


**MEMORANDUM**

TO: Planning, Housing and Economic Development Committee

FROM: Justina J. Ferber,  Legislative Analyst

SUBJECT: **Briefing:** Christopher P. Austin, M.D., Scientific Director  
NIH National Center for Advancing Translational Therapeutics

Dr. Christopher P. Austin, Scientific Director for the NIH National Center for Advancing Translational Therapeutics (NCATS), will brief the committee on the work of this new Center. In explaining the NCATS program, he will describe how the work of the Center will benefit the County's biotechnology industry and its economic impact.

The central role of the Center is to establish and provide focused, integrated, and systematic approaches for building new bridges that link basic discovery research with therapeutics (drugs, diagnostics, and devices) development and clinical care. Translational sciences are increasingly becoming multi-sector endeavors involving industry, government, academia and other sectors. The Center will play a key role in convening these cross-sector collaborations to advance therapeutics development. The Center will develop and offer innovative services and expertise to move promising products through the development pipeline, as well as develop novel approaches to therapeutics development, stimulate new avenues for basic scientific discovery, and complement the strengths of existing NIH research activities.

Attachment: Article from Dr. Francis S. Collins, NIH Director, Reengineering Translational Science  
(Dr. Collins' vision for the NCATS)

## POLICY

# Reengineering Translational Science: The Time Is Right

Francis S. Collins

Despite dramatic advances in the molecular pathogenesis of disease, translation of basic biomedical research into safe and effective clinical applications remains a slow, expensive, and failure-prone endeavor. To pursue opportunities for disruptive translational innovation, the U.S. National Institutes of Health (NIH) intends to establish a new entity, the National Center for Advancing Translational Sciences (NCATS). The mission of NCATS is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of diseases and conditions. The new center's activities will complement, and not compete with, translational research being carried out at NIH and elsewhere in the public and private sectors.

The medical benefits of the current revolution in biology clearly cannot be achieved without vigorous and effective translation. Yet the triple frustrations of long timelines, steep costs, and high failure rates bedevil the translational pathway. The average length of time from target discovery to approval of a new drug currently averages ~13 years, the failure rate exceeds 95%, and the cost per successful drug exceeds \$1 billion, after adjusting for all of the failures (1, 2). In this Commentary, I describe the goals, functions, and structure of the National Center for Advancing Translational Sciences (NCATS), a new entity currently being shaped by the U.S. National Institutes of Health (NIH) to reengineer the process of developing diagnostics, devices, and therapeutics.

## ADDRESSING THE BOTTLENECKS

The translation of basic biological discoveries into clinical applications that improve human health is an intricate process that involves a series of complex steps: the discovery of basic information about the pathogenesis of a disease; an assessment of whether that information has the potential to lead to a clinical advance; development of candidate diagnostics, devices, or therapeutics; optimization of the candidates in preclinical settings; regulatory assessment of the data to determine the potential for human use; testing in human clinical trials; application for approval for widespread clinical use; and, ultimately, the assessment of approved diagnostics, devices, and therapeutics during widespread use in real-world settings.

The upstream component of this developmental pipeline is progressing vigorously, aided by dramatic technological advances and associated basic insights into disease mechanisms—research that has been supported heavily by NIH and other funding agencies. The downstream end—premarket clinical trials—is traditionally the strong suit of the private sector because of its considerable expertise in assessing promising interventions. However, serious problems exist in the middle zone, in which attrition rates for candidate products are horrendously high. Many of the complex steps in this middle zone have been performed in the same way for a decade or more and have not been subjected to the kind of bold innovation that has characterized other branches of biomedical science. Thus, the time is right to take a comprehensive, systematic, and creative approach to revolutionizing the science of translation.

To shape and sharpen this new vision, NIH now proposes to establish NCATS.

Intended to serve as NIH's catalytic hub for translational innovation, the new center will complement—not compete with—translational research at the NIH and elsewhere in the public and private sectors. Simply put, NCATS's mission is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics, therapeutics, and devices across a wide range of human diseases and conditions.

NCATS-supported researchers will seek to advance the science of translation by identifying bottlenecks in the therapeutic development pipeline that may be amenable to reengineering; experimenting with innovative approaches to reduce, remove, or bypass these bottlenecks; and evaluating these innovations by assessing their performance in real-world applications. All of this will be done in a transparent scientific environment, using NIH-based online resources to ensure that information about successes—and failures—is made swiftly available to all stakeholders.

## CHALLENGING THE STATUS QUO

Basic science research conducted in the nonprofit sector has provided knowledge integral to clinical advances. NIH-supported scientists have played a fundamental role in the discovery of many receptors, enzymes, and disease-related pathways that spurred the development, by the private sector, of myriad therapeutics (3–6). But the research and development landscape has changed, and a new model is needed.

Scientific advances have moved us from an era in which most drug development was based on a short list of a few hundred targets with great depth of understanding to an era in which molecular technologies

**Table 1. The GWAS potential.** GWAS\* can reveal new therapeutic targets for complex diseases (8, 56, 57).

Disease	Total GWAS hits†	GWAS hits associated with marketed drugs‡	GWAS hits associated with drug effects§
Type 2 diabetes	44	6	8
Hyperlipidemia	39	2	10
Multiple sclerosis	36	5	2
Psoriasis	24	4	1

\*Genome-wide association studies (GWAS) assume no knowledge of disease pathogenesis and provide a comprehensive approach to the discovery of common genetic risk factors. Many known drug targets and associated pathways appear on the list of GWAS hits for common diseases, suggesting that other GWAS hits likely represent "druggable" targets worthy of further investigation. †Genetic variants strongly linked to disease susceptibility. ‡Genetic variants that are primary targets of drugs currently marketed for the listed indication. §Genetic variants associated with cellular, pharmacokinetic, pharmacodynamic, or clinical variations in response to one or more drugs currently marketed for the listed indication.

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provide thousands of new potential drug targets but limited information about their mechanisms and potential “druggability.” To give just one example, efforts that use the genome-wide association studies (GWAS) approach have revealed 1100 well-validated genetic risk factors for common diseases (7, 8). Given that many known drug targets have turned up in GWAS research (Table 1), it seems likely that previously unknown targets also lie hidden in the vast trove of GWAS data. Furthermore, in recent years research has uncovered the genetic bases of thousands of Mendelian disorders, suggesting possible interventional strategies for these rarer diseases and conditions.

Data-intensive research strategies—from GWAS analyses, to deep sequencing of the genomes of individuals with exceptional phenotypes, to studies of epigenomic regulation of gene expression, to more comprehensive methods to assess proteomes, metabolomes, and cellular pathways—have exposed many new potential avenues for clinical intervention. Further, these approaches have revealed that diseases once considered quite distinct can share similar molecular pathways; this realization suggests that the entire framework of medical taxonomy requires rethinking and that therapeutics of the future likely will be designed with cellular networks in mind, rather than being limited by historical designations of disease category.

This array of new opportunities should portend a revolution in therapeutics discovery. Clinical advances, however, have been frustratingly slow to arrive: Therapies currently exist for only about 200 of the ~4000 conditions (9) with defined molecular causes. Furthermore, the potential utility of most of the newly discovered molecular targets will not be easy to validate. Even worse, the serious challenges that currently confront the private sector may make it difficult to capitalize on these new opportunities. Current trends are indeed disturbing. Over the past 15 years, the annual rate of approval for drugs that address a new target class has not kept pace with the substantially increased investments that have been made in research and development (1, 10). Faced with economic stresses and patent expirations, many pharmaceutical companies are reducing their investments in research, and biotechnology companies are finding it difficult to obtain venture capital for projects that need many years of support to achieve profitability (11, 12).

Diverse commentators have expressed serious concerns about the sustainability of the current translational process. However, as can sometimes happen in the midst of crisis, this uncertainty is inspiring creative ideas among the various stakeholders and fueling quests for ground-breaking translational models. Consistent with our mission, NIH has envisioned ways to contribute to the building of a new translational paradigm.

### PARALLELS WITH THE PAST

Twenty-five years ago, a vigorous debate emerged in the scientific community over whether the government should invest in a large-scale effort to sequence the human genome. Many concerns were raised about technical feasibility and potential diversion of critical resources from other valuable research activities. However, most now agree that the Human Genome Project moved the fledgling field of genomic science beyond methods that were slow, expensive, and of variable quality toward organized, highly efficient approaches that have revolutionized biomedical research and continue to evolve (13, 14).

Although the parallels are not precise, the field of translational science today faces some challenges that are similar to those of the genomics field in 1990. For example, little focused effort has been devoted to the translational process itself as a scientific problem amenable to innovation. As was the case with genomics, translational science needs to shift from a series of one-off solutions toward a more comprehensive strategy. And as with sequencing of the human genome, many of the most crucial challenges confronting translational science today are precompetitive ones. The development of systematic approaches for target validation, the reengineering of rate-limiting and failure-prone steps in the therapeutic development process, and the urgent need to increase the critical mass of well-trained individuals to drive innovations are among the various translational challenges that are ill-suited for solutions derived solely from the private sector.

### NCATS: THINKING DIFFERENTLY

The capabilities being gathered into NCATS will offer researchers unparalleled opportunities for intense focus on the reengineering of the translational process, from initial target identification to first-in-human application of small molecules, biologics, diagnostics, and devices. Taking care to

avoid a “top-down” management approach, NCATS will count on the scientific community to conceive highly innovative ideas and propose potential implementation projects. The most promising programs will be funded through NIH’s highly respected, peer-reviewed grant- and contract-awarding process. Early discussions with a variety of stakeholders have identified several components of translational science that are ripe for the new scientific approach offered by NCATS and will likely be the subject of early targeted funding opportunities.

**Therapeutic target validation.** Translational science is awash with newly discovered but unvalidated therapeutic targets. NCATS will support broadly applicable rather than disease-specific target-validation approaches and the investigation of nontraditional therapeutic targets that are considered too risky for industry investment. These include systematic efforts to identify the functional variants that drive GWAS signals (15, 16), identification of the minimal set of functional modules used by the human cells to achieve homeostasis (17), a focus on targets that may be relevant to multiple diseases, and the application of whole-exome or whole-genome sequencing to identify rare individuals with loss-of-function mutations in proteins that then become candidates for therapeutic targeting, such as the much-cited example in which investigation of the PCSK9 gene led to a promising new approach to the treatment of heart disease (18).

**Chemistry.** Synthesis, isolation, derivatization, and characterization of small and large molecules are the foundations of much of drug development. In recent years, innovations in parallel synthesis and analysis methods have greatly increased. A variety of innovative approaches hold promise for expanding the currently druggable space and opening new vistas for therapeutic development (19), many of which can be accelerated by NCATS support. These approaches include the expansion of the types of molecules used as therapeutics (aptamers, peptoids, carbohydrates, locked peptides, and peptide nucleic acids); reinvigoration of natural products chemistry (20); and exploration of new methods for lead identification, such as fragment-based drug design and structure-activity relationships obtained with nuclear magnetic resonance. NCATS can also encourage innovations in chemistry for drug delivery, such as nanoparticles; imaging agents for use as biomarkers; and detection technologies

for use in diagnostics. In all of these areas, NCATS will seek to identify opportunities for precompetitive innovation that are not currently being supported by academic or industry initiatives.

**Virtual drug design.** As the database of protein structures rapidly grows, the ability to predict molecular structures with the desired properties of agonists or antagonists holds increasing promise, and yet the computational aspects remain extremely challenging (21). NCATS plans to encourage novel algorithm development in this area of research.

**Preclinical toxicology.** The use of small and large animals to predict safety in humans is a long-standing but not always reliable practice in translational science (22). New cell-based approaches have the potential to improve drug safety prediction before use in patients (23). The NIH-EPA-FDA Tox21 consortium has already begun this effort (24), which may benefit from the use of (i) three-dimensional tissue-engineered organoids representative of human heart, liver, and kidney and (ii) induced pluripotent stem cells derived from individuals of selected genotypes that may allow an in vitro assessment of pharmacogenomics (25).

**Biomarkers.** The identification of reliable predictors of therapeutic response, especially in cases where the natural history of the disease is prolonged, can be a critical component of a successful therapeutic development program (26). Similarly, biomarkers that allow stratification of patient populations may facilitate a reduction in the size of some clinical trials. The Biomarkers Consortium, managed by the Foundation for NIH with the involvement of more than 20 pharmaceutical companies, has made strides in this arena (27), but the need for better methodology and validation remains compelling.

**Efficacy testing.** The use of animal models for therapeutic development and target validation is time consuming, costly, and may not accurately predict efficacy in humans (28, 29). As a result, many clinical compounds are carried forward only to fail in phase II or III trials; many others are probably abandoned because of the shortcomings of the model. Building on a potentially extensive network of collaborations with academic centers and advocacy groups, NCATS will aim to develop more reliable efficacy models that are based on access to biobanks of human tissues, use of human embryonic stem cell and induced pluripotent stem cell models of

disease, and improved validation of assays. With earlier and more rigorous target validation in human tissues, it may be justifiable to skip the animal model assessment of efficacy altogether.

**Phase zero clinical trials.** Using as few as one or two human volunteers, phase zero trials allow in vivo testing of very low doses of appropriately labeled novel therapeutics to assess appropriate distribution to the desired target. Through access to academic research centers that received NIH Clinical and Translational Science Awards (CTSAs) and the NIH Clinical Center, NCATS can encourage further development of phase zero technologies such as positron emission tomography–ligand–assisted molecular imaging (30) and metabolomics (31) to provide a more direct pathway toward optimizing formulation, dosing, pharmacokinetics, and pharmacodynamics rather than depending so heavily on animal testing.

**Rescuing and repurposing.** Medicines that have been developed and approved for one indication are sometimes useful for the treatment of other diseases, leading to enormous savings in development time and costs. Notable examples of repurposing include thalidomide (Thalomid), originally (and tragically) developed to treat morning sickness and now found to be effective in the treatment of multiple myeloma (32), and losartan (Cozaar), a common blood-pressure medication now used to prevent aortic dissection in people with Marfan syndrome (33). However, broader and more systematic attempts at rescue and/or repurposing have not been attempted.

The recent development by NIH of a complete collection of compounds approved by the U.S. Food and Drug Administration (FDA) and its counterparts in Europe, Japan, and Canada, along with a comprehensive database of their known molecular targets, is a robust starting point for repurposing because that information can now be cross-referenced with data on the molecular causes of many rare and neglected diseases (34). An even bolder plan would be for NCATS to serve as an honest broker for matchmaking between compounds that have been abandoned by industry before approval and new applications for which these compounds might show efficacy (35).

**Clinical trial design.** Opportunities abound for experimenting with adaptive trial designs that can use interim data analyses to inform patient selection and the determination of optimal end points that

will demonstrate efficacy (36). Stratification on the basis of appropriate biomarkers can accelerate clinical candidate testing and eventual approval (37). In addition, through its network of academic clinical research centers, NCATS can support innovative designs for testing combination therapies, as optimal treatment of many diseases is likely to require multiple therapeutic agents (38–40). Such efforts will build upon what has been learned by NIH's early forays into this realm. Examples include (i) the I-SPY 2 clinical trial, a public-private effort involving the National Cancer Institute that is using an adaptive design to select and assess neoadjuvant chemotherapies for locally advanced breast cancer (41), and (ii) plans by the National Institute of Allergy and Infectious Diseases to develop adaptive designs for HIV vaccine trials, which will enable researchers to rapidly screen out poor vaccine candidates while extending evaluation of more promising ones (42).

**Postmarketing research.** The evaluation of therapeutics, diagnostics, and devices does not end at the time of FDA approval. In fact, growing opportunities for postmarketing research, facilitated by broader availability of electronic medical records, provides a critical component of the translational science agenda (43). Detecting signals of drug toxicity in rare individuals, assessing pharmacogenomic relationships, and evaluating the performance of health care delivery systems are just a few examples of the potential that lies ahead. One mission of the NIH is to ensure that the public reaps the full benefit of biomedical research, much of which is funded by taxpayers. To this end, NCATS is uniquely positioned and compelled to contribute to vigorous efforts in comparative effectiveness and implementation research as well as community outreach, which are often neglected late-stage components of the translational spectrum. Using the considerable strength of its clinical network, NCATS can support all of these endeavors as well as provide an enhanced focus on prevention research.

## A CATALYTIC HUB

With the establishment of NCATS in the fall of 2011, NIH aims to reengineer the translation process by bringing together expertise from the public and private sectors in an atmosphere of collaboration and precompetitive transparency. Obviously, the only way that a relatively small entity such as NCATS can hope to carry out its ambitious agenda

**Table 2. NCATS components.** Programs that will be incorporated into or managed by NCATS (excepting CAN, which has not yet been funded) together represent ~\$720 million annually in research support.

Program	Description	Contributions or expertises
CTSA program (48)	Infrastructure grants awarded to academic medical institutions to facilitate translational research	Network of 60 U.S. centers with expertise in preclinical science, clinical trials, comparative effectiveness research, training, and community engagement
Components of the Molecular Libraries Program (58)	Supports centers that provide access to large-scale screening, medicinal chemistry, and informatics for the identification of therapeutic and experimental chemical entities	Assays development, high-throughput screening, medicinal chemistry, and compound databases
Therapeutics for Rare and Neglected Diseases (TRND) (59)	A drug-development pipeline within the NIH used for research collaborations with academic scientists, nonprofit organizations, and companies working on rare and neglected illnesses	Preclinical development of promising compounds
Rapid Access to Interventional Development (RAID) (60)	A competitive granting program that provides resources for the development of new therapeutic agents	Access to resources for preclinical development, production, bulk supply, GMP manufacturing, formulation, development of an assay suitable for pharmacokinetic testing, and animal toxicity
Office of Rare Diseases Research (61)	A multifunctional NIH office that serves as a focal point for rare diseases	Coordination and support of research on rare diseases
NIH-FDA Regulatory Science Initiative (45, 46)	A competitive grant program that funds regulatory science	Support of research on applicability of novel technologies and approaches to regulatory review of drugs, biologics, and devices
Cures Acceleration Network (CAN) (62)	A competitive grant program to fund translational solutions to high-need medical problems; awaits appropriation	Support of translational research with greater flexibility to NIH to fund innovative research in therapeutic development

is through an extensive network of partnerships. Because of its relatively neutral position as a component of the largest public funder of biomedical research, NCATS can serve as an effective convener of many different stakeholders. Also, because of its role within the U.S. Department of Health and Human Services, NCATS can partner with its sister agency, the FDA, in synergistic ways to advance regulatory science (44). For example, NCATS will house the recently established regulatory science initiative co-funded by NIH and FDA (45, 46). Through this assembly of scientific and regulatory expertises and technologies as well as interdisciplinary cross-pollination, NCATS will catalyze the development of new insights that, when implemented, can have broad benefits across diverse translational projects.

To succeed in its objectives as a catalytic hub for translational science, NCATS will assemble a wide range of preclinical and clinical capabilities from within NIH (Table 2) and reshape these components into an integrated scientific enterprise with new leadership and a bold new agenda to advance translation. NCATS will work closely with institutes and centers at NIH that are already deeply engaged in the translation process; a 2010 survey identified more than 500 ongoing projects at NIH in translational science (47). NCATS also will seek and welcome

interactions with academic institutions, biotechnology and pharmaceutical companies, philanthropic organizations, and patient advocacy groups. Furthermore, for long-term success of the enterprise, NCATS will be connected closely with other related international efforts, such as the European Innovative Medicines Initiative.

The breadth of translational expertise inherent in researchers at the ~60 U.S. academic institutions that received NIH CTSA represents one of NCATS's most valuable assets, and CTSA scientists are likely to be a leading source of new translational ideas. In addition to conducting preclinical research, the CTSA institutions can enable first-in-human trials for clinical candidates across the spectrum of rare and common diseases in appropriate patient subpopulations; develop and test innovative trial designs; provide remarkable strength in the conduct of postmarketing clinical research, and offer a natural home for community outreach, training, and education (48).

The only component of NCATS that is not already established is the Cures Acceleration Network (CAN), which Congress will consider for funding in the next fiscal year. If supported, CAN would provide NIH with much-needed flexible funding authorities, including the ability to make grant awards of up to \$15 million per year to academic

and private-sector consortia and to manage projects actively and aggressively by using mechanisms similar to those used by the Defense Advanced Research Projects Agency (DARPA).

#### TIME TO MOVE FORWARD

In a time of fiscal constraints, some have questioned whether this new vision for advancing translational sciences is the best use of NIH resources. Because NCATS will be formed primarily by uniting and realigning already-funded components of the NIH research enterprise (Table 2), the new initiative will do little to shift the balance between funding allocation for basic and applied research in the NIH budget portfolio. In fact, given the well-recognized "virtuous cycle" (49) from basic research to clinical research and back again, a highly effective translational research program will be likely to stimulate fresh ideas in the basic science arena as well. The integration of these multiple components into a new entity will provide NCATS senior leadership—to be recruited in the next year—with the chance to shape a vibrant research organization, ensuring that the whole will become much greater than the sum of its parts.

Scientists and policy-makers also have voiced concerns about whether NIH possesses the necessary scientific expertise to



make useful contributions to translational science or whether such efforts should be left to the private sector. However, NIH investigators have often played roles well beyond target discovery, including successful pursuit of therapeutics through clinical trials and FDA approval (50). In fact, NIH-supported investigators derived fully 20% of the new molecular entities granted priority review by the FDA between 1990 and 2007 (51). NIH has also played a critical role in the development of biologics (52, 53) and vaccines (52, 54), as well as in the invention of devices (52, 55). In all of these examples, partnerships with the private sector have been essential for ultimate success.

The decision to focus the NCATS mission on the actual science of the translational process will distinguish it from other current public or private enterprises and make it abundantly clear that NIH is not attempting to become a drug development company. In fact, NCATS will avoid taking on any projects of immediate commercial interest. The new center will instead seek to invest in the kind of science that creates powerful new tools and technologies that can be adopted widely by researchers in public and private sectors to streamline and derisk the therapeutic development process.

Some have asked whether it is appropriate for taxpayer dollars to facilitate the success of commercial enterprise. However, medical advances that benefit the public generally arise from NIH-funded biomedical research only if actual products are developed and brought to market—and partnerships with the private sector are essential for this translation to succeed. For its part, NCATS plans to concentrate its efforts primarily in the precompetitive space, in which intellectual property claims are expected to be limited. NCATS will need to play an educational role in helping to sharpen the focus of the American public and U.S. policy-makers on the discipline of translational science.

Through partnerships that capitalize on our respective strengths, NIH, academia, philanthropy, patient advocates, and the private sector can take full advantage of the promise of translational science to deliver solutions to the millions of people who await new and better ways to detect, treat, and prevent disease. So, let us embark on this new adventure with eyes wide open—recognizing the tremendous scientific challenges and acknowledging the difficulties posed by fiscal constraints, yet fixing our vision on the pos-

sibility of profound benefits for humankind. Opportunities to advance the discipline of translational science have never been better. We must move forward now. Science and society cannot afford to do otherwise.

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