POLICY

Breaking Down Translation Barriers: Investigator's Perspective

Nathan P. Staff,* Bethany Kinseth Runge, Anthony J. Windebank

From our perspective as biomedical scientists, we analyze new initiatives from U.S. federal regulatory and funding agencies aimed at accelerating the process of clinical translation.

There are two broad pathways to improving human health. The first is through public health initiatives designed on the basis of behavioral research and enacted through the application of current knowledge, public education, and policy change. The second pathway includes the discovery, development, and application of new medical products—diagnostic tools, biomarker predictors of disease, and therapeutic drugs, biologics, and devices (Fig. 1). In order for new medical products to enter widespread use, they must clear the hurdles of regulatory institutions such as the U.S. Food and Drug Administration (FDA) and be approved for insurance reimbursement by entities such as the U.S. Centers for Medicaid and Medicare Services (CMS). Here, we discuss new approaches to streamlining and thus accelerating knowledge translation with the academic biomedical researcher in mind—many of whom are unfamiliar with these new initiatives.

Various estimates suggest that the average time for a basic scientific finding to be translated into a new therapy is 16 to 17 years in both the public health and medical arenas (*1*–*3*). Mounting costs (clinical trials, drug manufacturing, and regulatory compliance) and declining return on investment in research are also major concerns. The frequently quoted $1 billion to bring a new drug to market has risen to $4 to 5 billion by some estimates (www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs). To address this gap, the U.S. President's Council of Advisors on Science and Technology (PCAST) published a report in September 2012 on propelling innovation in the pharmaceutical industry, which commented that "the ecosystem for public health is under significant stress" and that research and development (R&D) productivity is declining (*4*). Using extensive national and global databases, PCAST demonstrated that investment in R&D by the pharmaceutical industry and the U.S. National Institutes of Health (NIH) has risen significantly over the past 45 years with no increase in the introduction of new molecular entities (NME) or new biological entities (NBE) in the United States.

Center for Regenerative Medicine and Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA.
*Corresponding author. E-mail: staff.nathan@mayo.edu

SYSTEMIC BARRIERS

Over the past 10 years, there have been detailed analyses of the translation process by funding agencies such as the U.S. National Cancer Institute (NCI) (*5*). NCI used case studies of 21 discoveries across the spectrum of drugs, biological agents, risk-assessment strategies, medical devices, and lifestyle alterations (*5*) to identify bottlenecks. Barriers included the hand-off of research from academia to industry, the transfer of manufacturing from research laboratory to good manufacturing practices (GMP), the development of robust disease biomarkers or drug screening assays, and difficulties in early-stage clinical trials because of regulatory issues.

Another recent study conducted by Angius and colleagues addressed translation barriers from the academic investigator's perspective (*6*) by performing a systematic study of 416 publications to identify a cohort of academic investigators who published the results of largely positive, preclinical animal model studies in nerve regeneration; very few of these discoveries had been translated into clinical practice. Similar to the NCI analysis, the study identified as barriers the hand-off of research between academia and industry, preclinical development using GMP, and lack of knowledge about the regulatory approval process among academic scientists. In addition, a significant number of investigators expressed the opinion that the end product of their research was publication and that they expected a company to take the knowledge and translate it into a product.

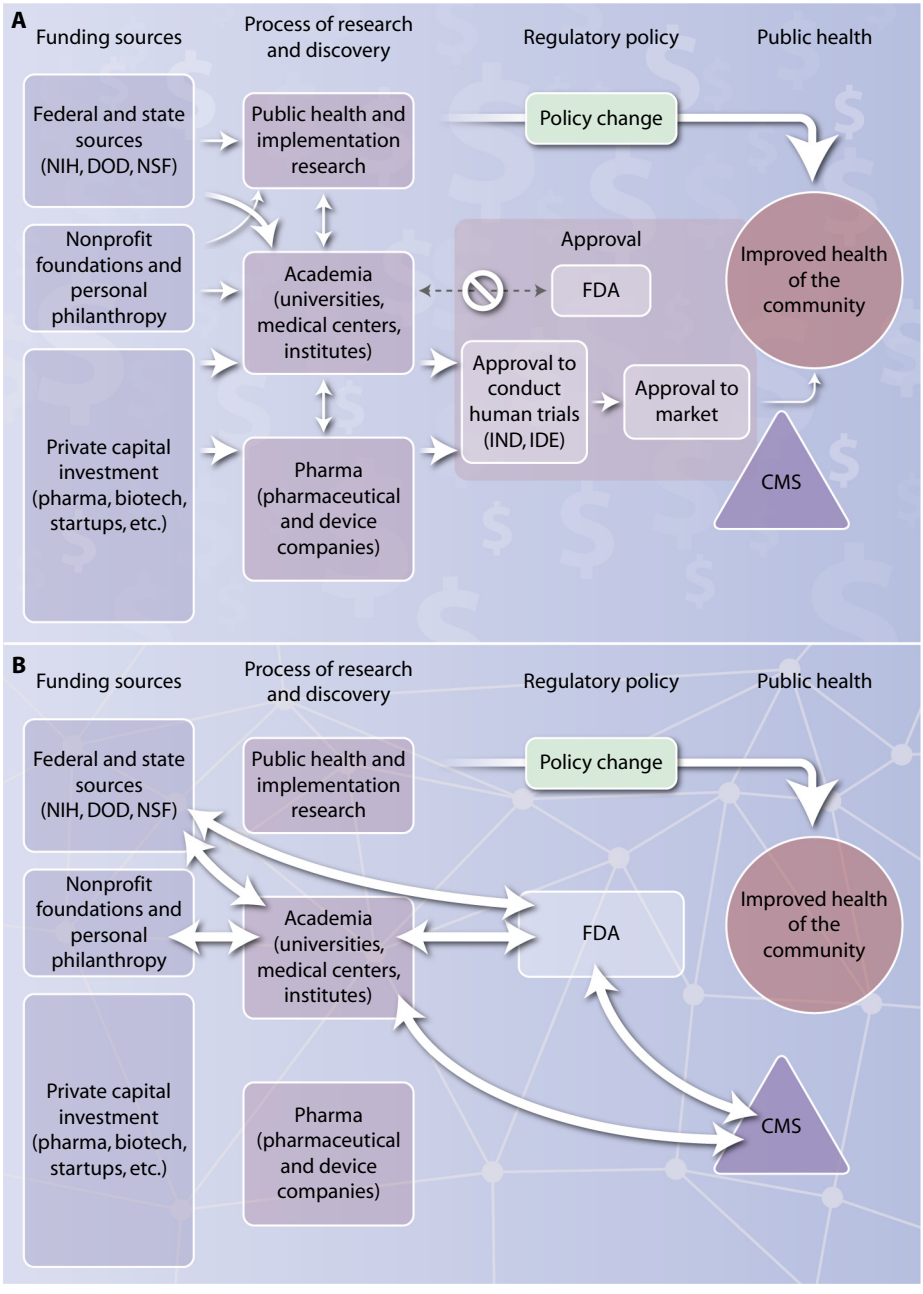
STRATEGIES TO DRIVE TRANSLATION

FDA. The FDA collected input from all segments of the biomedical research enterprise that resulted in the publication of a strategic plan for advancing translation (August 2011) that introduced the concept of regulatory science and set out eight priority areas designed to "allow the agency both to meet today's public health needs and to be fully prepared for the challenges and opportunities of tomorrow" (*7*). The plan also recognizes that FDA has a pivotal role in the translation process and that the regulatory segment needs improvement. The plan emphasizes the primary role of the agency in maintaining safety and expressly states that its goal is not to fundamentally change the regulatory process.

The eight goals are to (i) modernize toxicology to enhance product safety; (ii) stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes; (iii) support new approaches to improve product manufacturing and quality; (iv) ensure FDA readiness to evaluate innovative emerging technologies; (v) harness diverse data through information sciences to improve health outcomes; (vi) implement a new prevention-focused food safety system to protect public health; (vii) facilitate development of medical countermeasures to protect against threats to U.S. and global health and security; and (viii) strengthen social and behavioral sciences to help consumers and professionals make informed decisions about regulated products.

Although the plan describes detailed approaches for achieving these goals, the implementation processes, milestones, timelines, and resources are not clearly defined. In addition—and probably more importantly—although biomedical thought leaders outside of FDA provided major input, the outcome of this planning process is generally unknown to the majority of academic scientists. In a small survey of leaders in the biomedical translation field, only 2 of 11 were aware of the plan or any of the proposed outputs. One investigator who knew about the plan commented that "it was very helpful in formulating our regulatory strategy for the *specific* technology being developed." This comment suggests a need for increased marketing and dissemination of the plan.

The second goal centers on clinical trials—their designs, end points, use of biomarkers, and the use of "virtual physiological patients"—that is, device testing that uses robust computer models of human anatomy. Clinical trial innovation is a ripe area for strong collaboration between FDA and academic investigators. To this end, FDA now offers a three-day training course led by



CREDIT: H. MCDONALD/*SCIENCE TRANSLATIONAL MEDICINE*

Fig. 1. More talk, more action. (**A**) Shown is a simplified scheme of U.S. biomedical discovery research and regulatory science processes. Funding comes from three sources—government agencies (federal and state), nonprofit institutions (private philanthropies and disease-focused foundations), and the private sector (investment from venture capital and industry). R&D is carried out in both industry (pharmaceutical and medical technology companies) and academic centers, which also conduct increasing amounts of public health and new-product implementation research that require policy changes rather than FDA approval. Over the past 50 years, the relative return on biomedical research investment has declined (as measured by FDA submissions and product approvals) and the rate of knowledge transfer (translation) from discovery to improvements in clinical medicine has not improved. Bottlenecks include lack of knowledge in academia about the regulatory process; the essential requirement for acceptance and coverage of a new product by the CMS in order for it to be widely implemented; and the miniscule amount of prospective planning among academia, industry, FDA, and CMS. **(B)** Strengthening of communication pathways—most of which converge on individual institutions and investigators—can accelerate the pace of translation. Federal funding agencies and FDA also should exchange information about strategic priorities and required regulatory expertise in the funding review and regulatory approval processes.

FDA staff and guest lecturers to augment the training of current and future clinical investigators. The goals of the training course include but are not limited to "foster[ing] a cadre of clinical investigators with knowledge, experience, and commitment to investigational medicine"; "promot[ing] communication between clinical investigators and FDA"; and "[enhancing] investigators' understanding of FDA's role in experimental medicine" (*8*). The goal of strengthening communication between investigators and regulatory agencies has been stressed by others (*9*). The third goal, directed toward improving product manufacturing, is being addressed by FDA's recent introduction of a new Investigational Device Exemption (IDE) process for early clinical studies of feasibility for medical devices, including certain first-in-human studies (*10*). This new process allows for small clinical trials to start before product design is finalized. The way this process works is to permit just-in-time (JIT) testing wherein certain nonclinical testing is evaluated in collaboration with FDA and completed during or after the initiation of a study. In addition, this new process allows for flexible device and clinical protocol modifications during the study. These increased risks are balanced by requiring investigators to outline enhanced risk-mitigation strategies and patient-protection measures (*10*). The IDE process is intended to be a more iterative and interactive approach toward final approval.

Funding. Agencies that provide funding can drive the process of translation with two tools: funding to support acceleration and peer review of applications for funding. A major shift in this direction began in September 2004 when the then–NIH director published the *NIH Roadmap for Medical Research*. The *Roadmap* put forward a series of themes, implementation groups, and initiatives aimed at redefining the ways in which medical research is conducted and, ultimately, how scientific research leads to improvements in human health (*11*). A major pathway for implementation of the *Roadmap* was through the Clinical and Translational Science Awards (CTSAs) (www.ctsacentral.org). A prime example of a CTSA initiative was the inauguration of a national predoctoral clinical and translational science meeting that brings together research trainees at the professional (M.D., D.D.S., D.P.T., Pharm.D.) and graduate school (Ph.D.) levels to present and discuss their research. The emphasis of these annual meetings has

been on "articulating the path to translation." From the beginning of their research training careers, these future investigators should be able to describe how their research will be taken through the next steps in the translational pathway. The ability to articulate future steps will inform the design of their current experiments. The Institute of Medicine (IOM) recently endorsed the CTSA program in a report (*12*) that reviews the program's mission and strategic goals. The IOM committee concluded that "the CTSA program is contributing significantly to advancing clinical and translational research" and emphasized that "[t]he program must continue to emphasize innovative training, mentoring, and education to better prepare the next generation of researchers."

The shift toward translation in the context of limited resources has evoked concern in the academic biomedical research community centered on fundamental discovery research. Although basic science discoveries through implementation of new therapies are essential for improving clinical medicine, the value of increasing investments at various points in the translational pathway has not been rigorously evaluated. The 17-year life cycle from bench to bedside exceeds the 5- to 10-year terms of NIH directors and many other national scientific leaders. Thus the process of change tends to be influenced by preconception rather than data. Reliable markers of productive change in the translation process are needed that resemble qualified biomarkers for disease progression, a concept familiar to physician-scientists. Thus investigators must collaborate with program evaluators to develop robust markers of success for educational, funding, and R&D programs.

Funding is probably the most powerful tool for influencing the course of biomedical research. Virtually all academic investigators and programs require extramural funding, and strong arguments have been made for supporting fundamental discovery research to illuminate disease mechanisms that will pinpoint new therapeutic targets. Clinician-scientists and translational scientists propose research projects directed toward discovering and developing disease-specific therapies; however, these research projects rarely are judged on the basis of their likelihood of success in developing a new therapy. In the United States, most biomedical research funding to the academic community is awarded through a rigorous peer-review process to ensure that strong science and new ideas are supported. However, this selection process also guarantees that major changes in the biomedical research process will not occur, as the grant reviewers are all rooted in the status quo. Study section and scientific review board members often have little personal experience with the process of translation and may be poorly equipped to judge the likelihood that a project will produce translatable knowledge. The responsibility for raising this discussion is often in the hands of the administrative Scientific Review Officer, whose opinion may not carry weight in the discussion of the merits of the "hard science." Credible scientists with personal experience in translation of knowledge to product should be incorporated into review bodies.

An example in which NIH has provided direct funding to aid translation is the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) program (*13, 14*). This is a National Institute of Neurological Disorders and Strokes (NINDS) initiative with the goal of accelerating phase 2 clinical trials and biomarker validation studies for the treatment of neurological diseases by providing funding and a consortium that supports clinical investigators in academia, private foundations, and industry. The consortium includes multiple clinical sites, a clinical coordinating center, and a data coordinating center, made available to assist investigators with accepted proposals to conduct their clinical studies. NeuroNEXT is involved in all stages of the clinical trial process, starting with the conceptual stage. To date, it has funded phase 2 projects on spinal muscular atrophy, multiple sclerosis, myasthenia gravis, and stroke.

Another funding strategy to improve translation began in 2010 with a joint initiative between FDA and NIH (*15*) that focuses on combining translational science and regulatory science principles to speed clinical translation. Although this is not the first time the two agencies have collaborated, the fact that this effort was designed to improve the regulatory review process made this particular joint effort unique. The initiative has since provided significant grant support for cooperative grants (U01) throughout the country and established Centers of Excellence in Regulatory Science and Innovation at the University of Maryland and Georgetown University (in 2011).

U.S. federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants focus on commercialization of translated medical technology and fund small U.S. businesses that might otherwise not attract private investors. Many of the companies that use the SBIR funding mechanism are start-up companies associated with academic centers, and the STTR program requires an academic center partner. Congress has mandated that 11 federal agencies that support research (including NIH) allocate 2.5% of their budget for SBIR and 0.3% for STTR (totaling $2.35 billion in 2010). In 2012, these percentages were targeted to rise to 3.2% and 0.45% for SBIR and STTR in 2017. An average of 1163 new awards were made yearly over the last 10 years. The funding rate for these programs has averaged 21.2% of applications, which is a little higher than the overall average at NIH (http://report.nih.gov/catalog.aspx).

Reimbursement. A federal agency within the U.S. Department of Health and Human Services, CMS is responsible for administering Medicare and Medicaid and determines whether drugs, devices, or biologics will be paid for by these federal health insurance programs. Most private health insurance companies follow payment coverage recommendations set forth by CMS. The process to determine whether CMS will provide coverage for a medical procedure can take years and, therefore, has a great impact on biomedical research. Increased collaboration between funding (NIH) and regulatory agencies (FDA and CMS) could focus funding review processes so that new preclinical projects with an unclear pathway to implementation could be discouraged and those with a clearly articulated pathway through regulatory approval could be encouraged. Currently, there is virtually no communication between academic clinician-investigators and CMS. Many laboratory-based investigators are not even aware of CMS's role despite its importance in the translation process.

CMS has aided clinical translation by enacting changes designed to increase enrollment of Medicare and Medicaid patients in clinical trials. Coverage by the CMS for patient care costs associated with clinical trials is critical for patient enrollment in clinical trials and for new discoveries to be widely implemented. An executive order (referred to as the 2000 Clinical Trial Policy) signed by President Bill Clinton on 7 June 2000 authorized Medicare payments to cover routine costs and costs related to medical complications that occur during clinical trial participation (*16*). More senior patients may

be able to enroll in clinical trials when the financial burden associated with participation is reduced by CMS coverage. An NCI study was able to make this conclusion after assessing the percentage of seniors with cancer who enrolled in a cancer therapy–related clinical trial before and after the 2000 executive memorandum (*17*).

Clinician-investigators. The clinician-investigator needs to adopt a translation-centered research perspective in order to successfully accelerate translation. Research destined for translation must be designed from the outset in a way that ensures that experimental data are gathered such that they will be suitable for use in future submissions to the FDA. This approach requires a substantially expanded two-way knowledge-transfer highway between the community of academic investigators and FDA, who share the responsibility for expanding this knowledge exchange path. Two examples in which this strong two-way communication has yielded advances in the regulatory approval process are in the areas of stem-cell/regenerative medicine and tissue engineering.

Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) is a uniformly fatal neurodegenerative condition that leads to progressive loss of muscle function and death within 2 to 3 years after symptom onset. Despite 50 years of intensive, mechanism-based research, no effective treatments exist. There was great excitement in 1994 when Gurney and colleagues discovered that a mouse expressing a mutation associated with human familial ALS developed a motor neuron disease (*18*). The hope was that this genetic model would yield a mechanistic understanding of the disease and provide a system for assessing the efficacy of potential therapies. Unfortunately, many treatments that were successful in treating the mouse did not translate to humans (*18*–*20*).

With the advent of putative stem cell–based therapies for neurodegenerative diseases, investigators began to ask whether autologous adipose-derived mesenchymal stem cells (MSCs) that were genetically modified to secrete biologics might be effective vehicles for the delivery of neuroprotective molecules across the blood-brain barrier. But this approach would involve first developing a treatment platform (unmodified MSCs) in patients to deliver a therapy that had not yet been tested in a preclinical model.

Investigators entered advisory discussions with staff at the FDA Center for Biologics Evaluation and Research (CBER). Great attention was paid to preclinical studies of safety, with less emphasis on efficacy for a disease in which any step forward is important progress. The ethical justification accepted by FDA and institutional review boards for testing the treatment platform in patients was that the unmodified MSCs deliver a wide range of neuroprotective molecules that may have efficacy on their own. In addition, if this delivery route were demonstrated to be safe in patients, the treatment platform might be useful for delivering neuroprotective molecules not just for treatment of ALS but also for other brain disorders such as Parkinson's or Alzheimer's disease. FDA approved the strategy in a single-patient study in 2009 [investigational new drug application (IND) 13851, national clinical trial number (NCT) 01142856)] and an ongoing dose-escalation safety trial in 2011 (IND 14788, NCT01609283). This example illustrates how communication between academic investigators and regulatory scientists can reduce barriers to translation.

An example of a U.S. federal funding mechanism that drives clinical research toward product development is the Armed Forces Institute of Regenerative Medicine. In 2008, the U.S. Department of Defense provided funding for this initiative in response to the large numbers of life-altering injuries such as limb destruction and extensive burns suffered by young military survivors returning from recent theaters of war. The goal of the funding initiative was to bring together teams of investigators from a broad range of civilian institutions to focus on injuries that might benefit from tissue-engineering solutions, such as critical defects in nerve, bone, muscle, tendon, skin, and other organs, with a focus on limb injury.

One of the features of the funding was that it came with a contract that specified timelines and deliverables monitored on an annual basis, with funding expanding or contracting depending on the investigators' success in meeting milestones. This is a foreign concept and mode of operation for academic investigators; but in the first 4 years, 12 clinical trials, 4 INDs, and 3 IDEs were generated by investigators within the consortium. This project demonstrates that with some sacrifice of academic flexibility, it is possible for a federal funding agency to speed biomedical research translation, at least in the short term.

Academic investigators who choose to pursue commercialization of a product face many singular challenges. Considering intellectual property (IP) early in the translational process is crucial to future commercialization success. This process can be facilitated by technology offices within academic centers. Once IP is established, an investigator can pursue commercialization either independently by establishing a start-up company or via a licensing agreement with an established or privately held company. However, challenges arise when assembling a team to build and run a new company and when attempting to procure funding. Also, agreements on the legal relationships among an investigator, the academic institution, and an established company can be a long-drawn-out process.

A successful strategy that we have used at the Mayo Clinic is to create a new position called "translational integrator." This professional serves as a project manager whose responsibility is to facilitate negotiations between clinician-investigators, regulatory agencies, funding agencies, commercial sponsors, and contracting suppliers. Making this the "day job" for an appropriately trained person has transformed processes that used to take months or years into ones that can be accomplished in weeks.

UNMET MEDICAL NEED

There is an urgent need for evaluation and change in the process of therapy approval and translation at the very highest levels. Strategic plans forged at agencies including FDA, CMS, DOD, and NIH will have difficulty influencing change across administrative barriers. At the highest level, the PCAST report (*4*) identified two of the opportunities that directly address issues discussed here: Innovators require greater clarity about regulatory pathways for innovative products and approaches, and innovators require greater consistency, efficiency, and communication with respect to their individual drug applications. However, the report may not engender political action at a time when other health care delivery policies are the subject of intense debate.

However, members of the biomedical research community, individual institutions, and funding agencies can still take actions that responsibly speed the translation of biomedical discoveries to improvements in patient care. The ALS and AFIRM examples demonstrate that change is possible.

Two avenues to consider: (i) Individual institutions and investigators should take responsibility for learning about and understanding the process of translation from

discovery to application. They should use this knowledge to inform, from the beginning, the design of experiments, studies, and clinical trials. The vehicle for disseminating this knowledge to students, trainees, and investigators is in place at 60 major institutions that received CTSAs from NIH. Evaluation of the success of awardees should hinge on productivity related to the discovery of new diagnostics or therapies or on other markers that indicate improvements in human health and not only on the traditional markers of grants and publications. (ii) Agencies that fund research that has expressed translational or preclinical goals should adjudicate whether proposals clearly articulate a path to translation. This requires the incorporation in study sections of reviewers, such as regulatory scientists, who can critically evaluate the impact of a proposal using this criterion.

Science moves forward because of the work of individual scientists. In the process of bringing new therapies to communities, the biomedical investigator can play a critical role in accelerating translation within the existing framework. Institutions and funding agencies can facilitate this process by providing knowledge and incentivized direction to the individual research team.

REFERENCES AND NOTES

1. R. C. Brownson, M. W. Kreuter, B. A. Arrington, W. R. True, Translating scientific discoveries into public health action: How can schools of public health move us forward? *Public Health Rep.* **121**, 97–103 (2006).
2. J. M. Westfall, J. Mold, L. Fagnan, Practice-based research—"Blue Highways" on the NIH roadmap. *JAMA* **297**, 403–406 (2007).
3. E. A. Balas, S. A. Boren, Managing clinical knowledge for healthcare improvement. *Yearbook of Medical Informatics 2000*. **2000**, 65–70 (2000); www.ihi.org/resources/Pages/Publications/Managingclinicalknowledgeforhealthcareimprovement.aspx.
4. PCAST, "Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation" (Executive Office of the President, Washington, DC, 2012); www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf.
5. Report of the Translational Research Working Group of the National Cancer Advisory Board, "Transforming Translation—Harnessing Discovery for Patient and Public Benefit" (National Cancer Institute, Bethesda, MD, 2007); www.ida.org/~/media/Corporate/Files/Publications/STPIPubs/transformingtranslationfinalreport.ashx.
6. D. Angius, H. Wang, R. J. Spinner, Y. Gutierrez-Cotto, M. J. Yaszemski, A. J. Windebank, A systematic review of animal models used to study nerve regeneration in tissue-engineered scaffolds. *Biomaterials* **33**, 8034–8039 (2012).
7. U.S. Food and Drug Administration, "Advancing Regulatory Science at FDA" (2011); www.fda.gov/downloads/scienceresearch/specialtopics/regulatoryscience/ucm268225.pdf.
8. U.S. Food and Drug Administration, Clinical investigator training course. *Fed. Regist.* **76**, 45577–45578; www.gpo.gov/fdsys/pkg/FR-2011-07-29/html/2011-19149.htm.
9. S. Olson, A. B. Claiborne, *Accelerating the development of new drugs and diagnostics: Maximizing the impact of the cures acceleration network: Workshop summary* (National Academies Press, Washington, DC, 2012), p. 115.
10. U.S. Department of Health and Human Services and FDA, IDEs for early feasibility medical device clinical studies, including certain first-in-human studies (2013); www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf.
11. E. Zerhouni, Medicine. The NIH Roadmap. *Science* **302**, 63–72 (2003).
12. Committee to Review the Clinical and Translational Science Awards Program at the National Center for Advancing Translational Sciences, "The CTSA Program at NIH. Opportunities for Advancing Clinical and Translational Research" (Institute of Medicine, Washington DC, 2013); www.iom.edu/~/media/Files/Report%20Files/2013/CTSA-Review/CTSA-Review-RB.pdf.
13. National Institutes of Health, Neuro NEXT. The NEXT generation of neurologic treatments. NIH-Network for Excellence in Neuroscience Clinical Trials (2013); www.ninds.nih.gov/news_and_events/proceedings/20101217-NEXT.htm.
14. The Lancet Neurology, NeuroNEXT: Accelerating drug development in neurology. *Lancet Neurol.* **11**, 119 (2012).
15. U.S. Food and Drug Administration, NIH and FDA announce collaborative initiative to fast-track innovations to the public (2010); www.nih.gov/news/health/feb2010/od-24.htm.
16. Center for Medicare and Medicaid Services, Medicare Clinical Trial Policies (2013); www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies.
17. Medicare Advantage, Medicare advantage: Reforms needed to ensure access to clinical trials. *J. Oncol. Pract.* **5**, 144–145 (2009).
18. M. E. Gurney, H. Pu, A. Y. Chiu, M. C. Dal Canto, C. Y. Polchow, D. D. Alexander, J. Caliendo, A. Hentati, Y. W. Kwon, H.-X. Deng, W. Chen, P. Zhai, R. L. Sufit, T. Siddique, Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. *Science* **264**, 1772–1775 (1994).
19. H. B. van der Worp, D. W. Howells, E. S. Sena, M. J. Porritt, S. Rewell, V. O'Collins, M. R. Macleod, Can animal models of disease reliably inform human studies? *PLOS Med.* **7**, e1000245 (2010).
20. E. J. Sorenson, A. J. Windbank, J. N. Mandrekar, W. R. Bamlet, S. H. Appel, C. Armon, P. E. Barkhaus, P. Bosch, K. Boylan, W. S. David, E. Feldman, J. Glass, L. Gutmann, J. Katz, W. King, C. A. Luciano, L. F. McCluskey, S. Nash, D. S. Newman, R. M. Pascuzzi, E. Pioro, L. J. Sams, S. Scelsa, E. P. Simpson, S. H. Subramony, E. Tiryaki, C. A. Thornton, Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. *Neurology* **71**, 1770–1775 (2008).

10.1126/scitranslmed.3008252

Citation: N. P. Staff, B. K. Runge, A. J. Windebank, Breaking down translation barriers: Investigator's perspective. *Sci. Transl. Med.* **6**, 252cm7 (2014).

Science Translational Medicine

Breaking Down Translation Barriers: Investigator's Perspective

Nathan P. Staff, Bethany Kinseth Runge and Anthony J. Windebank

Sci Transl Med **6**, 252cm7252cm7.
DOI: 10.1126/scitranslmed.3008252