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COMMENTARY

Innovation in Therapeutics Development at the NCATS

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INTRODUCTION

Never before has there been such a sense of urgency to rethink the way in which therapeutics are discovered and developed. Drug development has grown less efficient with every passing year (http://www.phrma.org; Scannell *et al*, 2012), at the same time as fundamental understanding of human biology in health and disease has exploded. For example, the number of diseases with an identified molecular basis is fast approaching 5000, but the vast majority of these have no Food and Drug Administration (FDA)-approved therapy (http://www.omim.org/statistics/geneMap). Neuroscience has been particularly affected by these trends, such that, although advances in our understanding of neural development, plasticity, and circuitry were being celebrated at the end of the Decade of the Brain in 2010, many large and small pharmaceutical companies were abandoning neuroscience because of the high rate of failure in neuropsychiatric drug development.

In part to address these problems in therapeutic development, the NIH commissioned its Science Management Review Board (SMRB) to study the problems in translation and recommend changes to the NIH structure to address them. In response to the SMRB's report (http://smrb.od.nih.gov/documents/reports/TMAT_122010.pdf), NIH proposed the creation of a new Center at NIH that would address the scientific and operational roadblocks to translational efficiency. On 23 December 2011, the National Center for Advancing Translational Sciences (NCATS) was created through the Consolidated Appropriations Act, 2012, (P.L. 112-74), which amended the Public Health Service (PHS) Act to include the NCATS. The mission of the Center is to create and test innovative methods, strategies, and technologies that enhance the development, testing, and implementation of interventions that improve human health. The NCATS is focused on what is common among diseases and the translational process, to identify and disseminate general principles that will accelerate translation of fundamental discoveries into tangible improvements in human health.

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FOCUS ON TRANSLATIONAL SCIENCE PROCESSES

Unlike most other NIH Institutes and Centers, the NCATS does not target a particular disease or an organ system but rather focuses on innovative technologies, paradigms, and processes that will catalyze the translation of scientific discoveries into new diagnostic or therapeutic interventions. The NCATS frequently develops translational innovations in the context of particular diseases or organ systems but with the goal of the approach being applicable to other disease areas.

This principle is illustrated by the NCATS Discovering New Therapeutic Uses for Existing Molecules (NTU) program (http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html), in which 58 investigational agents from 8 pharmaceutical companies, AbbVie (formerly Abbott), AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline, Janssen Research & Development, L.L.C, Pfizer, and Sanofi, were made available to the scientific community to propose ideas for potential therapeutic uses of those agents. Because the NCATS does not have a particular disease focus, the indications proposed could focus on the best scientific fit to the characteristics of the agent, regardless of the disease area. The program is supporting studies in a wide array of common and rare diseases, including alcohol dependence, Alzheimer's disease, calcific aortic valve stenosis, Duchenne muscular dystrophy, lymphangioleiomyomatosis, nicotine dependence, peripheral artery disease, and schizophrenia (http://www.nih.gov/news/health/jun2013/ncats-18.htm).

NCATS' Therapeutic Development for Rare and Neglected Diseases (TRND) program conducts collaborative projects to develop small molecule and biologic agents for important diseases with low anticipated return on investment,

de-risking them to the point where they can attract commercial interest for the completion of clinical development and marketing. These projects typically require development of novel scientific or collaborative approaches that are generalizable to other disorders. A current TRND project on creatine transporter defect (CTD) provides an example. CTD is a rare disorder in which creatine cannot enter the brain, resulting in profound learning disabilities, autistic behavior, and recurring epileptic seizures; it affects approximately 42 000 male individuals and has no current treatment. In collaboration with Lumos Pharma Inc., TRND is developing a creatine analog (CincY) as a therapeutic for CTD, performing animal efficacy and toxicity studies, pharmacokinetic evaluations, development of appropriate formulations for human drug dosing needed for Investigational New Drug (IND) filing, and providing other scientific and regulatory supports required to get the drug to patients and allow Lumos to attract a biopharma partner to complete clinical development. In this project as in all NCATS projects, the novel approaches, successes, and failures of the program will be published to allow the research community to apply the lessons from this project to their own work.

ADDRESSING BARRIERS TO TRANSLATION

NCATS is focused on the systematic factors that limit the efficient and effective development and implementation of interventions that improve health. These barriers are frequently scientific, and much has been written about it, including in the neurosciences (Brady and Insel, 2012). However, equally common, translational projects fail not for strictly scientific, but rather for operational, reasons—including intellectual property, incentive, collaboration, and coordination issues. NCATS focuses on both new science and new operational models to advance translation.

The first new program launched by the NCATS, the NIH-Industry Pilot Program on Discovering New Therapeutic Uses for Existing Molecules (NTU), exemplifies a key aim for NCATS in terms of scientific and operational innovation. Scientifically, the program addresses the difficulty in identifying and testing a new therapeutic in all the diseases for which it could be effective. Operationally, it has been difficult and time-consuming for a company with an investigational therapy both to identify potential partners with ideas for alternative therapeutic uses and to come to agreement on terms with the partner's institution. The NTU program resulted from a 2011 NIH-Industry roundtable with representatives from academia, government, and the private sector tasked with assessing the potential for a joint program to overcome these hurdles (Collins, 2011). The NTU program is testing a new model for public–private partnerships (PPPs) using 'crowdsourcing' to identify potential indications by broad input from the academic research community. It also is uniquely using memoranda of understanding with participating pharmaceutical companies and template agreements to shorten the time it would take to establish collaborations between an academic institution and a pharmaceutical company.

The NTU program also illustrates NCATS' operating principles of the '3Ds: Development, Demonstration, and Dissemination' (18 June 2013: Translation in Three Dimensions: The 3Ds of NCATS http://www.ncats.nih.gov/about/director/directors-message-archive.html#jun2013). Because collaborative research agreements can be extremely time-consuming, NCATS and the NIH developed (the first D) template agreements, on behalf of the research community, that could be executed rapidly between applicant institutions and the pharmaceutical company providing the well-developed agent for repurposing. Template agreements were a key element for the pharmaceutical companies to help ensure timely and efficient execution of agreements, but these were also an essential element for the solicitation of applications. Without templates, the number of collaborative agreements that any given company would need to have executed would have resulted in few if any being secured in time for the application receipt date.

Through this funding opportunity, NCATS was able to demonstrate (the second D) the effectiveness of template agreements at streamlining the negotiation process, allowing the focus to stay on the research and getting it started rapidly. We have made these template agreements available to anyone who wants to use them, thus disseminating (the third D) the results of the program, enabling future use by pharmaceutical companies and other NIH Institutes and Centers for other initiatives.

PREDICTIVE TOXICOLOGY

Another of the systematic translational challenges NCATS is addressing is the difficulty in predicting which new therapeutics will have adverse effects in humans. More than 30% of promising pharmaceuticals have failed in human clinical trials because they are determined to be toxic despite promising pre-clinical studies in animal models (Kola and Landis, 2004). The NCATS is taking two complementary approaches to this problem. One is the NCATS Tissue Chip for Drug Screening program (http://www.ncats.nih.gov/research/reengineering/tissue-chip/tissue-chip.html). This is a highly collaborative program between NCATS, the NIH Common Fund and fellow NIH Institutes and Centers, the FDA, and the Defense Advanced Research Projects Agency (DARPA). The program aims to develop 3-D human tissue chips that model the structure and function of human organs that can be used to assess toxicity more accurately and more cost-effectively than is currently done with animal models.

The second approach is the Toxicology in the 21st Century (Tox21) program in which NCATS is collaborating with the National Toxicology Program at the National Institute of Environmental Health Sciences (NIEHS), the Environmental Protection Agency (EPA), and the FDA to develop a comprehensive understanding of the effects of

drugs and environmental chemicals on human pathways, to allow screening- and computation-based toxicity prediction. Tox21 is building a database of the integrated pathway data that will allow researchers to systematically analyze and model toxicity responses. The program solicits input from the research community for nomination of assays for high-throughput screening through a public website, http://iccvam.niehs.nih.gov/contact/Tox21-nomination.htm.

COLLABORATIONS AND PARTNERSHIPS

A recurring theme among the NCATS programs is the importance of collaborations and partnerships (26 February 2013: Translation Is a Team Sport, http://www.ncats.nih.gov/about/director/directors-message-archive.html#feb2013). One such collaboration, made possible by the NCATS' RDCRN (Rare Disease Clinical Research Network) and CTSA (Clinical and Translational Science Award) programs, recently resulted in demonstration of effectiveness of mexiletine, originally used to treat heart disorders, in treating non-dystrophic myotonia, a rare genetic muscle disorder that often results in debilitating muscle stiffness, fatigue, and paralysis (Statland *et al*, 2012). Patients were enrolled at four sites in the United States and at one site each in Canada, the United Kingdom, and Italy. To collect and manage the study data from the seven sites, the research team used the RDCRN's Data Management Coordinating Center at the University of South Florida. Each of the four U.S. sites used its CTSA resources, and funding of the study was also collaborative, with support from the FDA Office of Orphan Products Development and from the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH.

MOVING FORWARD

This brief sampling of the selected NCATS programs provides a glimpse into the direction and mission of this newest of NIH components. Biomedicine is in a period of unprecedented promise but also unprecedented challenges. The NCATS looks forward to working with its partners across the research spectrum to deliver on the promise of science for improved health.

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