CORRECTED 6 MAY 2015; SEE FULL TEXT

POLICY

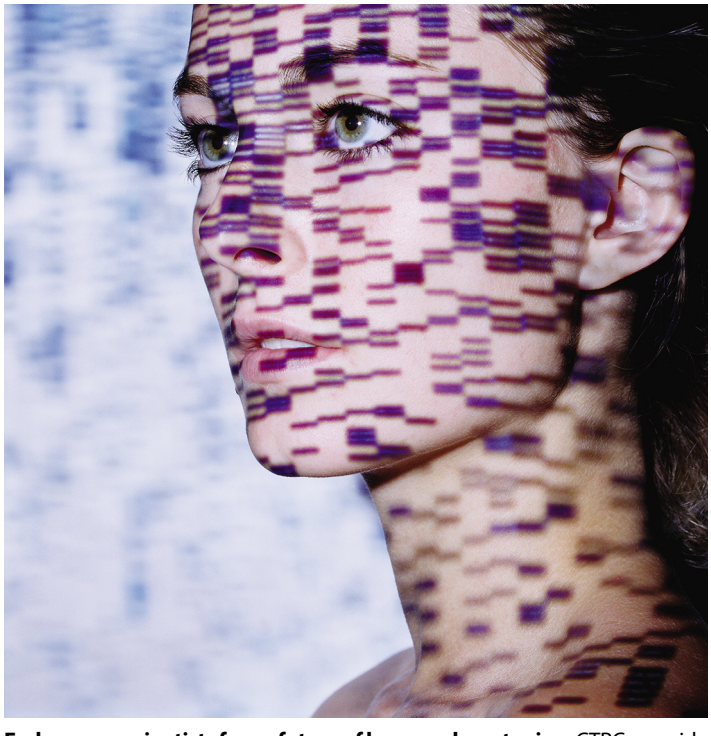
Evolution in translational science: Whither the CTSAs?

Garret A. FitzGerald

Clinical and Translational Science Awards-funded institutions are naturally equipped to drive research on human phenotyping and, in turn, shape the practice of precision medicine in the clinic of the future.

Launched in 2006, the U.S. National Institutes of Health (NIH) Clinical and Translational Science Awards (CTSAs) program was designed to foster the integration of basic and clinical science so that fundamental discoveries might more readily be translated into new therapies, devices, or approaches to the prediction and management of disease—all directed toward improving human health (www.ctsacentral.org). Currently, 62 academic institutions—now named "hubs"—hold CTSAs. NIH director Francis Collins has sustained the program and initiated a working group on translational medicine and therapeutics (http://smrb.od.nih.gov/documents/reports/TMAT_122010.pdf) that led to the formation of the National Center for Advancing Translational Science (NCATS; www.ncats.nih.gov). In 2012, the U.S. Institute of Medicine (IOM) published a report encouraging NCATS to play a more active leadership role in the CTSA network (*1*). The most recent CTSA funding opportunity announcement reflects a budgetary and programmatic shift responsive to that guidance.

But is this the most effective way for the CTSA network and NCATS to influence emergence of the clinic of the future—one designed to practice precision medicine? The nascent plan is to focus the hub network on conventional large-scale clinical trials. However, this era of clinical research is giving way to the application of adaptive-trial methodologies to smaller trials; the integration of electronic medical records (EMRs) with biobank data to pinpoint new disease pathways; and the pursuit of human phenomic science (HPS), deep phenotyping of small numbers of patients to elucidate the functional significance of genomic variation. Some CTSA hubs are well positioned to develop and sustain HPS, but this endeavor depends on continued support for (i) clinical and translational research centers (CTRCs), (ii) education of the next generation of interdisciplinary translational scientists in HPS, and (iii) pilot projects—that is, how, where, and by whom such research is performed and how it is funded.



Early-career scientists face a future of human phenotyping. CTRCs provide substantial support to young clinical and translational investigators. To frame this in fiscal terms alone, the Penn-CHOP integrated CTRC provided subsidies to investigators pursuing NIH-supported research—roughly half of whom are assistant professors—worth $5,325,648 in FY2010, dropping to $3,945,287 in FY2013 as charge-back fees to investigators were gradually introduced.

CREDIT: TIM FLACH/GETTY

Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-5158, USA.
E-mail: garret@upenn.edu

AWARD ACHIEVEMENTS

CTSAs are expensive, although not so when considering their geographical scope and ambitious objectives. The budget is less than 1% of what is spent by the pharmaceutical and biotechnology industries on research and development. Still, at a time when funding rates for investigator-initiated research are so low, an allocation by NIH of ~$500 million annually is understandably subject to sustained scrutiny. So what has come from this investment?

The CTSA program had ambitious goals, and its evolution has not been without challenges (*2*). Competing institutions were required to create academic homes for clinical and translational research. The form of the home—whether virtual or measurable in net square feet—was left to the institutions so that they could address their individual needs and visions within the confines of their available resources. As a result, academic institutions built diverse homes for clinical and translational science. With the use of pilot funds for driving interdisciplinary research, the hubs have developed innovative technologies and created new educational programs. They have jointly catalyzed collaborations across institutions in ways not achieved by NIH institutes and centers and breathed new life into clinical research by fostering its integration with basic science.

Furthermore, the program's successes can be measured by outcomes such as the number of graduates from CTSA-sponsored educational programs and surrogate markers of the subsequent success of these scholars (*3*); the growth and density of the interdisciplinary connectome of institutional scientists (*4*); various forms of transinstitutional collaborations among hubs (*5*); and the development of tools, such as REDCap (http://project-redcap.org) and i2b2 (www.i2b2.org), that facilitate translational research. Clinical and translational

science institutes (CTSIs) have become natural homes for institutional infrastructure initiatives relevant to this kind of research, including biobanks and regulatory support systems for clinical trials. However, despite this remarkable progress, how one relates these achievements to actual therapeutic or diagnostic breakthroughs remains a matter of debate.

It is important to realize the limitations of outcome measurements. First, we lack proper controls. For example, the translational connectome has grown dramatically during the lifetime of the University of Pennsylvania's Institute for Translational Medicine and Therapeutics (ITMAT) and is much denser among ITMAT members than among those who chose not to join the institute. But might this growth have occurred organically if membership simply reflects a self-selection of the collaborative scientists on campus? Second, true breakthroughs are rare and usually a long time in the making. In an assessment of research in the United Kingdom, the Wellcome Trust estimated that the average time from target discovery to drug approval is 17 years (www.wellcome.ac.uk/stellent/groups/corporatesite/@sitestudioobjects/documents/web_document/wtx052110.pdf). However, using an analysis of quality-adjusted life years, it calculated that, for an investment of £11 billion to £17 billion, the benefit to the UK economy was £55 billion to £91 billion. So the science takes a long time but, even by a narrow definition, affords a substantial return on investment. By extrapolation, the clinical value of NIH's investment in the CTSA program, now in its ninth year, would be expected to emerge over the next two decades.

During ITMAT's 11-year tenure (anteceding the CTSAs), two programs that have changed clinical practice dramatically are the use of gene therapy to arrest progression of some forms of inherited blindness (*6*) and the use of "serial killer" T lymphocytes in the treatment of leukemia (*7*). In both cases, ITMAT provided programmatic support at a time when the investigators had little or none from the private sector or philanthropies. Also, both are examples of science reliant on the integration of studies in model systems with deep phenotyping in small numbers of humans (that is, HPS) and conducted at the Penn–Children's Hospital of Philadelphia (CHOP) interface that has been the focus of ITMAT's efforts.

In light of these successes, one noteworthy feature of the CTSA program is its requirement that medical schools and their pediatric hospitals submit joint applications. This was a forced marriage in some cases (*8*), as pediatric hospitals lobbied hard for an independent funding stream. However, the biological continuum of health and disease evolution presents a compelling opportunity to address the pediatric-adult segmentation of medical science, and structures were put in place to sustain and develop pediatric research, which was also an emphasis in the recent IOM recommendations. In my view, this is an authentic achievement of the CTSA program.

THE FUTURE OF MEDICINE

> *When my information changes, I alter my conclusions.*
>
> ~Economist John Maynard Keynes

The recent announcement of the U.S. initiative to foster precision medicine highlights the emerging emphasis on parsing interindividual variability in therapeutic response and susceptibility to disease (http://www.nih.gov/precisionmedicine). For now, the focus is on collection and integration of huge amounts of clinical data from EMRs. But a complementary strategy for formulating or addressing hypotheses with EMR-based research requires HPS—quantitative measures of physiology, pathology, or drug response, in small numbers of individuals, that might be attributable to genetic and environmental variance. Detailed evocation of phenotypes, beyond the scope of what is possible in either large clinical trials or discernible from an EMR, facilitates the attribution of function to genomic variance in humans, just as in mice. To reap the full benefits of HPS, we need technologies for detection and characterization of variability, appropriately trained scientists, controlled environments in which to perform human phenotyping, and seed funding to gather preliminary data for attracting the support necessary to perform such expensive research. Last, our approach to HPS must be fluid, flexible, and fast enough to interact effectively and at scale with EMR and biobank studies. Bulky consortia or contract research organizations (CROs) designed to perform large phase 3 clinical trials lack flexibility and thus are ill-equipped to address questions through HPS.

But HPS is precisely the type of science that CTSA hubs are ideally positioned to advance. The CTSA program drove NIH's costly General Clinical Research Centers to extinction or repurposing. No longer individual fiefdoms, CTRCs at individual institutions have broadened their remit across the spectrum of clinical research to include community-engaged research, emphasize deep phenotyping, and integrate adult and pediatric research. These centers provide considerable support, often to early-career investigators, by offering venues in which to perform clinical science and obtain (at low or no cost) ancillary services such as expert nursing, nutritional, informatics, and statistical support. They also have developed approaches to quantitative phenotyping that range from evoked physiological responses to remote-sensing technologies that permit both ambulatory and inpatient elements in research protocols. Miniconsortia have facilitated studies of rare diseases in such environments, and individual CTSI hubs harbor expertise in quantitative sciences, such as metabolomics, which can readily be shared with other institutions in support of multisite studies. Most CTSIs have pilot-project funding that can be used to catalyze such research, establishing proof-of-concept or other such preliminary data that support the initiation of larger studies. Through their investment in educational programs, CTSIs are positioned to address the greatest limitation to the pursuit of translational science–investigators skilled in mechanism-based clinical research at the translational interface (*9*).

It is remarkable how few investigators integrate expertise in preclinical models with a sophisticated approach to quantitative phenotyping in humans. This blend of expertise forms a discipline that has no name and yet is crucial to the interests of NIH-funded science, the pharmaceutical and biotech industries, and the U.S. Food and Drug Administration. By setting aside a segment of educational dollars specifically for training in HPS, NCATs could foster a vital discipline within CTSA institutions and industry, which could in turn yield new sustainable career structures, including those that bridge the public and private sectors. The singular focus of disease-specific NIH institutes and centers precludes their spurring of such a revolution. In contrast, the current conditions present a natural opportunity for the multidisciplinary NCATs—but only if it fosters and sustains a funding stream for training in HPS. Last, the encouragement by funders that CTSA-

driven projects pair with research supported by the Patient-Centered Outcomes Research Institute (PCORI; www.pcori.org) constitutes a recognition that progress toward personalized medicine requires the integration of EMR- and biobank-driven research with HPS.

UNINTENDED CONSEQUENCES

Despite translational science's decades-long timeline to success, the most recent funding opportunity announcement from NIH signals a repitching of the CTSA program less than a decade into its existence. Roughly 20% of the program's funding will be removed from the hubs and used by NCATS, mostly to foster transconsortial interactions, in accord with the IOM-report recommendations (*1*).

Although collaboration across hubs is a worthy goal, we must maintain flexibility around the nature of these collaborations. Specifically, even if a collaborative network of 62 CTSA institutes (a rather political number) is a realistic near- or medium-term goal, it is highly unlikely to be as time- or cost-efficient as existing academic networks (such as the Duke Clinical Research Institute) or commercial CROs in the performance of large-scale clinical trials. In developed economies, conventional clinical trials are being outsourced or replaced by smaller, adaptive trials and the EMR-biobank-HPS approach to clinical research. Here is where miniconsortia of CTSA hubs could interact to great effect, with particular relevance to the pursuit of the goals set out in the precision medicine initiative.

Yet the money extracted from individual CTSA hubs to foster collaboration severely restricts support for CTRC-based research, pilot studies, and early-stage investigator training, all of which are fundamental to HPS—where, how, and by whom it is done. These restrictions fall most heavily on young investigators and our future work force, the element most crucial to success. There are many reasons for budding physician-scientists to choose clinical practice or drop out of training programs (*10*), and this erosion of support sends a chilling, albeit unintended, message; we neglect them at our peril. The flexibility to sustain HPS at CTSA hubs must be maintained if we are to realize the therapeutic potential of translational research.

The IOM report encouraged CTSA hubs to play to their strengths rather than to try to cover the breath of clinical and translational science with unrealistic resources. Intrinsic to such advice is the need to maintain flexibility among the missions of individual hubs. Perhaps it is time to consider "comprehensive" and "specialized" CTSA hubs akin to cancer centers. Comprehensive hubs might address multiple aspects of clinical and translational science, whereas specialized hubs would have smaller budgets and focus on a particular disease or type of science. Given the current appetite for precision medicine, conspicuously led by NIH, we should use at least some of the CTSAs to foster the development of HPS.

REFERENCES AND NOTES

1. IOM Report on CTSA program; www.iom.edu/Reports/2013/The-CTSA-Program-at-NIH-Opportunities-for-Advancing-Clinical-and-Translational-Research.aspx.
2. G. A. FitzGerald, NCATS purrs: Emerging signs of form and function. *Sci. Transl. Med.* **3**, 83ed2 (2011).
3. E. A. Meagher, Training translators in the PENN CTSA. *Clin. Transl. Sci.* **4**, 314–316 (2011).
4. M. E. Hughes, J. Peeler, J. B. Hogenesch, Network dynamics to evaluate performance of an academic institution. *Sci. Transl. Med.* **2**, 53ps49 (2010).
5. S. E. Reis, P. D. Patterson, G. A. Fitzgerald, D. Ford, R. S. Sherwin, J. Solway, B. A. Evanoff, The sharing partnership for innovative research in translation (SPIRiT) consortium: A model for collaboration across CTSA sites. *Clin. Transl. Sci.* **6**, 85–87 (2013).
6. J. Bennett, M. Ashtari, J. Wellman, K. A. Marshall, L. L. Cyckowski, D. C. Chung, S. McCague, E. A. Pierce, Y. Chen, J. L. Bennicelli, X. Zhu, G.-S. Ying, J. Sun, J. F. Wright, A. Auricchio, F. Simonelli, K. S. Shindler, F. Mingozzi, K. A. High, A. M. Maguire, AAV2 gene therapy readministration in three adults with congenital blindness. *Sci. Transl. Med.* **4**, 120ra15 (2012).
7. S. L. Maude, N. Frey, P. A. Shaw, R. Aplenc, D. M. Barrett, N. J. Bunin, A. Chew, V. E. Gonzalez, Z. Zheng, S. F. Lacey, Y. D. Mahnke, J. J. Melenhorst, S. R. Rheingold, A. Shen, D. T. Teachey, B. L. Levine, C. H. June, D. L. Porter, S. A. Grupp, Chimeric antigen receptor T cells for sustained remissions in leukemia. *N. Engl. J. Med.* **371**, 1507–1517 (2014).
8. K. Garber, Translational institute unites unlikely partners at Penn. *Science* **317**, 968–969 (2007).
9. C. Skarke, G. A. FitzGerald, Training translators for smart drug discovery. *Sci. Transl. Med.* **2**, 26cm12 (2010).
10. D. Daye, C. B. Patel, J. Ahn, F. T. Nguyen, Challenges and opportunities for reinvigorating the physician-scientist pipeline. *J. Clin. Invest.* **125**, 883–887 (2015).

Funding: This work was supported by UL1 TR000003 from NIH. G.A.F. is the McNeil Professor in Translational Medicine and Therapeutics.

10.1126/scitranslmed.aab1596

Citation: G. A. FitzGerald, Evolution in translational science: Whither the CTSAs? *Sci. Transl. Med.* **7**, 284fs15 (2015).

Science Translational Medicine

Evolution in translational science: Whither the CTSAs?

Garret A. FitzGerald

Sci Transl Med **7**, 284fs15284fs15.
DOI: 10.1126/scitranslmed.aab1596