declan Butler** asks how the ground shifted and whether the US National Institutes of Health can bridge the gap.

B. MELLOR

"NIH stands for the National Institutes of Health, not the National Institutes of Biomedical Research, or the National Institutes of Basic Biomedical Research." This jab, by molecular biologist Alan Schechter at the NIH, is a pointed one. The organization was formally established in the United States more than half a century ago to serve the nation's public health, and its mission now is to pursue fundamental knowledge and apply it "to reduce the burdens of illness and disability". So when employees at the agency have to check their name tag, some soul searching must be taking place.

There is no question that the NIH excels in basic research. What researchers such as Schechter are asking is whether it has neglected the mandate to apply that knowledge. Outside the agency too there is a growing perception that the enormous resources being put into biomedical research, and the huge strides made in understanding disease mechanisms, are not resulting in commensurate gains in new treatments, diagnostics and prevention. "We are not seeing the breakthrough therapies that people can rightly expect," says Schechter, head of molecular biology and genetics at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland.

Medical-research agencies worldwide are experiencing a similar awakening. Over the past 30 or so years, the ecosystems of basic and clinical research have diverged. The pharmaceutical industry, which for many years was expected to carry discoveries across the divide, is now hard pushed to do so. The abyss left behind is sometimes labelled the 'valley of death' — and neither basic researchers, busy with discoveries, nor physicians, busy with patients, are keen to venture there. "The clinical and basic scientists don't really communicate," says Barbara Alving, director of the NIH's National Center for Research Resources in Bethesda.

Alving is a key part in the NIH's attempt to bridge the gap with 'translational research'. Director Elias Zerhouni made this bridge-building a focus in his signature 'roadmap' for the agency, announced in 2003 (see *Nature* **425,** 438; 2003). Spearheading the NIH effort will be a consortium of 60 Clinical and Translational Science Centers (CTSCs) at universities and medical centres across the country, which will share some US$500 million annually when they are all in operation by 2012. Late last month, the NIH doled out the most recent grants in

this programme to 14 institutions, including Indiana University School of Medicine in Indianapolis and Harvard University, bringing the consortium up to 38 member centres since its launch in 2006.

Yet the money for the CTSCs will total only 1–2% of the NIH's annual budget of $29.5 billion, and at this early stage it is not clear how much these catalysts will be able to change the terrain. Even so, some people credit the organization and its leader for trying. "Lots of people say they hate Zerhouni. I love him. He had the courage to come forward and say that the NIH was not delivering on its promise," says Lee Nadler, head of the new CTSC at Harvard.

Ask ten people what translational research means and you're likely to get ten different answers. For basic researchers clutching a new prospective drug, it might involve medicinal chemistry along with the animal tests and reams of paperwork required to enter a first clinical trial. For groups wanting to developing diagnostics, imaging tools, or screening and prevention methods the route would be different.

New image

In some sense much translational research is just rebranding — clinical R&D by a different name. But it also involves investing in training, research and infrastructure to help researchers engage in clinical research — and cross the valley of death. Funding agencies hope that this will break down barriers in the transformation of basic-science breakthroughs into clinical applications ('bench to bedside') and enable more research on human subjects and samples to generate hypotheses that are more relevant to people than to animal models (see page 843).

The barriers to translational research are relatively recent. Back in the 1950s and 60s, basic and clinical research were fairly tightly linked in agencies such as the NIH. Medical research was largely done by physician–scientists who also treated patients. That changed with the explosion of molecular biology in the 1970s. Clinical and basic research started to separate, and biomedical research emerged as a discipline in its own right, with its own training. The bulk of biomedical research is now done by highly specialized PhD scientists (see graph), and physician–scientists are a minority.

The basic biomedical research enterprise has now evolved its own dynamic, with promotions and grants based largely on the papers scientists have published in top journals, not on how much they have advanced medicine. And many clinicians who treat patients — and earn fees for doing so — have little time or inclination to keep up with an increasingly complex basic literature, let alone do research. This has diminished the movement of knowledge and hypotheses back and forth between bedside and bench. At the same time, genomics, proteomics and all its cousins are generating such a volume of potential drug targets and other discoveries that the pharmaceutical industry is having trouble digesting them. With pharma spending more on research but delivering fewer products (see graph), it is no longer in a position to take forward most academic discoveries. "There is a real crisis in the industry," says Garrett Fitzgerald, head of the CTSC based at the University of Pennsylvania in Philadelphia.

One crude way of tracking the rupture is to see when people developed a new rhetoric to deal with it. The term 'translational research' first appeared in PubMed in 1993, sparked by the characterization of *BRCA1* and other cancer genes, which suggested immediate applications in early detection and treatment of cancers. Use of the term remained low throughout the 1990s, in just a handful of papers annually, until around 2000, after which it has cropped up in several hundred articles each year.

NIH

"There was a widening gap between basic and clinical research."
— Elias Zerhouni

In 2000, the US Institute of Medicine convened the Clinical Research Roundtable, which held a series of meetings that are credited with putting translational research high on the agenda. The process pinpointed two blockages in the transfer of research knowledge into practice (S. H. Woolf *J. Am. Med. Assoc.* **299,** 211–213; 2008). The first was preventing laboratory advances being converted into new medical products and tests in humans; the second was stopping proven improvements in treatment — a new drug combination, for instance — becoming adopted in medical practice.

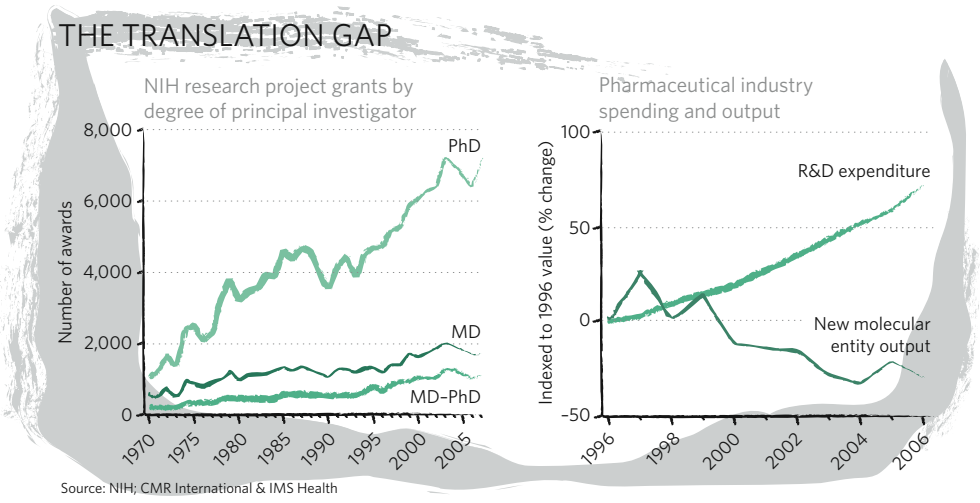
Out of the comfort zone

Biomedical research agencies are responsible for the first block. As anyone attempting translational research will testify, basic scientists have few incentives to move outside their comfort zone. It means getting involved with complex regulatory and patent issues. There is the risk of career damage to boot, because it is not the sort of research that gets published by the top journals and spurs promotion.

Publicly funded biomedical science has become disconnected from the processes that lead to cures and treatments, says Rudy Balling, a proponent of translational research at the Helmholtz Centre for Infection Research in Braunschweig, Germany. "Most biologists haven't a clue about real medical needs," he says, or about the difficulties of applying their research.

When Zerhouni became director of the NIH in 2002, "that's exactly the situation as I found it", he says. "There was a widening gap between basic and clinical research, which if left alone would have been a major barrier to progress." As head of the world's top-spending biomedical research agency, Zerhouni was under pressure to make progress. The NIH's budget had doubled since 1998 to $27 billion in 2003, and tax-payers were demanding a return on their investment. "That is the accountability factor that Congress is asking us to address," he says.

At the time, Zerhouni convened a series of whirlwind meetings with top clinicians and scientists who also realized they needed to change the way they worked so that existing



knowledge didn't end up sitting on shelves. These meetings convinced Zerhouni — a radiologist himself — that it was a priority "to get over this gap" by redesigning the agency's translational research programmes.

New lamps for old

The NIH already had projects under the old 'clinical research' label, including 78 General Clinical Research Centres (GCRCs) created in 1959 at universities and medical centres nationwide. But the centres were generally limited to providing services for conducting clinical trials. They did not tackle Zerhouni's new priority, spelt out in the roadmap, to boost the agency's ability to train physician–scientists and translational researchers capable of bridging the valley of death. The CTSCs will replace the GCRCs.

Science and innovation have become too complex for any nostalgic return to the physician–scientist on their own as the motor of health research. Reinventing that culture is therefore the focus of the CTSCs, in the form of larger, multidisciplinary groups, including both basic scientists and clinicians, but also bioinformaticians, statisticians, engineers and industry experts. Zerhouni says he expects them to be breeding grounds for a new corps of researchers who will effectively stand on the bridge and help others across. Scientists at the centres will be evaluated with business techniques, such as milestones and the ability to work in multidisciplinary groups, rather than by their publications alone.

NCRR/NIH

"The clinical and basic scientists don't really communicate."
— Barbara Alving

Since 2006, Fitzgerald's centre in Philadelphia is using its CTSC money to pull together 400 or so staff who were previously scattered across research centres and hospitals and install them in a new bricks-and-mortar institute. For researchers with work to translate, the new centre offers support with regulatory issues, patents and clinical trial design. Fitzgerald would ultimately like 20% of new medical-school graduates to follow translational research courses, and the centre also offers master's and other degrees in the new discipline for MDs and PhDs. One of Fitzgerald's programmes is exploring the aftermath of painkillers called COX2 inhibitors, which were more or less abandoned by the pharmaceutical industry after they were found to increase the risk of heart attack and stroke. Researchers at the centre are looking for biomarkers that might identify those who escape these side effects and salvage a future for the drugs.

Scientists in other countries are watching the NIH flagship effort with interest. In Britain, which is second only to the United States in biomedical research output, the government last year announced a doubling of the Medical Research Council's budget to almost £700 million (US$1.3 billion) by 2010, largely to finance a new focus on translational research. In Europe, around 20 national research and government agencies are exploring a European version of the CTSCs. Coordinated by Balling, the European Advanced Translational Infrastructure in Medicine wants to create a multimillion-euro network of biomedical translation hubs across Europe, based on existing research centres.

J. IDE/HARVARD UNIV. NEWS OFFICE

A new breed of researchers will aim to bridge the translational divide.

Time will tell whether the NIH's translational centres can come up with the goods. Gary Pisano, an expert in innovation at Harvard Business School, calls them "an experiment worth doing". Government support has been used with some success to further application of other research fields, he points out, such as defence funding that supported applied research in electronics, communications and the Internet.

Measuring the outcomes of translational research is notoriously difficult, as they do not lend themselves to the simplistic bean counting of publications. Because drug development can take up to 20 years, the eventual impact of such efforts on the drug pipeline will only emerge with time. At the NIH, Alving has set up a commission to advise how the CTSCs should be evaluated. This might be done by tracking researchers' career paths and surveying productivity by, for example, counting patents, clinical trials and collaborations with industry. But until patients see a benefit, the aims of the programme risk appearing laudable but vague.

Some basic scientists baulk at the $500 million annual costs of the centres when the NIH budget is under extreme pressure. But Zerhouni says there will be no significant diversion of resources to translational research and that the CTSCs will be funded largely by absorbing the $290 million budget of the old GCRCs. Some $95 million will come from the NIH's Common Fund, and the rest will be redirected from other clinical projects. Zerhouni says the NIH has a current balance of 60% basic and 30% clinical and argues that it needs more, not less, basic research to feed the translational pipeline. Others assert that the 30% clinical figure is artificially inflated because it classifies a proportion of work — such as that on animal models — as clinical that others would call basic, something Zerhouni denies.

With a tiny fraction of the NIH budget, and much of that shuffled from existing clinical programmes, critics might charge that the CTSCs are little more than business as usual. Schechter thinks that the NIH needs to go further down the translation road by reforming the monopoly of investigator-driven research grants as the agency's main funding mechanism. This system rewards individual success and does little to encourage the type of collaboration that translational research demands. He points to alternative models for doing translational research, such as the Multiple Myeloma Research Foundation, based in Norwalk, Connecticut, and other charitable groups that operate more like businesses in their drive to get research into clinical trials. "There are other structures for doing biomedical research than that which the NIH has hewed to for 40 years."

Zerhouni is sensitive to the need for reform, and points to new awards for multiple investigators. He acknowledges there is no 'right' model for translational research, but he is confident that the NIH will learn about the best ones by giving the CTSCs the freedom to explore a diversity of approaches. As to what the NIH stands for — National Institutes of Health, National Institutes of Biomedical Research or National Institutes of Basic Biomedical Research — "we are all of the above", says Zerhouni. And perhaps it will take many aliases and many attempts to cross this particular chasm. ■

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See also pages 823 and 843, and online at http://tinyurl.com/3tt3y3.

Steven H. Woolf, *The Meaning of Translational Research and Why it Matters*, 299 JAMA 211, 211–213 (2008)

The Meaning of Translational Research and Why It Matters

Steven H. Woolf, MD, MPH

TRANSLATIONAL RESEARCH MEANS DIFFERENT THINGS to different people, but it seems important to almost everyone. The National Institutes of Health (NIH) has made translational research a priority, forming centers of translational research at its institutes and launching the Clinical and Translational Science Award (CTSA) program in 2006. With 24 CTSA-funded academic centers already established, other universities are transforming themselves to compete for upcoming CTSA grants. By 2012, the NIH expects to fund 60 such centers with a budget of $500 million per year.[1] Besides academic centers, foundations, industry, disease-related organizations, and individual hospitals and health systems have also established translational research programs and at least 2 journals (*Translational Medicine* and the *Journal of Translational Medicine*) are devoted to the topic. By some accounts, translational research has become a centerpiece of the European Commission's €6 billion budget for health-related research, and the United Kingdom has invested £450 million over 5 years to establish translational research centers.[2]

What exactly is translational research? For many, the term refers to the "bench-to-bedside" enterprise of harnessing knowledge from basic sciences to produce new drugs, devices, and treatment options for patients. For this area of research—the interface between basic science and clinical medicine—the end point is the production of a promising new treatment that can be used clinically or commercialized ("brought to market"). This enterprise is vital, and has been characterized as follows: "effective translation of the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for prevention, diagnosis, and treatment of disease is essential for improving health."[3]

For others—especially health services researchers and public health investigators whose studies focus on health care and health as the primary outcome—translational research refers to translating research into practice; ie, ensuring that new treatments and research knowledge actually reach the patients or populations for whom they are intended and are implemented correctly. The production of a new drug, an end point for "bench-to-bedside" translational research, is only the starting point for this second area of research. According to McGlynn et al,[4] US patients receive only half of recommended services. The second area of translational research seeks to close that gap and improve quality by improving access, reorganizing and coordinating systems of care, helping clinicians and patients to change behaviors and make more informed choices, providing reminders and point-of-care decision support tools, and strengthening the patient-clinician relationship.

The distinction between these 2 definitions of translational research was articulated by the Institute of Medicine's Clinical Research Roundtable,[5] which described 2 "translational blocks" in the clinical research enterprise and which some now label as T1 and T2. The first roadblock (T1) was described by the roundtable as "the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans." The roundtable described the second roadblock (T2) as "the translation of results from clinical studies into everyday clinical practice and health decision making."

Referring to T1 and T2 by the same name—translational research—has become a source of some confusion.[6] The 2 spheres are alike in name only. Their goals, settings, study designs, and investigators differ. T1 research requires mastery of molecular biology, genetics, and other basic sciences; appropriately trained clinical scientists working in strong laboratories and with cutting-edge technology; and a supportive infrastructure within the institution—all elements the CTSA seeks to nurture.

In contrast, the "laboratory" for T2 research is the community and ambulatory care settings, where population-based interventions and practice-based research networks[7] bring the results of T1 research to the public. T2 requires different research skills: mastery of the "implementation science"[8] of fielding and evaluating interventions in real-world settings and of the disciplines that inform the design of those interventions, such as clinical epidemiology and evidence synthesis, communication theory, behavioral science, public policy, financing, organizational theory, sys-

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tem redesign, informatics, and mixed methods/qualitative research. T1 and T2 face different challenges. T1 struggles more with biological and technological mysteries, trial recruitment, and regulatory concerns. T2 struggles more with human behavior and organizational inertia, infrastructure and resource constraints, and the messiness of proving the effectiveness of "moving targets" under conditions that investigators cannot fully control.[9,10]

Both T1 and T2 research are vital, but T1 seems to overshadow T2 in the United States.[6] Most individuals have T1 in mind when they use the term translational research and T1 attracts more funding. According to Moses et al,[11] the $22.1 billion NIH budget for 2002 included $9.1 billion for "applied and development research" ($13.0 billion for basic research) but only $787 million for health services research. The NIH maintains an active program in "dissemination" research,[12] but across all funding sources in 2002—federal and foundations—spending on health services research represented only 1.5% of biomedical research funding.[11] National Institutes of Health leaders and the CTSA program advocate both T1 and T2, but the focus is on T1. The CTSA program does encourage "community engagement," but whether this entails T2 is often unclear. Rather than promoting the efferent process of exporting research findings to the community and facilitating their implementation in practice, CTSA often portrays community engagement as an afferent process for researchers; ie, a way to "foster collaborative research partnerships and enhance public trust in clinical and translational research, facilitating the recruitment of research participants from the community."[13]

Arguably, the federal responsibility for T2 research lies not with the NIH but with the Agency for Healthcare Research and Quality (AHRQ). According to its recent report to Congress, "the ultimate goal [of AHRQ] is research translation—that is, making sure that findings from AHRQ research are widely disseminated and ready to be used in everyday health care decisionmaking."[14] But Congress allocates AHRQ only approximately $300 million per year for this work: just over 1% of the NIH budget. AHRQ does what it can—in 1999 and 2000 it issued 27 Translating Research into Practice (TRIP) grants,[15] and it has also sponsored TRIP conferences—but funding for TRIP later declined as congressional earmarks began carving out much of AHRQ's budget for specific topics (eg, patient safety, information technology). In 2000, AHRQ spent $7 million (3% of its budget) on TRIP studies,[16] but by 2004 it spent only $2 million (1%).[17]

The T2 research community is still defining itself, both in name and in scope. Being named TRIP, T2, or even translational research is unsatisfactory to many in the discipline, but no consensus has coalesced around alternative terms (eg, dissemination, health services, knowledge translation/transfer, implementation, or quality improvement research). The scope of T2 research is also unclear. The roundtable model[5] portrays T2 as one step—the translation of new knowledge into clinical practice—but the process is rarely that simple.[8,18] Westfall et al[19] redrew the model to include a third step (T3), practice-based research,[7] which is often necessary before distilled knowledge (eg, systematic reviews, guidelines) can be implemented in practice.

Even this expanded model is incomplete because it sees knowledge implementation only through the eyes of physicians, but practitioners other than health care professionals also translate research into practice. Science informs choices about health habits (eg, diet, smoking), environmental policy, injury prevention, parenting, healthy workplaces and schools, population health campaigns, and other interventions outside the clinic. The "practitioners" who apply evidence in these settings include patients, public health administrators, employers, school officials, regulators, product designers, the food industry, and other consumers of evidence. Trials that test the implementation of evidence in these settings can be just as vital as similar T2 work in clinical settings.[20]

How attention and resources are apportioned to T1 and T2 matters because, for many diseases, T2 could save more lives than T1. The "bench-to-bedside" T1 enterprise occasionally yields breakthroughs that markedly improve the prognosis for a disease,[21,22] but most new drugs and interventions produced by T1 only marginally improve efficacy. These incremental advances are certainly welcome, but patients might benefit even more—and more patients might benefit—if the health care system performed better in delivering existing treatments than in producing new ones. For example, greater fidelity in administering aspirin to eligible patients might prevent more strokes than developing more potent antiplatelet agents.[23] At a time when experts warn of the fragmented health care system and of a widening "chasm"[24] in access, quality, and disparities, interventions to close these gaps—the work of T2—may do more to decrease morbidity and mortality than a new imaging device or class of drugs.

Public interest therefore requires T2 to come out from under the shadow of T1. It needs a new name; translational research is now too vague a term for T2 (or T1) and not using the same label for both endeavors would help to reduce confusion. More than a new name, however, T2 needs new recognition and emphasis. Policy makers and the academic research community must come to a clearer understanding of the distinction between inventing treatments and getting them used in practice. Those who fund research must weigh carefully the relative capacity of each research sphere to improve health and economic outcomes and should fund each endeavor accordingly. Disproportion has consequences,[25] and the current policy of spending 1.5% of research dollars on health services research[11] is probably costing lives.

Moreover, adequate investment in T2 research is vital to fully salvage investments in T1 research. Bringing a drug to market without knowing how to bring it to patients un-

dermines its larger purpose and can only diminish its profitability for investors.

A consequence of a stronger commitment to T2, especially outside clinical settings, is to expand the boundaries of basic science beyond the bench research that T1 typically showcases. Successful health interventions in hospitals, homes, and statehouses require the translation of other "basic sciences"—such as epidemiology, behavioral science, psychology, communication, cognition, social marketing, economics, political science—not only the translation of biotechnological insights and novel therapies. These disciplines deserve their place not only in definitions of basic science but also in funding priorities. Poverty matters as much as proteomics in understanding disease.

Discovering better ways to ensure that patients receive the care they need—safely, compassionately, and when they need it—is not easy and poses formidable methodologic challenges. Scientific discoveries and spectacular new devices are more fascinating to the public and more lucrative for industry. The betterment of health, however, should dictate priorities in health research. Funders should strike a balance between areas of research—T1 vs T2, clinical vs population-based research—and emphasize each endeavor in proportion to its ability to improve health.

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The Financial Tools Available for Innovative Funding Models

In order to navigate the complex practical and ethical challenges posed by having for-profit financing of earlier stage science, we need the right financial instruments, with appropriate incentives. For the business community the question is primarily one of risk as funding translational research has requires a significant amount of capital with long time horizon and a high failure rate. These realities tend to push investors towards projects with clearer, more immediate returns. For stakeholders on the other side of the transaction, a pressing concern is to ensure that the funding models do not threaten the integrity of their research. Additionally, institutions and researchers are drawn to funding vehicles that enable and encourage investment in more speculative, longer-term studies. Successful funding models address the needs of all parties to the transactions.

The purpose of this discussion is to better understand the financial vehicles for investing for-profit capital into early stage translational research, to compare these financial tools against each other to get a better sense of when each tool is appropriate, and to articulate the frequent challenges facing research institutions and scientists as they negotiate innovative funding deals.

Andrew W. Lo, *Can Financial Engineering Cure Cancer?,* 7 MIT Alumni Magazine 18–19 (2013)

Can Financial Engineering Cure Cancer?

There is growing consensus that the bench-to-bedside process of translating biomedical research into effective therapeutics is broken. In a paper published in the October 2012 issue of Nature Biotechnology, my coauthors, Jose-Maria Fernandez and Roger M. Stein, and I suggest that this is caused in large part by the trend of increasing risk and complexity in the biopharma industry. This trend implies that the traditional financing vehicles of private and public equity are becoming less effective for funding biopharma because the needs and expectations of limited partners and shareholders are becoming less aligned with the new realities of biomedical innovation. The traditional quarterly earnings cycle, real-time pricing, and dispersed ownership of public equities imply constant scrutiny of corporate performance from many different types of shareholders, all pushing senior management toward projects and strategies with clearer and more immediate payoffs, and away from more speculative but potentially more transformative science and translational research.

We propose a new framework for simultaneously investing in multiple biomedical projects to increase the chances that a few will succeed, thus generating enough profit to more than make up for all the failures. Given the outsized cost of drug development, such a "megafund" will require billions of dollars in capital; but with so many projects in a single portfolio, our simulations suggest that risk can be reduced enough to attract deep-pocketed institutional investors, such as pension funds, insurance companies, and sovereign wealth funds.

A key innovation of this proposal is to tap into public capital markets directly through securitization, using structured debt securities as well as traditional equity to finance the cost of basic biomedical research and clinical trials. Securitization is a common financing method in which investment capital is obtained from a diverse investor population by issuing debt and equity that are claims on a portfolio of assets—in this case biomedical research. Debt financing is an important feature because the bond market is much larger than the equity market, and this larger pool of capital is needed to support the size of the portfolios required to diversify the risk of the drug development process. In addition, this vast pool of capital tends to be more patient than the longest-horizon venture capital fund.

Our findings suggest that bonds of different credit quality can be created, which could appeal to a broad set of short-term and long-term investors. The results from the simulations we ran indicate that a megafund of $5 billion to $15 billion may be capable of yielding average investment returns in the range of 9 percent to 11 percent for equity holders, and 5 percent to 8 percent for bondholders. These returns may be lower than traditional venture capital hurdle rates, but are more attractive to large institutional investors.

To calibrate and test our simulation of the investment performance of a hypothetical cancer drug megafund, we accessed the databases of hundreds of anti-cancer compounds assembled by Deloitte Recap LLC and the Center for the Study of Drug Development at Tufts University School of Medicine. These simulations not only yielded attractive investment returns on average, but also implied that many more drugs would be successfully developed and brought to market. Such an outcome would be particularly welcome given the current scarcity of investment capital in the life sciences industry despite the growing burden of disease. One in two men and one in three women in the United States will develop cancer at some point in their lifetimes, making this one of the major priorities facing society.

We acknowledge that our analysis is only the first of many steps needed to create a private-sector solution to the funding gap in the life sciences industry. The practical challenges of creating a megafund would require unprecedented collaboration among medical researchers, financial engineers, and biopharma practitioners. Support from charitable organizations and the government also could play a critical role in expediting this initiative. In an extension of this simulation, we show that the impact of such support can be greatly magnified in the form of guarantees rather than direct subsidies. The MIT Laboratory for Financial Engineering will be hosting a conference at MIT in June where representatives from all the major stakeholder communities will be invited to explore these ideas together.

Finally, our proposal is clearly motivated by financial innovations that played a role in the recent financial crisis, so it is natural to question the wisdom of this approach. Despite Wall Street's mixed reputation in recent years, we are convinced that securitization can be used responsibly to address a host of pressing social challenges. With lessons learned from the crisis and proper regulatory oversight, financial engineering can generate significant new sources of funding for the biopharma industry, even in this difficult economic climate. Raising billions of private-sector dollars for biomedical research may seem ill timed and naive—but given the urgency of cancer, diabetes, heart disease, and other medical challenges, the question is not whether we can afford to invest billions more at this time, but rather whether we can afford to wait.

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Bridging science and technology through academic–industry partnerships

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ABSTRACT

Partnerships that foster the translation of scientific advances emerging from academic research organizations into commercialized products at private firms are a policy tool that has attracted increased interest. This paper examines empirical data from the Danish National Advanced Technology Foundation, an agency that funds partnerships between universities and private companies. We assess the effect on participating firms' innovative performance, comparing patent count, publication count and proportion of cross-institutional publications between funded and unfunded firms. Specifically, we measure the impact on each of these variables based on three dimensions – small and medium-sized enterprises (SME), younger firms, and size of the collaboration firms participated in – to establish boundary conditions. Our results suggest that receiving funding affects firms' innovative behavior differently depending on the type of firm, where (1) peer-reviewed publications increased significantly more for SMEs and larger projects, (2) granted patents increased significantly up to 4 years after funding for young firms and those in larger projects, and (3) proportion of cross-institutional publications increased significantly more 3 years after funding for all three sample specifications.

1. Introduction

How ideas are produced and the means by which they are diffused is an area of great interest to researchers. This is driven by the belief that technological innovations, which are grounded in basic research, spur wealth creation and stimulate economic growth. Research universities, with their primary missions of educating and creating knowledge, are an important source for such ideas. The Bayh–Dole act of 1980 in the US and similar legislation in European countries enabled universities to patent technologies resulting from government funded research, and as a consequence universities have undertaken a third role of fostering knowledge and technology transfer to spur economic growth (Etzkowitz et al., 2000). As a result, universities have employed many instruments to push newly generated knowledge into industry (Feldman et al., 2002; Mowery et al., 2004; Thursby and Thursby, 2002), while firms have used various ways to draw upon the research and pull new technology from academia (Henderson and Cockburn, 1996; Liebeskind et al., 1996). Despite these efforts knowledge still tends to be trapped in the ivory tower (Bikard, 2014). In light of these results, many countries have increasingly turned toward academic–industry partnership programs that combine these mechanisms to facilitate and foster the bridging between academic science and commercialization of technology.[1] Though there are many such programs globally, there is little research that assesses the impact of academic–industry partnership funding on participating firms' innovative performance compared to non-participants.

We examine academic–industry partnerships sponsored by the Danish National Advanced Technology Foundation[2] (DNATF), a funding agency of the Danish government. DNATF awards grants for projects that partner at least one academic institution and one

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[1] In the US, National Science Foundation Shared Resources Centers often require partnership with private firms to accelerate product development, while the National Institute of Health Academic–Industry Partnership Program seeks cross-boundary opportunities that link biomedical research with commercial opportunities. In Germany, the Fraunhofer–Gessellschaft is a partially state-supported application-oriented research organization with direct utility to private and public enterprises. The Technology Strategy Board in the UK runs programs such as its Knowledge Transfer Partnership that support businesses wanting to improve their competitiveness by accessing the expertise available within universities.

[2] Højteknologifonden in Danish, DNATF was merged into the InnovationsFonden in May 2014.

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firm in a co-funding structure where academic partners provide one sixth of the budgeted amount, industry partners one third, and the agency providing the remaining half. As few existing works explore how academic–industry funding affects subsequent firm innovative performance, our analysis is mainly exploratory. We contrast a sample of funded firms with those that applied for DNATF funding but did not ultimately receive a grant, comparing on an annual basis up to 5 years after funding. Since all proposal applications were ranked, we mitigate selection bias by including qualitatively similar participant and non-participant firms. We first assess how such partnerships affect collaborations with academic research institutions in helping firms partake in innovative activities translated from basic research by studying the quantity and the collaborative nature of peer-reviewed publications. We then explore how these partnerships affect commercialization by studying the quantity of granted patents. Finally, we investigate three dimensions – the size and age of the participating firms, and the size of the collaborations – in order to establish the boundary conditions of such a funding scheme.

Although our results do not show consistent significant effects of academic–industry funding on the full sample of heterogeneous participating firms, we find significant effects along the three dimensions. For the samples of qualitatively similar small and medium-sized enterprises (SMEs) and firms in large projects, peer-reviewed publications increased significantly among funded compared to unfunded firms. For the young firm and large project qualitatively similar samples, granted patents increased significantly for funded firms compared to unfunded firms up to 4 years after funding. Moreover, for all three sample specifications, the proportion of cross-institutional publications increased significantly for funded firms compared to unfunded firms, when looking at a point 3 years after the start of funding. Taken together, our findings suggest that receiving the grant affects firms' innovative behavior differently depending on characteristics of the firm.

This work departs from prior works in a number of novel ways. It showcases a hybrid model that incorporates both academic engagement (Perkmann et al., 2013) and university entrepreneurship (Rothaermel et al., 2007) – academic–industry partnerships – and lends empirical evidence to the effect of governmental grants that foster these bridging partnerships on the resulting scientific and technological knowledge that is created. It takes a distinctive perspective from most works that study university technology transfer. Instead of focusing on academic scientists who cross institutional boundaries (Ding and Choi, 2011; Stuart and Ding, 2006), this work centers on the firm as the level of analysis and investigates the impact of academic–industry projects on firm innovative performance. Finally, given the nine-year window that we employ in our analysis (4 years before and 5 years after funding), we possess a rare longitudinal dataset that shows the dynamic and longer-term effects of the funding on firm innovative performance.

The structure of this work is as follows. We begin by presenting the theoretical framework from the literature. We then describe the setting from which we compiled our data, detail the estimation methodology employed to run our analyses, and interpret our results. Finally, in the discussion we elaborate on our quantitative results with interviews of project managers working in funded firms and explore potential factors that explain our findings. We also discuss the contributions this work brings to extant literatures and consider the implications for policymakers and managers.

2. Academic engagement, university entrepreneurship and government funding

Merton (1957) first pointed out the distinctive incentive systems between the institutions of science and technology. Science is primarily embodied in research universities where scientists are free to choose the direction of research, outputs are mainly encoded in the form of peer-reviewed publications, and the reward system is based on priority. Technology, in contrast, encodes ideas in protected modes, using patents, trademarks or copyrights to facilitate commercialization and appropriation of economic rewards (Dasgupta and David, 1994). The two institutions also differ in the nature of goals accepted as legitimate, as well as norms of behavior, especially with regard to the disclosure of knowledge. Science is concerned with additions to the stock of open knowledge, whereas technology is concerned with additions to the stream of rents that may be derived from possession of private knowledge. Though theoretically the two institutions are distinct, starting with the Bayh–Dole act of 1980 (Mowery et al., 2001) and analogous policies in Europe, the boundary between science and technology have become blurred as universities started to transfer technology by patenting their research and increasing their involvement with industry.

The literature that examines the relationship between science and technology has illustrated their interplay using two models. The first perspective depicts a linear model with science exogenous to technology, in which knowledge initiated from science spills over into technology thereby creating positive externalities for innovation and commercialization (Freeman, 1992; Mansfield, 1995). The second perspective suggests that there is a more complex bidirectional relationship rather than a pure linear model, where progress in science may be due in part to feedback from technology (Murray, 2002; Nelson, 1995). In other words, science is not viewed as a self-contained exogenous process but rather endogenous to technical progress and commercialization. However, as knowledge tends to be sticky (von Hippel, 1994), there are many challenges that prevent it from being diffused easily across institutional boundaries.

Practically, both institutions have used various means to enhance the transfer of knowledge and technology that they create as they co-evolve together. From the perspective of science-based firms, a number of mechanisms of how science influences technological progress and ultimately financial performance through knowledge spillovers have been identified. These include publishing in peer-reviewed journals (Henderson and Cockburn, 1994), coauthoring with academic scientists (Cockburn and Henderson, 1998; Liebeskind et al., 1996), movement of human capital through hiring of academic talent (Dasgupta and David, 1994), and geographically collocating close to academic organizations (Zucker et al., 1998). From the perspective of research universities, academic researchers engage in knowledge-related collaborations with firms (Perkmann et al., 2013) in the form of collaborations, contract research, or consulting, and as well as the founding of science-intensive firms (Murray, 2004; Stuart and Ding, 2006; Stuart et al., 2007). Universities actively foster commercialization (Rothaermel et al., 2007) through technology transfer offices that patent and license inventions from academic laboratories (Bercovitz and Feldman, 2006; Debackere and Veugelers, 2005), science parks to create clusters of expertise and incubators to nurture university spin-outs (Phan et al., 2005), and equity investment in start-ups (Feldman et al., 2002). Conceptually, academic engagement pursued for broader objectives, such as to assess resources and obtain learning opportunities (Lee, 2000), is seen as separate from and precedes university technology transfer (Perkmann et al., 2013), with the main goal of reaping financial reward from universities technologies.

The setting of this paper is a hybrid model of academic engagement and university entrepreneurship. The academic–industry partnerships under study entail collaborations between university scientists and industry researchers with the goal of developing technologies important to industry. These partnerships differ from the traditional model of separately generating basic scientific

specification. In the interest of conciseness, results are not shown herein but can be obtained from the corresponding author.

5. Discussion and conclusion

5.1. Empirical contributions to literature

This work provides empirical evidence on the effect of a funding program targeting academic–industry partnerships on firm innovative performance. To our surprise, we found no significant positive effect of funding on the full sample of qualitatively similar firms, especially for patents, as Kaiser and Kuhn (2012) documented an increase in filed patents in a similar program. We posit that the discrepancy in findings may be due to differences in how patents are measured as well as the counterfactual sample of comparison. In our design, we used patents filed up to 5 years after funding grants, whereas Kaiser and Kuhn use applications of patents that may or may not have been issued. Unless all filed patents are granted (which is relatively uncommon), firm's filed patents will be greater than granted patents. Moreover, we used in our counterfactual sample firms that were denied funding but still submitted a comprehensive proposal, whereas Kaiser and Kuhn employed a matched nearest neighbor sample of firms similar to funded ones based on observables. Our points of comparison are different, since we compare our funded firms to firms that already had the intention of pursuing the proposed project, while Kaiser and Kuhn compare their funded firms that may or may not have had the intention to pursue an R&D project.

For the samples of qualitatively similar SMEs, publications increased significantly and steadily for funded firms more than unfunded firms in all 5 years after funding while the impact on granted patents was not sustained. Referring back to our model of academic–industry partnerships as hybrid between academic engagement and commercialization, SMEs saw a heightened impact for academic engagement as measured by number of publications. The uptick in publications for SMEs, which is an unusual outlet for the encoding of firm knowledge, could be because organizational routines are easier to break in smaller firms than bigger ones. It could also indicate that SMEs take longer (outside of our span of analysis) to find commercializable consequences. The increase in granted patents for younger firms demonstrates that participation in academic–industry partnerships is more geared toward commercialization activities rather than academic engagement, and they may be more preoccupied with achieving or sustaining a profit, as this can take start-ups several years. These divergent findings for SMEs and younger firms may also suggest that government R&D funding is used for different purposes. SMEs participate in academic–industry partnerships with the goal of broadening their knowledge base by collaborating with academic experts, while young firms are more focused on directly commercializable outputs due to more imminent financial pressures. Future research could better understand the various motivations that bring different types of firms in engaging with such partnership funding.

Taken together, the null results of the full sample and positive results on publications for SMEs and early patenting for young firms also add to the debate on the additionality of R&D funding by governments (David et al., 2000). On the one hand, some works in the literature argue that public R&D funding is a complement and may stimulate private R&D investments (Aerts and Schmidt, 2008; Gonzalez and Pazo, 2008). While on the other hand, other works have also found evidence that public R&D funding is a substitute to private R&D funding and crowds it out (Busom, 2000; Lach, 2002; Wallsten, 2000). Our findings suggest that whether public R&D subsidies act as complement or substitute to private R&D is conditional on characteristics of the firm: when public R&D funding is provided to larger and older firms it crowds out their private R&D spent, whereas when SMEs and younger firms receive public R&D support the impact is additive.

For firms that participate in academic–industry collaborations with more partners, the consistent and large significant increase in both publications and patents in all 4 years after funding is an indication that more firms on a project not only increase the production of more basic knowledge as encoded in publications, but it also improve the chances of these project technologies of finding and being developed into suitable commercializable outlets.

Cross-institutional publications starting at 3 years after funding increased significantly for funded firms compared to unfunded firms for all three sample specifications. In these partnerships, industry researchers work hand-in-hand with academic scientists, thereby facilitating knowledge spillovers from science to technology. Partners are no longer ingrained within their own institutional logics where traditional approaches and norms prevail, as they participate in a setup designed to break through established boundaries. Interviews with a small set of participating firms ($n = 10$) corroborate these results and reveal that as firms do more basic research, collaborations between academic and industrial partners goes beyond the level of sharing equipment and extends importantly to the exchange of ideas.

Taken together, our results lead us to believe that academic–industry grants do fit the proposed hybrid model of concurrent academic engagement and commercialization, where participating firms do not always increase their traditional innovative productivity as measured by the generation of patents, but also steer the direction of their innovative outputs toward more basic research as demonstrated by our findings with publication data and the proportion of academic coauthoring of publications. Thus, participation in these partnerships has major effects on bridging science and technology and directing the focus of innovative output from more basic research. In the longer term, changes in research direction suggests that government support for academic–industry partnerships enables firms to invest more into risky and basic innovative activities, increasing their stock of knowledge (as encoded in publications) than they otherwise would have. Capabilities gained through basic research can in turn help firms make more effective decisions about applied research activities. Thus, we contribute to the knowledge spillover and industry–science relationships literatures by providing empirical evidence of an under-investigated area – a hybrid model of academic engagement and university commercialization.

5.2. Implications for practitioners and policymakers

The academic–industry partnership structure that we studied in this paper creates the potential for a different, hybrid model for bridging between the realms of science and technology. It moves away from the conventional model of separately generating basic scientific discoveries and translating them into commercialized technology through mechanisms such as licensing, startups, or dedicated gatekeepers that straddle both institutions. Instead of the unidirectional push of technologies into industry or having single actors transfer knowledge back and forth between the independent silos of science and technology, deliberate steps taken to break down the boundaries between the two institutions enable teams of individuals from both sides to work alongside one another. Our results suggest that governments can therefore motivate firms to undertake research that is more basic in nature yet still retain broad applicability – as evidenced by increased publications and cross-institutional collaborations that we found in this study. This is potentially highly significant, as it suggests laying the

groundwork for early commercialization farther forward in the innovation pipeline.

These findings are also relevant for managers who do not necessarily rely on government funding to support advanced research. By initiating collaborations with academic scientists, and recognizing and then actively managing the institutional boundary and organizational impediments, they can improve the translation of novel technologies from more basic research and thereby broaden their organization's innovative focus. Moreover, when choosing how many collaborators to work with on a project, managers should err toward larger projects as these were found to have higher effect sizes on both patents and publications.

5.3. Limitations and future research area

Despite our careful analysis and resulting outcomes, this work still suffers from several limitations and weaknesses. Thus, the interpretation of our results should be made with care. Since we have studied one specific funding and management scheme, the generalizability of our results may have limitations. However, as we have not concentrated on the intricacies and idiosyncrasies specific to our setting, and instead attempted to explore at a higher level the effect of participation, we strongly believe that the implications of our results can be interpreted more broadly. Moreover, by exploring outcomes on samples of participating firms with different characteristics the policy implications of this work is more targeted.

Even though we were very careful in our empirical design to address endogeneity concerns, there may still be subtle selection issues. We do not know whether funded firms received other funding grants besides those from DNATF. If they did, our findings would be overestimated. However, given that we observe no significant increase for the full sample of qualitatively similar participating firms, we are less worried about this alternative explanation. We also do not have information on whether unfunded firms undertook their proposed projects, but if they did, our results would be underestimated and conservative as the counterfactual outcomes currently include the impact of these projects. Together, the underestimation from unfunded firms undertaking the project irrespective of funding and the overestimation from funded firms obtaining other grants likely should have a canceling effect.

We are unable to address an important question for practitioners: how partnerships in which team members come from very different institutional roots can be effectively managed. In effect, we explore the relationship between input – participation and funding, and output – firm innovative performance – without delving inside what remains a black box. Preliminary qualitative interviews ($n = 10$) with project managers of these academic–industry partnership projects indicate that some big challenges they faced were getting individuals from different institutions to align their goals, understand each other and collaborate effectively. This is consistent with guidance on managing across organizational and cultural boundaries.

From a policy standpoint, this work did not emphasize nor tease apart the effect of funding and participating from the active mediated model specific to DNATF since our sample of firms does not provide us with any source of variation on this intervention dimension. The mediation model implies active follow-up on each project where a DNATF staff member is assigned and acts as the single point of contact throughout the funded project's lifetime. In effect, the model is a combination of the governance usually associated with private equity and venture capital with the funding style associated with pure government grants. Compared to more conventional grant funding schemes where funded projects are left on their own to meet pre-established deliverable deadlines, DNATF stays much closer to each project, frequently intervening in and mediating conflicts that arise among funded parties. If the proactive identification of obstacles and active management across institutional boundaries yielded long-term benefits in fostering the desired spillovers, governments can use such an approach to facilitate the unlocking of knowledge created in academia, leading to faster and more effective commercialization as a way to help companies maintain competitiveness.

Despite these limitations and weaknesses, we have exposed several interesting future research topics. From a managerial perspective, understanding the challenges of managing conflict inside partnerships that are "virtual companies" with multiple cross-institutional stakeholders is vital. Research can explore how such projects can be effectively managed and what factors make them more successful. For policymakers designing effective funding programs, understanding DNATF's mediated intervention model can offer powerful insights into cross-discipline and cross-boundary project management. Finally, from the perspective of the literature on the micro-foundations of innovation we can study academic scientists – the other major stakeholder in these academic–industry partnerships. Understanding the effect of such partnerships from the perspective of an individual scientist's productivity and subsequent impact is also interesting and important. This would provide a complete picture of the impact of such bridging programs and whether similar effects will be seen or whether they generate distractions and end up diverting basic science research to more commercializable areas of focus.

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Additional Reading:

David E. Fagnan et al., Financing Translation: Analysis of the NCATS rare-diseases portfolio, 276 SCI. TRANSLATIONAL MED. 276 (2015) http://stm.sciencemag.org/content/7/276/276ps3.full

Jose-Maria Fernandez, *Commercializing biomedical research through securitization techniques*, 30 NATURE BIOTECHNOLOGY 964, (2012) https://www.nature.com/articles/nbt.2374#discussion

David E. Fagnan et al., *Financing drug discovery for orphan diseases*, 19 Drug Discovery Today 533, (2014) https://www.sciencedirect.com/science/article/pii/S1359644613004030

The Right Attitude: Institutional Culture to Support Innovation

In order to successfully pioneer innovative academic-private partnerships each stakeholder involved must understand and respect the needs of their partners. Academic institutions must work to establish a robust culture of innovation and entrepreneurship within their scientific and technology transfer departments to support these projects and collaborations. Academic institutions must also give greater focus on attracting and maintaining top-talent within these departments. In turn, investors have to come in with a greater understanding of the academic culture and priorities.

The purpose of this discussion is to understand the changes that institutions must implement to foster a culture of innovation and successfully pursue new funding models, to explore how institutions can support investigators pursuing and receiving for-profit funding, to consider how institutions can attract the right talent to handle innovative funding deals.

Markus Perkmann & Ammon Salter, *How to Create Productive Partnerships With Universities*, 54 MIT SLOAN MGMT. REV. 79, 79–80 (2012) (Excerpt)

How to Create Productive Partnerships With Universities

Too often, companies pursue collaboration with university researchers in an ad hoc, piecemeal manner. But by giving more thought to the relationship structure, companies can achieve better results.

BY MARKUS PERKMANN AND AMMON SALTER

THE LEADING QUESTION

How can companies work most effectively with universities?

FINDINGS

- Companies' relationships with universities are too important to be managed in an ad hoc fashion.
- When structuring a collaboration, managers should consider two key dimensions: time horizon and degree of openness.
- Each model of industry-university collaboration has benefits and drawbacks; the best format will depend on the goals and capabilities of both partners.

COMPANIES INCREASINGLY recognize that to successfully innovate they cannot exclusively rely on their internal R&D. Working with external partners allows them to access different pools of knowledge and save R&D costs.[1] Universities are among the external partners that offer high promise, since they allow access to an enormous global pool of talent and skills.

Sometimes managers think dealing with universities equals only "technology transfer." While the use of university-owned intellectual property[2] has spurred much innovation in business, it is only the tip of the iceberg. Rather than merely licensing inventions, another often-underappreciated opportunity for companies is to get help from universities during the whole life cycle of their innovation projects.[3] For example, in the United Kingdom, businesses already spend more than 20 times more on university collaboration than on licensing technology from universities.[4]

However, working with universities poses considerable challenges for managers.[5] Two fundamental issues afflict collaboration. First, the open nature of academic science is at times in conflict with companies'

The pharmaceutical companies Novartis, GlaxoSmithKline, Merck and Pfizer have invested together in open science initiatives even though they are otherwise fierce competitors.

COURTESY OF NOVARTIS

need to protect technologies they use. Second, while academic research focuses on long-term challenges and thus may move more slowly, industrial R&D is driven by time-sensitive product development projects and day-to-day project solving. As a result, companies can sometimes find universities too slow and too bureaucratic to be good partners. Given that in the Organisation for Economic Co-operation and Development countries, expenditures on higher education R&D represent about $160 billion per annum, businesses that don't work with universities may be missing opportunities of significant proportions.[6]

These tensions are exacerbated by the fact that companies' collaborations with universities are often pursued in an ad hoc, piecemeal manner, led by individual initiatives rather than any corporate strategy. Managers who would never dream of leaving their customer or supplier relationships to chance may take an ad hoc approach to their university relationships, which can lead to duplication of effort, lost opportunities or squabbles over intellectual property.

Our research suggests that businesses can structure their relationships with universities in ways that make them much more valuable. (See "About the Research.") To do this, companies must actively embrace universities, using the differences between industry and academia to their advantage. As Claus Otto, program manager at Royal Dutch Shell PLC, says, "It is important to ask yourself: What can these university centers do better or different than we can?" Shell, for example, invests in university partnerships in areas where it does not yet make business sense for the company to build extensive technology capability.

To leverage value from universities, we argue that business executives need to consider two key dimensions. The first of these is the time horizon of the collaboration. Short-term collaborations are useful, common and relatively easy to facilitate if they are targeted and aligned to universities' and academics' ways of working. However, they require creative structuring, as the clock speed of academic research and business practice can be wildly divergent. Conversely, many academics think long-term, and this can be an advantage for a business as it may overcome managers' tendency to look to the next quarter. "Going long" with academics in the search for new ideas can unlock a range of possibilities and even help to create a new innovation ecosystem that will sustain the business five or 10 years into the future. However, such long-term collaborations require more patient investment and managerial attention to the design and governance of the collaboration or they can go easily awry.

The second dimension is the degree of disclosure of the results of the partnership. Openness facilitates rapid publishing, which constitutes the lifeblood of public science[7] and has the advantage of reducing transaction costs related to intellectual property. For companies, however, protection facilitates the commercialization of discoveries.

If we combine these two dimensions, we can see four different collaboration modes:

1. The idea lab, where managers put aside their desire for secrecy and work with academics to create new options and contacts.
2. The grand challenge, where managers and academics work together to create a new knowledge base that will be shared in the public domain.
3. The extended workbench, where managers work rapidly with university partners on proprietary problems and solutions.
4. Deep exploration, where the company creates rich and long-lasting relationships with university partners that, in turn, offer the business rights of first refusal to license collaboration results. (See "Four Models of University-Industry Collaboration.")

1. Open, Short-Term: Idea Labs In this type of collaboration, businesses engage university partners to work on problems that are relatively short-term, while providing the option for the academics to openly publish results. At first glance, this type of collaboration seems to provide little benefit to companies, given that they are not able to exclusively appropriate research outcomes. However, open exploration has a series of advantages. First, it can act as a "honey pot," helping to attract academics to the problems and challenges of the business. As these projects are well aligned to academic norms, many scientists find ways of drawing academic capital even from incremental, applied research. Second, not unlike speed dating, open ex-

ABOUT THE RESEARCH

This article draws on a series of research projects the authors carried out in recent years. Two waves of a mirrored survey were conducted in 2004 and 2009, collecting responses from hundreds of companies collaborating with universities and thousands of academic scientists.[i] The authors also conducted hundreds of formal interviews of at least an hour's duration with company executives, entrepreneurs and academic scientists in Europe and North America. They analyzed this material using inductive research techniques, including a study of how academic scientists generate academic capital from working with industry,[ii] an in-depth study of the Structural Genomics Consortium and a comparative study of university-industry centers. Finally, the authors draw on extensive secondary material, stemming from a systematic literature review of all peer-reviewed articles published between 1990 and 2011 on academic scientists' engagement with industry.

Kenan Fikri, *Where the Innovation Partnership between Business and Academia is thriving… and where it's not*, 7 BROOKINGS INST. 1, (2015) https://www.brookings.edu/blog/the-avenue/2015/07/22/where-the-innovation-partnership-between-business-and-academia-is-thrivingand-where-its-not/ [https://perma.cc/VHX6-TR4Y]

BROOKINGS

The Avenue

Where the innovation partnership between business and academia is thriving...and where it's not

Kenan Fikri Wednesday, July 22, 2015

U.S. research and development (R&D) is an increasingly troubled enterprise. So conclud colleagues Scott Andes and Mark Muro in a recent assessment of the quantity and cor the country's R&D investments.

Not only is the scale of the U.S. research effort insufficient, but its format is frequently sub-optimal as well. Too often federally financed basic research remains completely divorced from industry-led developmental work, to the detriment of the nation's innovation outcomes. After all, with technology growing ever more complex, collaborative forms of R&D—where researchers from different sectors actively engage with a wider ecosystem of users, competitors, and developers of complementary technologies—promise to be the most productive.

One place to look for insight into the nation's collaborative research scene is the National Science Foundation's (NSF) Higher Education R&D Survey, tracking the total value and source of all R&D expenditures routed through universities each year. In 2013, $67.2 billion worth of R&D was conducted at U.S. universities—$39.5 billion of that was funded by the federal government; $15.0 billion by the institutions themselves; and, coming in just below non-profit organizations and state and local governments, $3.5 billion by businesses. That's just 5 percent of the total.

The small size of this slice belies its importance: The metric is a useful proxy for the extent to which industry and academia are engaged in a productive, innovation-oriented partnership in a region. The table below lists the 10 major metro areas where these funds were most significant relative to the size of the local economy.

Metro Area	University-based R&D funded by business (in thousands)	University-based R&D funded by business per thousand dollars of GDP	Universities w/ >$1 million in R&D funded by business
Albany-Schenectady-Troy, NY	$208,653	$4.48	SUNY Albany, C. of Nanoscale Science & Eng.; Rensselaer Polytechnic Institute; Albany Medical College
Columbus, OH	$110,551	$0.97	Ohio State U.
Wichita, KS	$27,534	$0.87	Wichita State U.
New Haven-Milford, CT	$32,357	$0.73	Yale U.

Austin-Round Rock, TX	$72,587	$0.70	U. TX, Austin; TX State U., San Marcos
Raleigh, NC	$46,415	$0.69	NC State U.
Boston-Cambridge-Newton, MA-NH	$199,997	$0.54	MIT; Harvard; Tufts; U. of NH; Brandeis; Northeastern; Boston; U. of MA, Lowell; Boston College
Madison, WI	$22,168	$0.52	U. of WI, Madison
Salt Lake City, UT	$37,178	$0.49	U. of Utah
Charleston-North Charleston, SC	$15,222	$0.47	Medical U. of SC

Download the full dataset with information for the country's 100 largest metro areas here.

Albany, NY, is an outlier at the top of the list. There, public-private investment in a nano-technology center of excellence has seeded a rapidly-expanding cluster of firms around semiconductors that has already registered some major breakthroughs. Astonishingly, after more than doubling from the previous year, by 2013 the scale of private sector R&D conducted at university-based facilities in Albany surpassed Boston in both absolute and relative terms. (Examine R&D expenditures across all sources of funding, however, and five times more R&D is conducted in Boston). Similarly, the National Institute for Aviation Research, housed at Wichita State and embedded in a vibrant aerospace industry cluster, propels Kansas' largest metro area to the top of the ranks. From Austin to Boston and Salt Lake City, it appears that applied R&D institutions whose core competencies align squarely with the local industry base tend to attract the most private investment.

This measure is only suggestive of the strength of the relationship between the private sector and academia in a place, though. The businesses funding the R&D may not be located in the same region as the university where it is performed. Universities also use many other avenues to push their innovations out to market: licensing intellectual property or fostering spin-offs, for example.

Nevertheless, the measure captures something important. The metro areas at the top of the list are prosperous and dynamic locales with thriving advanced industry bases. Many places lack the robust university-business collaborations observed in these lucky few, however. Fully one-fifth of the country's large metro areas saw less than $1 million of business-funded R&D at their universities in 2013. A few places, such as Boise and Bridgeport sustain innovative economies through a variety of other avenues. More commonly, though, the places without such high-performing anchor institutions are the very places struggling to transition into high-value industries, such as Grand Rapids, Scranton, Jackson, Las Vegas, and Stockton. These NSF data reveal that the financial resources that academia and the private sector jointly bring to bear for R&D remain too small in most places and too thinly spread nationwide.

Yuqi Liao contributed to this post.

Karen Tkach Tuzman, *Doctors in the House*, BIOCENTURY (2017)
https://www.biocentury.com/printpdf/291228

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BC INNOVATIONS | STRATEGY

DOCTORS IN THE HOUSE

BY KAREN TKACH TUZMAN, SENIOR WRITER

While academic partnerships have become par for the course in pharma, GSK is going a step beyond the standard model of external alliances by bringing professors in-house with virtually unrestricted access to its activities. The initiative is the latest example of pharmas lowering their guard in order to both access cutting-edge science and foster the ecosystem's future innovators.

It's a necessary but worthwhile price to pay, according to Paul-Peter Tak, who created the program, dubbed Immunology Network, in 2015. Tak is Chief Immunology Officer and SVP of the R&D Pipeline at GlaxoSmithKline plc.

"Our philosophy is to be very open with the external world in terms of target identification and target validation. We compete in terms of molecules," Tak told BioCentury.

The core of the Immunology Network involves providing academic researchers with three-year sabbaticals inside GSK's R&D hub in Stevenage, where they are given a lab, personnel and access to the pharma's technology, compound libraries and internal meetings and data.

Tak noted the program is "not transforming them into GSK employees. They continue to be employees of the university, and we reimburse the university."

Moreover, the researchers can take their discoveries with them when they leave.

"If they discover something within our facilities that's completely based on their own research, then they actually own the IP. I think no other company has done it in this way," said Tak.

Louise Modis, the Immunology Network's scientific director, told BioCentury that the program's IP terms boil down to the principle that "they own the biology IP that they bring and that they do, and GSK protects molecules that are going into the clinic."

Thus far, the program has brought in seven investigators, expanded the indications of two internal programs, and founded an undisclosed newco in a white space area, which GSK is funding as a minority investor and has the option to buy.

Luke O'Neill, a program participant and a professor of inflammation research at Trinity College Dublin, gives GSK credit for creating something "brand new," and based on the program's success so far, thinks other companies should follow suit. "GSK was taking a risk, because nobody had done this before."

"Our philosophy is to be very open with the external world in terms of target identification and target validation. We compete in terms of molecules."

Paul-Peter Tak, GSK

TRANSPLANT MODEL

Tak joined GSK in 2011, and is one of the two primary leaders reporting to outgoing CSO and President of R&D Patrick Vallance, who on Jan. 1 will hand the reins over to Hal Barron, currently president of R&D at longevity company Calico LLC.

Vallance is leaving the pharma at the end of March to become the U.K. government's chief science adviser and head of the government's Office for Science. The Immunology Network program will continue under GSK's new leadership.

Having spent the bulk of his career as an academic researcher and physician, Tak created the Immunology Network to fill what he believed was a crucial gap in the pharma's extensive roster of external partnerships (see "Out of the Dark").

SIDEBAR: OUT OF THE DARK

In one of its most ambitious academic partnerships, GlaxoSmithKline plc and its collaborators in the ATOM consortium are feeding reams of shelved data into U.S. Department of Energy supercomputers, with the goal of using the resulting algorithms to go from target identification to a clinic-ready compound in 12 months.

John Baldoni, SVP of R&D at GSK, told BioCentury the consortium aims to tap the wealth of information hidden in the pharma's "dark data." "Companies have an obligation to share the data they're never going to use again," he said.

The Accelerating Therapeutics for Opportunities in Medicine (ATOM) consortium was launched last month by GSK, the DOE's Lawrence Livermore National Laboratory, NIH and the University of California San Francisco.

The project taps into a growing consensus that data locked away in pharma archives could provide valuable clues to either speed up drug development or serve as starting points for new projects.

The consortium will use the partners' chemical, biological and clinical data to create a series of computational models to guide drug discovery and development. The idea is that the models will capture underlying patterns governing small molecule properties such as toxicity, PK, blood-brain barrier penetration and effects on gene expression in disease models.

Baldoni said the first steps are to establish an organizational structure, computing infrastructure and data management policies.

"We're establishing architectures for digesting dissimilar data from different organizations," he said, including safety and tox data on hundreds of compounds, over 1,000 crystal structures, readouts from over 60 clinical trials, and thousands of rat and dog PK studies.

In the consortium's third year, the partners will test the models by attempting to create a personalized therapy for a single cancer patient, focused on a target specific to his or her disease.

ATOM is building laboratory space in San Francisco, where it plans to partner with companies with technologies that can "fill gaps in the algorithms," such as high throughput organoid screens and high-content single-cell imaging, said Baldoni.

He believes that because ATOM crunches its data into algorithms, other pharmas could join in without risking IP.

"What if it was set up such that they couldn't see the GSK compounds -- they could only see algorithms derived from the compounds?" said Baldoni. "The only group that sees all the molecules is Livermore." The companies could then take the models and use them to create their own IP in-house, he said. "We don't want to generate any molecule IP in ATOM except for the one molecule we make to treat that one patient."

-- *Karen Tkach Tuzman*

"There was one piece missing. That piece was actually bringing in senior academics into GSK," said Tak, who remains affiliated with University of Amsterdam, Ghent University and University of Cambridge. "We do this of course all the time to make them GSK employees. But here we did it differently, where they continue to do their academic research in a much more 'blue-sky thinking' way."

John Hamilton, a professor of medicine at University of Melbourne and the first investigator recruited into program, told BioCentury the program creates a microcosm inside the company that allows for unprescribed discoveries. "There's no pressure for people to come up with targets, because that's not how it really should work in academia. Some of the best results will probably come out of left field."

GSK has toyed with various structures for partnering with academia, such as its Discovery Partnerships with Academia (DPAc) program, and for incubating innovation from GSK scientists within in its Discovery Performance Units (DPUs).

Tak noted that unlike the DPAc program, which is "focused on very specific projects that could lead to a medicine," the Immunology Network is geared to capitalize on emerging areas that are further from the clinic. They can also fall outside the purview of the DPUs.

"When you talk about business development opportunities in fields that do not fit in the DPU's territory, then people are not interested, because they need to be focused," he said. "These very new opportunities are very high-risk, because there's less data. So I think the Immunology Network can complement that model with the creation of new companies."

While Tak's background as a rheumatologist played a role in the program's immunological focus, he said the field's recent successes, and relevance to a broad range of therapeutic areas such as autoimmunity, cancer and neuroinflammation, made it "a very good starting point to work in a new model."

"GSK was taking a risk, because nobody had done this before."

Luke O'Neill, Trinity College Dublin

HOST ENVIRONMENT

The Immunology Network has four pillars, the center of which is the Immunology Catalyst Program, through which academics join GSK's campus. The Immunology Innovation Fund supports the Catalyst investigators, while the External Immunology Board contains academic experts who advise the company and its professors-in-residence.

The fourth pillar is a series of Immunology Network Summits that convene immunologists and vaccinologists from inside and outside the company.

Immunology Catalyst investigators are selected based on their expertise and projects in white space areas such as immunometabolism, crosstalk between pattern recognition receptors and complement signaling, and systems approaches to understanding autoimmune disorders (see "Immunologists-in-Residence").

TABLE: IMMUNOLOGISTS-IN-RESIDENCE

So far, seven academic researchers have participated in GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)'s Immunology Catalyst sabbatical program. Professor John Hamilton from the University of Melbourne participated in a seven-week pilot version of the program; the subsequent six participants may stay at GSK for sabbaticals lasting up to three years.

Date joined	Name	Primary academic institution	Research focus
June 2015	John Hamilton	University of Melbourne	Macrophage and granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2) biology in inflammation and osteoarthritis
February 2016	Luke O'Neill	Trinity College Dublin	Immunometabolism
April 2016	Kathy Triantafilou	Cardiff University	Pattern recognition receptors and complement signaling
April 2016	Seth Masters	Walter and Eliza Hall Institute of Medical Research	Autoinflammatory disorders
July 2016	Timothy Radstake	University Medical Center Utrecht	Systems approach to understanding autoimmune disorders
July 2016	Florent Ginhoux	Agency for Science Technology and Research (A*STAR)	Myeloid cell development
October 2016	Clare Bryant	University of Cambridge	Pattern recognition receptors and innate immunity

"All the people that were recruited are working on frontier science," said O'Neill. "One motivation for GSK is to make sure they're on top of these emerging areas, and the Catalyst allows them to do that."

The Immunology Innovations Fund provides financing to turn the academics' translational work into commercial opportunities.

Tak runs proposals for new immunology investments by members of the External Immunology Board with relevant expertise to see "whether they can survive the challenge of academics who probably know more about that field than anyone else."

"When an idea bubbles up in the Immunology Catalyst that could lead ultimately to a drug -- say you need a mouse experiment for £100,000, whatever it may be -- if it's a great proposal, we will spend the money to bring it to the next inflection point," said Tak.

And if those experiments yield positive results, Tak said GSK is "completely free in our thinking" about how to take Immunology Catalyst projects further.

"It may lead to an additional investment from the Immunology Innovation Fund to bring it to the next inflection point," he said. "If it seems like a very exciting early idea that needs to be incubated further in the academic institute, maybe we'll support it with a grant. If it's more mature it could even lead to a DPU, the basic discovery entity within GSK. Or, we could co-create a biotech company based on new emerging science."

"We're raising a new generation of leaders in academia. The idea is that they go back, and become very strong leaders who understand pharma."

Paul-Peter Tak, GSK

OUTPUTS FROM INSIDE

Tak said the Immunology Network has given GSK "an incredible wealth of deliverables in the last two and half years," both in terms of commercial opportunities and relationship building.

According to Tak, both External Immunology Board and the Immunology Catalyst investigators have guided the pharma's business development decisions, and have pointed the pharma to new opportunities for its compounds.

GSK sees an acquisition opportunity in the first newco founded by an Immunology Catalyst investigator, which the pharma is co-financing with VCs.

"We will be minority shareholders by design, we don't want to control it," said Tak. "When it matures, at least to a medicine, then we will be the first to say this is really interesting, we want to buy it at a competitive price."

The program has also helped GSK get insights on new indications for an undisclosed compound based on research that is not in the public domain.

"We in-licensed a medicine that was developed for one indication, whereas we knew based on knowledge in the Immunology Catalyst that has not been published that it should also work for a completely different indication," said Tak. "That's where we're going to develop it now."

In addition, Hamilton made the case that GSK should test its anti-GM-CSF mAb GSK3196165, which the company had in-licensed for rheumatoid arthritis, in osteoarthritis (OA) based on his research. The pharma and partner MorphoSys AG now have the mAb in Phase II testing for both OA and RA, and in Phase I testing for multiple sclerosis.

In January, Hamilton and Tak co-authored a *Nature Reviews Drug Discovery* article summarizing the therapeutic applications for GM-CSF and other colony-stimulating factors. "It has led to an expansion of indications," said Tak.

Tak said the cross-disciplinary Immunology Network Summits have already launched "concrete new projects" at GSK, including a collaboration looking at undisclosed factors "from the world of immuno-inflammation" that keep activated T cells out of tumors, or promote immune suppression by stromal cells and macrophages.

"If they discover something within our facilities that's completely based on their own research, then they actually own the IP. I think no other company has done it in this way."

Paul-Peter Tak, GSK

Tak also counts the visiting investigators' growing understanding of pharma as a key gain.

"We're raising a new generation of leaders in academia. The idea is that they go back, and become very strong leaders who understand pharma," said Tak.

He added that the academics change in the GSK environment, and not only because they start to think more about drug discovery. "They also get an understanding of what it takes take to become excellent in delivering projects, what quality really means in terms of industry standards, and what it means to develop people," Tak said.

For example, he thinks the investigators' experiences will improve future licensing negotiations with their home institutions, as the researchers will have more informed perspectives on the values of their preclinical assets and the investments required to develop them.

O'Neill said GSK researchers have also been learning from the Immunology Catalyst members, in some cases by temporarily joining an investigator's lab.

"It's a great opportunity because they step out of their traditional role," said O'Neill. "Then they go back to their original tasks, and hopefully have picked up new skills and approaches."

Hamilton thinks the sabbatical model is particularly well suited to fostering trust between academic and industry researchers. “When you get to know people and you build up relationships, then you can start talking freely,” he said.

Modis noted the company had to commit significant human resources to build that trust. “We really invested in people here who are experts in operations, communications, immunology and drug discovery to build a relationship with them and to really make their transition to industry manageable. Just giving them money and space is not going to work.”

“These are all things that sound like soft values, but they’re very important,” said Tak.

COMPANIES AND INSTITUTIONS MENTIONED

Calico LLC, South San Francisco, Calif.
Ghent University, Ghent, Belgium
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
MorphoSys AG (Xetra:MOR; Pink:MPSYY), Martinsried, Germany
National Institutes of Health (NIH), Bethesda, Md.
Trinity College Dublin, Dublin, Ireland
University of Amsterdam, Amsterdam, the Netherlands
University of California San Francisco, San Francisco, Calif.
University of Cambridge, Cambridge, U.K.
University of Melbourne, Melbourne, Australia
U.S. Department of Energy, Washington, D.C.

TARGETS

GM-CSF (CSF2) - Granulocyte macrophage colony-stimulating factor

REFERENCES

Hamilton, J., et al. **“Anti-colony-stimulating factor therapies for inflammatory and autoimmune diseases.”** *Nature Reviews Drug Discovery* (2016)

The Ethics of For-Profit Funding

The prospect of for-profit research funding raises a number of significant ethical concerns regarding the independence of the research and the well-being of the subjects. Much of the work in research ethics presupposes a more traditional funding source, such as grants from government institutions and non-profit foundations. Adding in the dimension of for-profit funding results in changed incentives that may or may not require additional ethical safeguards to protect patient safety and academic integrity.

The purpose of this discussion is to explore the unique conflicts of interest that arise from pursuing for-profit capital for translational research, to understand how for-profit funding changes the research agenda of an institution, and to articulate the checks and balances that must be implemented as an institution shifts from public funding to for-profit funding in order to safeguard research subjects and ensure ethical research.

Jane Maienschein et al., *The Ethos and Ethic of Translational Research*, 8 AM. J. OF BIOETHICS 43, at 43–44, 49–50 (2008) (Excerpt) https://www.tandfonline.com/doi/abs/10.1080/15265160802109314

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Target Article

The Ethos and Ethics of Translational Research

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Calls for the "translation" of research from bench to bedside are increasingly demanding. What is translation, and why does it matter? We sketch the recent history of outcome-oriented translational research in the United States, with a particular focus on the Roadmap Initiative of the National Institutes of Health (Bethesda, MD). Our main example of contemporary translational research is stem cell research, which has superseded genomics as the translational object of choice. We explore the nature of and obstacles to translational research and assess the ethical and biomedical challenges of embracing a translational ethos.

Keywords: Translational science, history, National Institutes of Health, stem cell research

Translational research has become a mantra in Washington, DC, and beyond. Inspired by United States (US) congressional demands for "results," the National Institutes of Health (NIH, Bethesda, MD) issued a "Roadmap" that has marked the parade route for translational research. Groups such as the National Academies of Science (Washington, DC), medical advocacy groups, scientific professional societies, and private foundations have widely embraced the emphasis on translation and the funding that has come with it. This is bringing a new social contract for the way science works in society. Instead of implicit promissory notes about eventual results, scientists must promise specific results up front. Moreover, they must produce results sooner rather than later and more specifically targeted for particular ends rather than for general good. Finally, there is now far more guidance from public investors. The result is an ethos of translation.

It is time to examine this emerging translational ethos critically. We explore what the call for translation means, discuss stem cell research as the most revealing example of translational research, and analyze implications of the translational imperative. We probe the translational metaphor, arguing that language matters. Due to space constraints, we focus on the US, although the ethos of translation in biomedical research has become prevalent globally. We conclude by arguing that the widespread push to translation distorts the science, sometimes in indeterminate ways, and also distorts bioethical discussion.

ESTABLISHING TRANSLATIONAL RESEARCH: WHO, WHAT, WHEN, WHERE, AND WHY?

It is not the case, of course, that the term *translational research* has brought entirely new meanings to the whole biomedical research enterprise. Yet when NIH Director Elias Zerhouni issued a new Roadmap focused on translation into clinical results, the world noticed. It is worth understanding what the Roadmap envisions in order to assess its implications. The process of developing the Roadmap began in 2002 and, by 2003, concluded that:

> Ideally, basic research discoveries are quickly transformed into drugs, treatments, or methods for prevention. Such translation lies at the very heart of NIH's mission. Although NIH has historically been successful by funding medical research that has helped to transform once acute and lethal diseases into more chronic ones, it has become clear to the scientific community that our country will need to recast its entire system of clinical research if we are to remain as successful as in the past (NIH) Office of Portfolio Analysis and Strategic Initiatives [OPASI] 2008a).

Note the suggestion that the "scientific community" had already embraced this vision and that we must therefore change the way we do science and "recast the entire system." This was a broad call for change. But change in what way? It is important to examine the Roadmap language closely because it is a carefully

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negotiated political instrument that has had broad impact in shaping thinking about biomedical sciences and their applications.

Scientists have been excellent at making discoveries, with some clinical successes, the Roadmap acknowledged: "Yet the exciting discoveries we are currently making require us to conduct even more efficiently the complex clinical studies needed to make rapid medical progress, and to further inform our basic science efforts. This is undoubtedly the most challenging, but critically important, area identified through the NIH Roadmap process" (NIH OPASI 2008a). How can we move more efficiently from discovery to clinical applications? According to the Roadmap, we must develop strong new partnerships among laboratory researchers, clinical researchers, clinicians, community clinics, those developing medical delivery systems (e.g., drugs, devices), and clinical research networks; moreover, we must "fully involve and empower the public in the research process" (NIH OPASI 2008a).

It is taken for granted that: "To improve human health, scientific discoveries must be translated into practical applications (NIH OPASI 2008a)." This is a two-way process in which, "Basic scientists provide clinicians with new tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations" (NIH OPASI 2008a). Already, "Translational research has proven to be a powerful process that drives the clinical research engine" (NIH OPASI 2008b). Yet to carry out successful translations, the NIH claims that we need a "stronger research infrastructure" (NIH OPASI 2008b) and other enhancements (Sidebar 1). With these changes, the NIH can improve the health of the nation by promoting the translational research enterprise that will move us more quickly, effectively, and across a wider range of medical problems from bench to clinic (Pober et al. 2001).

On May 23, 2003, the NIH held a meeting in Crystal City, VA, on "Enhancing the Discipline of Clinical and Translational Sciences" to discuss the challenges (the content of Sidebar 1 was one of the key topics of discussion). To help overcome barriers to translation, part of the program was to streamline the process by which products are taken up by private companies, tested, developed, and marketed by the medical industry. For present purposes, our focus is on the translational research itself, leaving the industrial developments in the background.

The idea of translating research into clinical applications is not new; indeed, it may be coextensive with the history of biomedical research. But what is supposedly different here is an explicit recognition that translation is not easy, not inevitable, not unidirectional, and, indeed, not happening. This recognition resulted in the attempt to re-engineer health research institutions and practices so as to facilitate the bench-to-bedside translation.

ACCEPTING THE TRANSLATIONAL IMPERATIVE

By 2003, the NIH had thus issued a strong challenge to change the way scientists work, and the research and business communities had begun to respond. Often private foundations can act more quickly than large public or academic institutions, as indeed happened in this case. For example, the Bill and Melinda Gates Foundation (Seattle, WA) highlights the Grand Challenges in Global Health initiative, "a major effort to achieve scientific breakthroughs against diseases that kill millions of people each year in the world's poorest countries" (Bill and Melinda Gates Foundation 2008). As indicated in the press release accompanying the first round of grants (43 grants averaging $10 million each for research projects involving collaborations in 33 countries), "the ultimate goal of the initiative is to create 'deliverable technologies'—health tools that are not only effective, but also inexpensive to produce, easy to distribute, and simple to use in developing countries" (Bill and Melinda Gates Foundation 2008). The program began in 2003, in collaboration with the NIH, as an explicit response to the challenges of translation, though the Foundation was focusing on the side of deliverables.

Voluntary health organizations have always had mission-oriented programs explicitly emphasizing development of therapeutics for specific medical disorders, but they have also undergone transformations in the push to translation. They have felt pressures to produce results in areas ignored by major industry, and mission-oriented organizations seek urgently to do what they see as essential rebalancing of the overall funding portfolio. The feeling is that not only will such investment programs generate a greater awareness of the challenges and opportunities of translating research into action, but it will also help with workforce shortages by attracting a more diverse and deeper talent pool to the translational activities (Duyk 2003).

Additionally, NIH reactions are instructive. Earlier in 2003, in an article in *Science* (Collins et al. 2003), leaders of the National Human Genome Research Institute (Bethesda, MD) programs had announced steps for genomics research and applications. We now have the human genome, Francis Collins and his collaborators had declared happily, and so in this 50th year after the discovery of the structure of the DNA molecule, "the genomic era is now a reality" (835). They continued, noting that it was time for a new vision for genomics, as "an opportunity to explore transformative new approaches to achieve health benefits" (Collins et al. 2003, 836). The Human Genome Project had generated a vast amount of data and now, they declared, "The practical consequences of the emergence of this new field are widely apparent" (835).

Yet development of genome-based diagnostics and therapeutics does not happen on its own, and the adoption and integration of genomic tools requires appropriate stewardship: "Translating the success of the HGP into medical advances intensifies the need for proactive efforts to ensure that benefits are maximized and harms minimized in the many dimensions of human experience" (Collins et al. 2003, 836). To move forward most effectively, Collins and colleagues offered a model for the architecture of the emerging research enterprise, an elaborate multi-tiered building

incidentally and incompletely. At some point, we must address the tensions created within science by the rush to translation. Stem cell research raises questions about relationships between basic biological research, clinical research, and medical therapies. It suggests that the push for translational research may actually transform the participating disciplines.

Separate research fields often share goals. For example, both basic developmental biology and certain subfields of clinical medicine want to find ways to repair or regenerate compromised systems using stem cells, while basic toxicology and clinical pharmacology ask how stem cell lines might serve as assays for testing new drugs. Shared goals encourage making connections across disciplines to promote conceptual unification and efficiency (economic and otherwise). The agenda for translational research encourages such connections (and perhaps also more interdisciplinary or multidisciplinary research) yet also raises questions about how they can be more than superficial.

Skeptics might note that, although stem cell researchers often invoke the rhetoric of translation, and even provide evidence of their commitment to it by having research teams with both basic and clinical researchers, actual practices of such interdisciplinary translational research teams have not been adequately documented or scrutinized (Wainwright et al. 2006). The excitement surrounding stem cells has brought together an unusual range of research programs, both within and across disciplines. Underneath the surface of what often are presented as unified goals lay different fundamental concepts: some researchers are searching for "stemness" and examining how stem cell development works, in detail and in order to understand the processes themselves. Others have turned to stem cells because they appear to provide the most promising approach to questions previously asked within different contexts (e.g., clinical researchers interested in neural degenerative diseases). Questions remain about how these different approaches can best work together and what difference it makes when they do.

Furthermore, the institutional contexts where stem cell research is done have changed dramatically: there are institutes devoted to stem cell research (often termed *regenerative medicine*) ,which include researchers from different fields and explicit discussion of translation in their mandates. New biotech enterprises are arising with a range of promises and proposals to promote stem cell science and results. How these changing institutional contexts affect the science and influence the likelihood of "success" remains unclear.

LESSONS FOR SCIENCE, LESSONS FOR ETHICS

Science policy decisions are typically shaped by powerful political forces with particular assumptions, and often policy is driven primarily by funding interests. Scientists lobby for increased funding; patient advocacy groups push for more funding (and presumed results) while also raising funds and investing in translational projects; and other advocacy lobbyists push their own set of values that influence the funding. As we accept a translational model for research, including the expectation of applied payouts, what are the consequences? What are the effects for scientists? For societal expectations? What are the policy implications? The ethical implications?

We can, as usual, bring ethical considerations to bear in assessing particular research protocols. But how does that change if we are assessing both the research and its expected translational results at the same time? If we are indeed entering a new social contract, we have much to learn about how it will work and the implications for scientists, for the scientific enterprise, and for scientific institutions as well as for the public.

Stem cell science reveals new ideas about the 'right way' to do science. Although we have seen historical examples of "mission-driven science," such as the push to build atomic bombs, reach the moon, or sequence the human genome, this case is different. In this case, scientists are not the main experts for deciding how their mission is to be accomplished. Rather, those considered relevant "experts" have expanded dramatically, to include not only politicians but also bureaucrats, members of voluntary health organizations, ethicists (and would-be ethicists), clinicians, and even celebrities. Public, political, and industrial demands, particularly with regard to what the products of the research should be, shape the landscape within which the research trajectory is determined, and that landscape is dominated by various demands for translation. Where the Vannevar Bush model emphasized purity of science in its own right (even when it could also have worthy applications), today's translational research builds certain (and sometimes dubious) end goals into the research from the start. One lesson is that *assuming* outcomes (however well-intentioned) alters the research endeavor.

In addition, the translational ethos can lead to distorted ethical results. For example, some ethical discussion surrounding stem cell science has addressed how science might offer a technical "solution" to ethical problems associated with embryonic stem cells (Snyder et al. 2006). In particular William Hurlbut has suggested altered nuclear transfer as a technological end-run around some ethical problems posed by harvesting embryonic stem cells (Hurlbut 2005). Altered nuclear transfer involves manipulating the genome of eggs prior to fusion with somatic cells, in order to prevent the resultant embryos from developing normally beyond the blastocyst stage, thereby rendering the non-viable and supposedly solving all ethical problems associated with their procurement.

We are concerned that this proposal has an important negative effect on the ethical discourse about stem cell research. It distorts the discourse by taking the desire for translating science into results as given, then asserts that technology can determine when life begins and what life is and thereby purportedly solve the ethical problems while preserving the translational objectives. Yet technology and translational assumptions cannot solve a highly contentious

issue with a long, rich and complicated history (Maienschein 2003). Furthermore, this approach suggests that the *only* ethical problem with stem cell research is the "when life begins" issue, thereby highlighting the "potential person" or "viability" problem at the expense of the many other ethical issues raised by embryonic stem cell research (e.g., Baylis and Downie 2005; Lysaght et al. 2006; Giacomini et al. 2007)—including those raised by embryonic stem cell research as translational research (Robert et al. 2006). Moreover, such putative "solutions" risk derailing stem cell research from more scientifically sound paths, inappropriately delaying potential clinical applications while contributing nothing to our basic understanding of development or of the clinical potential of human embryonic stem cells. The problem is taking the translation as an unquestioned desirable goal and trying to make the ethics fit. This distorts the ethical discussion as well as the science.

What about the impact of the translational ethos on our notions of science and scientific change? Does all the rhetoric about translation and the requirement that scientists make their translational outcomes clear and of first priority actually bring more than a new model for scientific research? Does it actually change the science done, and if so in what way is it truly new? And what difference does that make? Does a translational model demand a different role for individual scientists in doing science, such that they are now driven by the need for translation and must choose particular kinds of scientific questions or methods or organisms? If so, is the translational model actually a stable strategy for scientific research? Or by pushing so much emphasis on development and results does this approach, in fact, distort the generation of scientific knowledge? Here, we have aimed to show that distortion is indeed occurring in the case of stem cell science both within the basic science and in the surrounding ethical discussions. This case leads us to wonder how other areas of biomedical research might be similarly affected and leads to this call for further analysis.

It is not the case that reflecting on outcomes is always problematic, of course. Although assuming (and imposing) the expectation of meeting particular outcomes can be problematic as a guide for the scientific research enterprise, openly and collaboratively *negotiating* outcomes for scientific research may nonetheless be entirely desirable. Crafting tools for undertaking such negotiations is a fraught task, but an important one to foster connections between scientific research and valuable social goals - especially but not exclusively where the research is publicly funded (Sarewitz 2000; Guston 2004; Pirtle 2006; see also Kitcher 2001). The problem with the translational ethos is not translation as such, but rather the nature of the source language and certain presumptions about outcomes. We all want results from our science, but too many questions—what will count as results, who will certify these, and who is left out as a result of the choices—remain wide open. It should be simultaneously possible to protect the integrity of the source language, generate new understanding through "translation," and negotiate frankly and responsibly about the desirability of particular outcomes. That is a task to which historians and philosophers of science, ethicists, and policy scholars should turn their sustained and focused attention.

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Risky Business, 9 NATURE CHEMICAL BIOLOGY 1 (2013)

Risky business

Public-private partnerships can reinvigorate precompetitive scientific research and de-risk drug discovery programs to help them meet demand for better and safer therapies.

With the establishment of the National Center for Advanced Translational Sciences (NCATS) in December of 2011, the National Institutes of Health (NIH) and the US government made a commitment to directly invest in translational research. With NCATS, the NIH will invest tax payer dollars in the riskiest 'precompetitive' stages of drug discovery. NCATS has also articulated a commitment to bring together expertise from the public and private sectors to promote collaboration and transparency. A year after the formation of NCATS, it remains less than clear why public monies should be allocated to de-risk drug discovery; how precompetitive space will be defined, especially as it relates to intellectual property (IP); and how their investments will be leveraged to draw private sector involvement and to maximize efficiency in a manner that is distinct from approaches that have failed to keep pace with the needs of society.

Important aspects of the vision that shaped NCATS are shared with other emerging models for research. Public-private partnerships (PPP), which are funded and operated as collaborations between government (or governments) and one or more private companies or institutions, are one such model. In this issue, Knapp and colleagues (Commentary, p. 3) outline a progressive PPP, a kinase chemical probe partnership, where reagents, data and knowledge resulting from the partnership are made publically available and the scientific strengths of these disparate sectors are combined to maximize efficiency by eliminating duplication of effort.

Improving efficiency or getting more high-quality science per investment dollar is a tangible outcome that justifies the investment of public money in these types of programs, and this objective should be intrinsic to any program launched by NCATS. Despite technological advances and efforts to increase productivity over the past 60 years, the rate of new drug approvals has remained constant at the same time that research and development (R&D) costs have grown exponentially (*Nat. Rev. Drug. Discov.* **8**, 959–968, 2009). Thus, modern paradigms for R&D are functioning at maximum capacity. In these R&D models, scientists at different institutions often work on similar or even identical problems; the outcomes of these programs can remain hidden behind the walls of IP or can take years to reach the public domain. By mandating public dissemination of all major findings, costly and time-wasting redundancies can be eliminated.

Involvement of the public sector in PPPs is the best way to ensure that participants will make reagents and the data generated by the initiative openly accessible. Thus, a public partner is necessary to maintain open access to emerging scientific knowledge, and having this information in the public domain provides the type of end value beyond efficiency gains that merits public investment. Indeed, the competition that ensues once precompetitive data is released can be a powerful force driving innovation. Thus, public dissemination of emerging scientific knowledge should be another major objective for NCATS.

This open-access model, however, comes at a cost. Information in the public domain becomes more limiting as research progresses; it can restrict opportunities for IP, which is the engine that ultimately drives private sector involvement in research. Thus, defining precompetitive space and adopting a plan for IP is a major challenge for any drug-discovery initiative.

Defining precisely what constitutes precompetitive research and whether precompetitive research should be subject to patent protection are major questions that NCATS has yet to address. Precompetitive space can be defined by the state of biological understanding, where research is focused on discovery as opposed to optimization. Most agree that early-stage research with relatively high biological risk (pretarget validation), where cost-benefit models for sharing information are most advantageous, constitutes precompetitive space. Some argue that precompetitive space extends through Phase II clinical trials, where targets are ultimately validated in humans (*Nat. Chem. Biol.* **5**, 436–440, 2009). A challenge for the PPP model as projects are selected and research progresses will be finding consensus among partners as to where this space ends and where protected research should begin. This distinction will most likely need to be made on a case-by-case basis. Likewise, NCATS has delineated specific priority research areas (*Sci. Transl. Med.* **3**, 90cm17, 2011); the institute should provide scientists and potential collaborators with information about how precompetitive space has been or will be defined and how they will handle IP to encourage private sector investment without stifling efficiency or innovation.

The leadership at NCATS should look to existing initiatives to identify innovative ways to fund biomedical science. The Structural Genomics Consortium (SGC; http://www.thesgc.org/), a PPP with binational and multicorporate support, provides an interesting example. The SGC, which was started by the private sector with the directive to carry out basic science of relevance to drug discovery, has successfully provided open access to precompetitive data and explicitly never files patents. In particular, the government agencies behind the SGC can help NCATS address challenges implicit in collaborating with the private sector, investing in the best science while being restricted by their geographic jurisdiction (defined by national boundaries) and moving beyond traditional funding mechanisms that are based on a competitive process following a call for proposals. Because these traditional mechanisms are not suited to the type of objective-driven, collaborative and open-access research that are precisely the factors that distinguish these new models from those that have failed, we are eager to see NCATS discard tradition and find a new approach for funding high-priority science.

Risk-sharing partnerships that leverage the expertise and resources of the public and private sectors offer efficiency advantages that justify an optimistic outlook for the future of drug discovery. Given the immutable reality that drug development is an expensive and high-risk but necessary enterprise, public money should be invested in this space. The type of PPP described in the Commentary in this issue outlines a paradigm-shifting mechanism whereby public dollars can draw private sector funding toward the public good by providing an efficient, objective-driven and IP-free research plan. NCATS, which has articulated objectives in common with this PPP and the SGC, has an unparalleled opportunity to reformulate drug discovery models, but it must face the substantial challenges of defining the scope of precompetitive research, negotiating the complex IP landscape and creating new funding models that entice the private sector to co-invest in discovery science.

Megan E. Collins et al., *Navigating the Ethical Boundaries of Grateful Patient Fundraising*, JAMA (August 27, 2018) https://jamanetwork.com/journals/jama/fullarticle/2698675 [https://perma.cc/8PGZ-84MS]

VIEWPOINT

Navigating the Ethical Boundaries of Grateful Patient Fundraising

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Health care institutions in the United States receive more than $10 billion annually in charitable gifts.[1] These gifts, often from grateful patients, benefit physicians, institutions, and other patients through the expansion of clinical and research activities, community-based programs, and educational initiatives. With a decade-long reduction in federal funding for research, which has just been partially restored, and constraints on state and local budgets for clinical programs, the relevance of grateful patient philanthropy has increased over the past decade.

Philanthropy provides a way for patients to contribute to a cause that they find meaningful and exert a positive influence on the health and well-being of future patients.[2] These donations are often provided in response to excellent medical care.[3] Ethical issues can arise within the course of grateful patient fundraising that are related not only to the clinical context but also to the often-complex relationships among grateful patients, development officers, clinicians, and medical institutions. These issues require careful consideration.

There is limited literature examining the ethical issues that grateful patient fundraising raises for physicians. The last American Medical Association report on this topic was issued in 2004.[4] The report recognized the value of philanthropy and physicians' role in it, but rightly emphasized the paramount importance of patients' rights and welfare in efforts directed at grateful patient fundraising. As such, the report highlighted the need to ensure that gifts are voluntary, that patients should not perceive an obligation to give, and the need to protect privacy. In addition, the report cautioned against physicians initiating discussions about philanthropy during direct patient care. Furthermore, there is also limited literature about the ethical issues grateful patient fundraising poses for development professionals and the health care institutions they represent. Grappling with the ethical issues in grateful patient fundraising necessitates considering them from all of these perspectives.

> [F]urther efforts must be directed toward filling the knowledge gaps related to the practice of grateful patient fundraising and its associated ethical issues

A meeting convened in 2017 to address these issues included participants who represented a broad range of perspectives, including bioethics, development, law, medicine, patient advocacy, psychology, and regulatory compliance and were from public and private universities, academic and private medical practices, and professional associations from across the United States. The group cataloged ethical issues in grateful patient fundraising and developed recommendations for addressing them.[5]

Among the key issues were challenges related to clinicians having discussions about philanthropy with patients who might be especially vulnerable due to their diseases or conditions, the tensions related to conflicts in regard to clinicians' primary obligations to patient care and a competing obligation to fundraising, the potential effects of fundraising on patient care, possible unintended consequences of concierge services provided to donors, and concerns about privacy.[5] The recommendations for clinicians include those concerning when grateful patient fundraising is appropriate (eg, ideally separate from the clinical encounter, not in situations of heightened vulnerability), minimizing conflicts of obligation and commitment, and respecting the donor's intent of a gift. The recommendations for fundraising professionals and institutions include the need for transparency in relationships, not interfering with clinical care, attending to confidentiality and privacy, appropriateness of concierge services, and institutional policies and training in grateful patient fundraising.[5]

This Viewpoint briefly reviews the limited empirical data that have been reported regarding the ethical issues in grateful patient fundraising for physicians and patients, and outlines an agenda for further research, education, and deliberation, with the goal of helping to ensure that grateful patient fundraising is conducted in an ethically appropriate manner.

Physicians

Many physicians lack preparation for grateful patient fundraising.[6] The limited published literature suggests that physicians' attitudes about grateful patient fundraising vary widely, and that these attitudes can affect physician participation in grateful patient fundraising and their engagement with development professionals. In a survey of 405 oncologists, 77% of respondents indicated that they had a duty to participate in fundraising for the disease(s) they treat but they generally did not feel comfortable talking to their patients about philanthropy and were concerned about how gifting would influence patient-physician relationships.[6] Sixty-two percent indicated there was a potential conflict of interest for physicians directly soliciting donations from their pa-

tients. Although respondents overwhelmingly perceived that patients felt empowered by donating, 48% had been taught how to identify potential donors and 26% had received ethical guidelines about soliciting donations from their own patients.

In a small qualitative study of 20 physicians with an established record of successful grateful patient fundraising, 90% of respondents reported that the potential effect on the patient-physician relationship was the most significant ethical concern raised by grateful patient fundraising, given that a purely therapeutic alliance between a physician and patient may be altered when that relationship also includes a role for the physician in cultivating and stewarding a philanthropic gift.[3] The interviewees also raised concerns about justice and fairness; some felt uncomfortable with the idea of treating grateful patients differently. Twenty-five percent of the interviewees also raised issues related to patient vulnerability, especially for situations in which a patient's decision-making capacity could be compromised by cognitive impairment or clinically unstable conditions.

Patients

The literature on patient attitudes about fundraising is also limited, with only 1 known publication describing grateful patients' perspectives on philanthropy.[7] Interviews were conducted with 20 patients who had previously donated to a single institution. Patients identified exemplary "humanistic" care as key to their giving; they felt gratitude for their care and a desire to advance science and to improve the health and well-being of others. Patients varied in their opinions about whether it was appropriate to discuss philanthropy during clinical encounters, but most wanted their physicians to be more comfortable about discussing philanthropy with them. No specific ethical issues were raised by this sample of grateful patients, including any concerns about the potential effects of grateful patient fundraising on relationships with their physicians.

Looking Ahead

This description of the ethical issues and recommendations for managing grateful patient fundraising will hopefully serve as a foundation on which to engage clinicians and health care institutions in deliberations about grateful patient fundraising practices.[5] Direct assessments of the utility of the recommendations could help inform further specificity, implementation, and potential revision of these recommendations in the future.

While this is an important initial step, further efforts must be directed toward filling the knowledge gaps related to the practice of grateful patient fundraising and its associated ethical issues. First and foremost is the need for a better understanding of the potential donor's perspective. This should include studies of patients who do not donate to improve understanding of how these patients would feel about being asked to give, by whom and when. There is also a need for data on the perceptions and reactions of potential donors regarding the use of wealth screening, a widely used but poorly understood technique, to identify potential donors. In addition, prior research has suggested a correlation between philanthropy and improved health and wellness[8]; however, no research has specifically looked at this with regard to grateful patient philanthropy. Research in this area is needed.

Physicians often feel unprepared and uncomfortable discussing financial issues with their patients, in part because physicians rarely receive adequate training to do so. This could undermine successfully establishing a philanthropic relationship with a patient or, even worse, risk compromising the therapeutic patient-physician alliance. Thus, there is a need for curricula to teach consensus-based, professional standards to development professionals and to clinicians.

Grateful patient fundraising is widespread and important but clearly raises ethical issues. The time is right to engage in research, education, and deliberation about these issues to help ensure that this activity is conducted in an ethically appropriate manner.

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Additional Reading:

Marc J. Roberts et al., *Public-Private Partnerships for Public Health* 67–85 (Michael R. Reich eds. 1st ed. 2002) http://health21initiative.org/wp-content/uploads/2017/08/2001-Harvard-PPPs-for-Global-Health.pdf#page=12 (ethics chapter)

Jennifer Washburn, *Science's Worst Enemy: Corporate Funding*, DISCOVER MAG. (October 2007) http://discovermagazine.com/2007/oct/sciences-worst-enemy-private-funding

Jharna Mandal et al., *Ethics of funding of research*, 2 TROPICAL PARASITOLOGY 89, 89–90 (2012) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680878/

The Researcher's Perspective on Innovative Funding

One issue that has frequently come up is that often, even with all the potential that these innovative funding models represent, the practical experience of those in these partnerships is very different. Researchers sometimes avoid seeking for-profit funding because the real or perceived pressures or constraints that these sources place on their research deters them. They may also struggle to evaluate the for-profit opportunities being offered to them. Researchers often feel that they need additional tools, expertise, or supports in order to navigate this new world of for-profit translational research funding successfully.

The purpose of this discussion is to provide the researcher perspective on the current challenges and opportunities presented by for-profit funding, to understand the needs of researchers, and how those can be reflected in funding models, and to explore the pitfalls in the current system and proposed solutions, and how they may be addressed.

Julia Belluz et al., *The 7 biggest problems facing science, according to 270 scientists*, VOX (Sep 7, 2016) https://www.vox.com/2016/7/14/12016710/science-challeges-research-funding-peer-review-process [https://perma.cc/3ECM-FYSN] (Excerpt here: https://perma.cc/P3VQ-XEWQ)

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The pace of scientific progress is quickening with researchers publishing important discoveries every day. However, the science community has been highlighting the fact that modern science is afflicted with several problems that threaten to ruin its very fabric. To understand what the larger scientific community perceives to be problems, Vox [1] – an American news website that publishes discussions on world affairs, science, politics, etc. – conducted a survey [2] involving 270 researchers. The respondents included graduate students, senior professors, Fields Medalists, and laboratory heads from all over the globe. All the respondents unanimously opined that the current scientific process is "riddled with conflict" and that they are forced to "prioritize self-preservation over pursuing the best questions and uncovering meaningful truths." Through the responses of these research professionals, it emerged that there were seven problems that science was facing:

1. Financial crunch in academia

Researchers face perpetual struggle to secure and sustain funding. While the scientific workforce is increasing, the funding in most countries has been on a decline over the past decade. The situation is particularly perilous for early career researchers who find it hard to compete for funds with senior researchers. This extreme competition is also impacting the way science is conducted [3]. The respondents of the Vox survey pointed out that since most grants are allotted only for a couple of years, researchers tend to opt for short-term projects, which can sometimes be insufficient to study complex research questions. This means researchers make choices based on what would keep the funding bodies and their institutions happy. However, the consequences of these choices are an increasing number of published papers with sub-standard quality and low research impact.

2. Poor study design in published papers

Poorly designed studies have become a major concern for academia. One of the primary reasons behind this problem is that statistical flaws in published research often go undetected. Since breakthrough results are valued the most, researchers feel compelled to hype their results in order to get published. Moreover, they tend to focus on particular patterns in data and manipulate their study designs to make the results more attractive for the journals. Instances of "p-hacking" in which researchers report only those hypotheses that end in statistically significant results are also on a rise. In particular, biomedical studies have come under the spotlight [4] for misusing p-values. Thus, a huge chunk of published results are scientifically insignificant, which also means a routine waste of money and resources.

3. Lack of replication studies

The inability to reproduce and replicate results is a major problem plaguing research. Recently, *Nature* published the results of a survey that attempted to understand researchers' views on reproducibility and reported that a majority of participants believed the "crisis of reproducibility" is real [5]. Inherent problems in studies also hinder replication, such as inadequate data and complicated study design. However, major stakeholders of science are in general skeptical about pursuing replication studies [6]. Most journals prefer publishing original and groundbreaking results because replication studies lack novelty [7]. Researchers and funding bodies are reluctant to invest their resources in replication studies on similar grounds. This is a major

loss to academia since results of most experiments are never validated and tested.

4. Problems with peer review

Although peer review is often considered the backbone of scientific publishing, it is not without problems [8]. Peer reviewers help in weeding out bad research and ensuring that a manuscript does not have any obvious flaws. However, because it is not an incentivized task, reviewers have been known to delay their work or provide unhelpful reviews. Moreover, authors regularly report facing reviewer bullying wherein reviewers force authors to conduct additional experiments [9], cite certain papers, make unnecessary changes, and so on. Most journals opt for single-blind peer review, which leaves room for biases and professional jealousy to creep in. Apart from this, the excessive dependence on the peer review system has led authors, editors, and third-party services to take advantage of it leading to peer review scams [10]. As a result, the peer review system in its present form is questioned by many academics.

5. The problem of research accessibility

Academia is gradually moving towards open science and open access by signing open data mandates [11] and making data sharing mandatory [12]. However, there are many big publishers that operate their journals on subscription-based models. Paying for paywalled research is becoming difficult for researchers as well as institutions, particularly in the developing countries, due to the ever-increasing subscription fees. Many of the Vox survey respondents were critical of this as it affects the way scientific research is disseminated. Moreover, subscription-based publishing model is probably the single most important factor responsible for the foundation of Sci-Hub [13], a website that provides unauthorized access to almost all paywalled research papers. The only way of avoiding such consequences is developing methods to make access to research easier for the science community.

6. Lack of adequate and accurate science communication

It is a well-known fact that a wide communication gap exists between the scientific and the non-scientific community. This has resulted in miscommunication of science, divided opinions about scientific matters, and lack of informed decision-making among the public. Researchers are partly responsible for this because they lack time or sometimes the inclination to engage with the public [14] about their research work. Therefore, the public is largely dependent on the media, which is often blamed for misconstruing scientific facts [15]. The competitive nature of academic research is also responsible for poor communication of research. In an attempt to grab attention, sometimes researchers, universities, and even journals mislead the public [16] by hyping the results or promoting only positive results. However, the science community should take the responsibility of projecting an accurate picture of science to the public since so that they can become cognizant of scientific issues and have a say in the way their tax money is invested in research.

7. Stressful nature of academic/postdoc life

Unarguably, the life of a postdoctoral researcher is grueling. Although it is the postdocs who drive academic research in many labs and are the future of academic research, they face challenges due to fierce competition, low income, and low job security [17]. While the number of postdoctoral researchers is increasing, the number of permanent positions in academia is not increasing at a similar rate. Moreover, PhD programs fail to train postdocs to find a non-academic job, which leaves them struggling to find a route to advance their career. For scientific research to make strides, these young researchers should be absorbed in mainstream science.

The Vox survey outlines some of the biggest concerns academia is grappling with at present. Apart from these, academics are also not unknown to other rampant problems such as gender inequality, research/academic misconduct, and excessive dependence on impact factor. Despite these problems, there is still hope for

science. The science community is attempting to avoid the stagnation of scientific progress by taking steps toward bringing more transparency, spreading awareness about the importance of ethics, and making science more inclusive rather than exclusive. However, there are no quick fixes when it comes to science; thus, while bringing these changes will take time, each step would mean a leap toward scientific progression.

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Rahim Rezaie et al., *Brazilian health biotech—fostering crosstalk between public and private sectors*, 26 NATURE BIOTECHNOLOGY 627 (2008) https://www.nature.com/articles/nbt0608-627

The Use of Data and Transparency

In recent years open access to data has become more widely adopted by the scientific community. Open access allows research to use that data to check the initial study, bolster their own data, or inform their experimental design. Proponents of open access say that it is a key part of fulfilling the promise for science to democratize knowledge. This increased access has also been instrumental in establishing the discipline of data science, which relies on researchers to gather the data that data scientists will use to do their own independent analysis. Patient groups are often also supportive of open access efforts, arguing that the data is just information about the patient, which they have freely chosen to give in order to advance the cause of science as a whole, not the interests of a particular researcher or institution.

Data ownership, however, is more complicated than proponents of open access may allow. Institutions invest a significant amount of resources into compiling and developing significant datasets. They are also best placed to maximize the impact that use of these datasets can have by thoughtfully commercializing or developing products based on their data. Patients also have concerns about the security of the data shared through open access.

The purpose of this discussion is to compare and contrast public policies encouraging open access with private interest in data ownership, to explore the value of data in negotiating innovative funding, and to consider the role of patients and research subjects in determining data use.

Gregory A Petsko, *Who owns the data?,* 6 GENOME BIOLOGY 107 (2005)

Comment

Who owns the data?

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Besides an astronomical amount of sequence data and a lot of useful technology, perhaps the most significant legacy of the genomics revolution has been an insatiable appetite for data. This hunger was part of the reason that the privately funded human genome project at Celera Corporation released its sequence information sooner than intellectual property considerations would have made desirable (competition from the publicly funded human genome sequence project was the other part). The same hunger motivated the US National Institutes of Health (NIH), the National Science Foundation, and the Howard Hughes Medical Institute to require that structural biologists funded by those agencies deposit their atomic coordinates into a public database in a timely manner. But this flood of information hasn't curbed the appetite at all. Like Cleopatra in Enobarus's marvelous description from Shakespeare's *Antony and Cleopatra*, it seems genomics makes hungry where most she satisfies.

Of course, this desire wars with another fundamental human appetite: that for money. Much of modern life science is driven by the longing to make a profit. It fuels the biotechnology and pharmaceutical industries. It underlies the choice of research problems in many academic laboratories. And at its heart is the concept of property, of ownership, both of ideas and of data. This concept would seem to be perpetually opposed to that of free, publicly available sequences, structures and technologies.

Historically, the battlefield on which this conflict was fought was the courtroom, where scientists and corporations would engage in Talmudic-style disputes over dates in notebooks, interpretations of patents, and other claims to priority. In the immediate post-World War II era these arguments tended to be over technology developed by physicists, chemists and engineers. Biologists didn't join the fray until after 1980: in part there was no biotechnology industry until about then, but it was largely because most academic biology was publicly funded, in the US by the NIH. That would seem to make the results of such research public property.

The Bayh-Dole Act, passed by the US Congress in 1980 and named for its co-sponsors Senators Birch Bayh and Robert Dole, changed all that. The Act provided recipients of federal research and development funds with the right to retain ownership of their patents. It did even more: it charged them with the responsibility of ensuring commercial use of inventions created with federal financial support. While it is technically possible for a university to have different policies regarding the patenting and licensing of inventions which were not developed as a result of federally funded research, in general the universities' interest in maintaining the flexibility to draw research funds from multiple sources, including the federal government, and the desire to avoid applying conflicting policies, have led to most of them having a single policy that is consistent with the Act. The underlying tenet of the Bayh-Dole Act is that federally funded inventions should be licensed for commercial development in the public interest. That principle is now reflected in virtually all university policies in the US, whether or not the invention is federally funded.

Since the Bayh-Dole Act permits universities, other nonprofit organizations such as teaching hospitals, and, in most cases, commercial federal contractors to retain title to inventions that are conceived or first reduced to practice in the performance of a federal grant, contract, or cooperative agreement (in exchange for certain obligations on the part of the contractor), it immediately created a huge economic incentive for academic biologists to start their own companies or to become involved with existing ones. Bayh-Dole was directly responsible for the explosive growth of the biotechnology industry in the 1980s. It also created the culture of intellectual property that underlies that industry. For over twenty years, the answer to the question "Who owns the data?", according to the Bayh-Dole Act, has been "the scientist who collected it and the organization for which he or she was working at the time". Since raw facts could not be property (you may patent a mousetrap, but not data on mice; you may copyright an article, but not the data on

which it is based - although the patenting of gene sequences is a blow to this tradition), this answer led to a culture in which data were hoarded, often to be published only after the application itself was developed.

This answer is now being challenged by a new one, driven by the cultural change genomics is creating in the life sciences - a culture of public databases and open access. The first area of modern biology to reel under the challenge has been the scientific journal publishing industry. Some journals, such as *Science*, are published by not-for-profit scientific societies (which derive a hefty chunk of their operating expenses from the subscriptions); more, like *Nature*, are revenue-generators of for-profit publishing houses. About ten years ago, a group of scientists headed by Nobel Laureate Harold Varmus, then Director of the NIH, began to argue that it was unfair to ask other scientists, who are after all members of the public, to pay to read the results of research that had been publicly funded. They quickly found allies in patients' advocacy groups, who believe advances in medicine would come about more quickly if everyone had equal access to discoveries. Despite considerable skepticism by many scientists - and much gnashing of teeth from publishers - about five years ago the first 'Open Access' journals began appearing. Their business model is that authors of papers appearing therein must pay a fee for the privilege (peer review is still required for acceptance), but in return, all rights to the material in the paper remain with the author and anyone can access the full text and any supplemental information free of charge forever. Scientists in developing countries, in particular, benefit greatly from such a policy, since many journal subscriptions, online or in print form, are beyond their means.

And on 3 February, NIH announced that as of 1 May this year it expects that all research papers resulting from research it funds will be deposited into an open-access electronic archive that will be maintained by the US National Library of Medicine (which currently runs the PubMed journal database and PubMed Central full-text archive, within a year of their appearing in any journal. Current estimates are that over one third of all highly cited papers in the life sciences report the results of NIH-sponsored research, so the policy is likely to have a big impact almost immediately, even though there is no active enforcement. If the existing open-access journals like *PLoS Biology*, *Journal of Biology*, and this journal (which makes all refereed research articles freely available online but charges a subscription price for access to other content, such as my Comment columns - which are worth every penny) are able to stay in business by, for example, charging authors rather than subscribers, and if they start to attract top-flight papers, the closed-access journals will come under severe financial pressure to adopt a similar business model. In any case, given the new NIH policy, it would seem that for much of their content, closed-access journals will only have a year - and maybe eventually a lot less than that - to make their profits. The Wellcome Trust in the UK is also a big supporter of Open Access, and is considering establishing a joint archive of papers with the US National Library of Medicine. Where Wellcome goes, the UK Medical Research Council is likely to follow. Add in Germany, France and Japan and most of the literature will be covered.

Even more intriguing is the advent of open-access technology. Here there is a model from outside biology: so-called 'open-source' software. Programs developed under the open-source concept have their source code freely available to users, with the restriction that any improvements made by anyone must be offered to the user community free of charge. A variation of this model levies a cost to commercial users while allowing academics and other non-profit groups to obtain the code free of charge. The first example, the Linux operating system (named after its inventor, Linus Torvards, who is popularly credited with the open-source model), has proven so successful that it is making Bill Gates and Microsoft nervous about the future of their closed-source, very much for-profit Windows operating system. Open-source software has begun to have a big impact in structural biology, where programs like Coot, PyMol, Phenix and so on are making high-quality crystallographic computing available to all.

And now this idea is being applied to biotechnology. Early in 2005 an exploratory project called Science Commons was launched. The mission of Science Commons - an offshoot of Creative Commons, which provides less restrictive copyright licenses to authors - is to develop open licenses for technologies. As a model, it could do worse than look to a remarkable new concept developed by CAMBIA, a non-profit biotech research group affiliated with Charles Stuart University in Canberra, Australia. In a paper published, ironically, in the closed-access journal *Nature* on 10 February (Broothaerts *et al.*, Gene transfer to plants by diverse species of bacteria, *Nature* 2005 **433:**629-633), researchers at CAMBIA report a breakthrough in biotechnology by successfully transferring foreign genes to plants using several bacteria other than the usual *Agrobacterium tumefaciens* (At). They introduced a specially modified Ti plasmid into *Rhizobium, Sinorhizobium* and *Mesorhizobium* - all organisms closely related to At - and showed that the transformed strains could be used to express foreign genes from the plasmid in tobacco, rice and *Arabidopsis*. Integration of the inserted segment into the plant genomes was also confirmed. The work is exciting because many plants, especially crop plants, are resistant to gene transfer by At. But it's also noteworthy because of what CAMBIA is doing with it.

CAMBIA has applied for a patent on the technology, which they call TransBacter™. But they are offering this technology as an 'open-source' alternative to At technology, which is controlled by Monsanto, the large agricultural firm that holds the relevant patents. CAMBIA calls its license concept

BIOS - Biological Innovation for Open Society. The way it works is simple. Others may commercialize products based on the procedure. But any improvements in the technology must be shared freely, to the benefit of all users. The intent is that researchers in poor countries especially, where agricultural research is very important, will thus have open access to a method that may help their efforts. There's a website, Bioforge [https://www.bioforge.net/], to help biotech researchers collaborate on this and other developments (among them new reporter/marker genes and microarray-style genotyping technologies). There are several levels of projects, some open only to BIOS licensees, some open to all and some open at intermediate levels. Joining a project enables the participants to see, use, and deposit information that will not necessarily be available in the public domain. It will allow them to share their improvements with other members of the protected commons community of BioForge. In order to join a project, organizations and individuals must agree to the community norms about confidential sharing of improvements and biosafety data, and must provide information on their institutional affiliation and policies that may apply to sharing of data. Access to certain projects may require a legal commitment to the sharing of improvements in return for being able to obtain the benefit of the technology and improvements.

For humanitarian efforts and work on crops that are of limited interest in developed countries, CAMBIA's model promises to be truly revolutionary. It doesn't do away with the incentive to invent, or to develop, but it makes the information needed to do such things available to everyone. If there is an untapped reservoir of creativity in the Third World, an idea such as this might unleash it. It will be interesting to see whether the concept catches on, as open-source software clearly has. No one wants to see the financial incentives that have fueled the biotechnology explosion removed. But companies can clearly live within the open-source model - IBM does, for example (open-source software even contributes to its revenues, since among other things IBM makes much of its money by selling services to people who have open-source software and need help). CAMBIA, by the way, was funded by the Rockefeller Foundation, Horticulture Australia, and Rural Industries R&D Corporation, so in a sense its work represents a triumph of the Bayh-Dole concept. It remains to be seen whether the pharmaceutical industry, which in my opinion would benefit greatly from increased sharing of ideas and information, could find an open-source model it could live with. But if scientific publishing and software development are any indication, this is not an idea that's going to go away any time soon.

Who owns the data? Increasingly, at least for some things, the answer is starting to be nobody. Or everybody.

Monica M. Bertagnolli et al., *Advantages of a Truly Open-Access Data-Sharing Model*, 376 NEW ENGLAND J. OF MED. 1178 (2017)

SOUNDING BOARD

Advantages of a Truly Open-Access Data-Sharing Model

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Multi-institutional randomized clinical trials have been a feature of oncology research in the United States since the 1950s. Since that time, cancer-treatment trials have been continuously funded by the National Cancer Institute (NCI) through a program that has evolved to become the National Clinical Trials Network (NCTN). Currently, approximately 19,000 patients with cancer participate in NCTN clinical trials each year. Approximately 70,000 additional patients with cancer are enrolled each year in treatment trials sponsored by the pharmaceutical industry.[1,2]

It is important to honor and reward the altruism of patients who participate in clinical trials. One way to do so is to share the data gathered in clinical trials with other researchers in a responsible and meaningful way. The cancer research community, encouraged by recommendations from the Beau Biden Cancer Moonshot, is finally moving data sharing forward from its traditional, largely unfunded, place at the end of the long list of clinical research responsibilities to center stage.

There are a number of reasons why it has it taken more than 60 years for this issue to receive the attention that it deserves. Although the incentives for doing so may differ, competitive forces lead both academic researchers and pharmaceutical companies to protect data and to use data exclusively for their purposes. This approach protects their intellectual property and also shields the primary study team and the sponsor if the release of data from a trial for analysis by others leads to conclusions or interpretations that the primary researchers deem to be misleading or erroneous. When the academic and monetary stakes are high, the chance of this situation occurring is real. Another reason for the delay is that the protection of research participants dictates that confidentiality is the highest priority, and this risk may be greater with wide sharing of the new data-dense individual data sets that are required in order to develop personalized medicine approaches. Finally, and probably most important of all, data sharing has been hampered by a lack of resources, including access to enabling data systems technology, bioinformatics expertise, and legal agreements that facilitate sharing.

The idea of data sharing is moving beyond these hurdles with a variety of models. One such model, the so-called gatekeeper model,[3] uses a distinct entity to house information in a central repository, with access to specific data sets that are provided to qualified research teams on the basis of a research proposal review by an independent expert committee. Examples of this approach include ClinicalStudyDataRequest.com, a website sponsored by pharmaceutical partners, and the Vivli platform (http://vivli.org), a nonprofit corporation created to support global sharing of clinical research data. Gatekeeper models provide substantial customization and oversight for individual data requests so that contributing investigators can maintain a level of control over how their data are used. This model may appropriately address barriers to sharing for studies in which the identification of participants is a risk, such as those that involve sensitive topics, genomic data, or limited numbers of participants. This model can also offer some protection to research teams that require limitations on the use of proprietary data. A limitation of gatekeeper models is that many barriers to data use remain.

A substantial body of readily available data

from clinical trials can be shared with minimal risk to patients or researchers. Examples include data sets of already published trials, particularly if the treatments that were tested are not undergoing review for regulatory approval. In addition, industry-sponsored clinical trials generally involve a comparator group for which valuable patient-level data can be shared without risk to proprietary interests. As long as the data are appropriately anonymized to protect confidentiality and there are no restrictions related to the institutional review board, the consent form, or the sponsor with regard to the patient-level data, it should be possible for the data to be freely available to the public to download, analyze, and reuse for research purposes. This approach may enable the identification of baseline characteristics of the patients or outcomes that could be identified only by means of an analysis of larger numbers of patients than would be included in an individual trial. What has been lacking, until recently, has been the infrastructure required to achieve this goal.

An example of an active open-source data-sharing model, with which some of us are affiliated, is Project Data Sphere (PDS). PDS is a free digital library-data laboratory that was launched in 2014 as an independent, nonprofit initiative of the CEO Roundtable on Cancer (www.ceoroundtableoncancer.org), which was founded in 2001 to develop and implement initiatives that reduce the risk of cancer, enable early diagnosis, facilitate access to the best available treatments, and hasten the discovery of new and more effective anticancer therapies. A Web-based platform for accessing open-source data was developed for PDS by SAS Institute. Using this website, researchers can download, share, integrate, and analyze patient-level data. Data contributors are provided access to deidentification and data-standardization protocols, as well as to templates of legal agreements, including standardized data-sharing and online-services user agreements.[4-6] Users of the site have access to analytic tools developed by SAS Institute. Anyone interested in cancer research can use the website, provided that they register and agree to a responsible-use attestation. PDS is funded by the engagement of a wide range of stakeholders that together ameliorate the burden of securing adequate funding from a single organization or institution.

At present, PDS contains data from more than 41,000 research participants from 72 oncology trials, covering multiple tumor types. The data have been donated by academic, government, and industry sponsors. These numbers are increasing quickly as use of the PDS accelerates. More than 1400 unique researchers have accessed the PDS database more than 6500 times. As one interesting example, a challenge was issued in 2014 that asked respondents to use PDS to create a better prognostic model for advanced prostate cancer. A total of 549 registrants from 58 teams and 21 countries responded. Accessible data included control groups from prospective, randomized, industry-sponsored trials. Solvers had backgrounds in statistics, data modeling, data science, machine learning, bioinformatics, engineering, and other specialties. Unexpectedly, the winning entrant, a team of researchers from Finland, had never worked on prostate cancer in the past, and this team considerably outperformed the best existing model for predicting overall survival among men with advanced prostate cancer.[7] Thus, the PDS Prostate Cancer DREAM Challenge confirmed that an open-access model empowers global communities of scientists from diverse backgrounds and promotes crowd-sourced solutions to important clinical problems. This level of engagement is not possible with gatekeeper models.

PDS is provided to users free of charge, but the usefulness of the PDS website is limited to the trials that it contains and the data analytics provided by the platform. Expansion of this concept to the broader research community outside the field of oncology will be time consuming and costly, and it is open to debate whether publicly funded or private concerns are the most appropriate environment to assume responsibility for data storage and sharing. The DataNet program of the National Science Foundation is one example of a public–private partnership that has been designed to achieve these goals.[8]

The data-sharing community is undergoing rapid development, with several potential models and approaches (Table 1). We encourage multiple models to coexist, either as a single platform with tiered access or as discrete platforms with

Table 1. Oncology Clinical and Translational Research Data Archives.*

Name	Description	Type	Funding Source	Website
Database of Genotypes and Phenotypes	Archives and distributes the data and results from studies investigating the interaction of genotype and phenotype in humans	Gatekeeper	NIH	www.ncbi.nlm.nih.gov/gap
Cancer Imaging Archive	Image data organized into purpose-built collections of data from participants who typically have a cancer type or anatomical site of cancer (lung, brain, etc.) in common	Gatekeeper	NIH	www.cancerimagingarchive.net
Genomic Data Commons	A unified data repository that enables data sharing across cancer genomic studies in support of precision cancer medicine; this program supports several cancer genome programs at the NCI Center for Cancer Genomics, including the Cancer Genome Atlas, the Therapeutically Applicable Research to Generate Effective Treatments program, and the Cancer Genome Characterization Initiative	Gatekeeper	NIH	https://gdc.cancer.gov
NCTN–NCORP Data Archive	Centralized repository of patient-level data from phase 3 clinical trials conducted by the trial groups that are part of the NCI NCTN, NCORP, and the National Cancer Institute of Canada Clinical Trials Group	Gatekeeper	NIH	https://nctn-data-archive.nci.nih.gov
Oncology Research Information Exchange Network	Research partnership among cancer centers coordinating collection and access to clinical and translational data on a per-patient level; founders include the Moffitt Cancer Center and the Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute	Gatekeeper	Academic institutions	http://oriencancer.org
National Cancer Database	Nationwide oncology outcomes database of data on new cancer diagnoses in the United States; primarily developed as a clinical surveillance and quality-improvement mechanism for cancer programs participating in the American College of Surgeons Commission on Cancer program	Gatekeeper	Professional society	www.facs.org/quality-programs/cancer/ncdb
American Society of Clinical Oncology CancerLinQ	Data acquisition and analysis system designed to improve cancer-treatment outcomes by tracking the quality of oncology patient care in real time; also provides deidentified patient-level data for research and development	Gatekeeper	Professional society	https://cancerlinq.org
Project Data Sphere	Repository of clinical-trials data at a per-patient level within a website that contains analytic tools for research use	Open access	Nonprofit foundation	www.projectdatasphere.org

* NCI denotes National Cancer Institute, NCORP NCI Community Oncology Research Program, NCTN National Clinical Trials Network, and NIH National Institutes of Health.

the potential for cross-communication that includes truly open platforms. We think that as the community sees the benefits of sharing trial data, more will be shared.

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