

National Center for Advancing Translational Sciences

2012–2013 REPORT

NCATS



NIH National Center
for Advancing
Translational Sciences

Table of Contents

Director's Message	i
Introduction	1
Pre-Clinical Research	4
NIH Chemical Genomics Center (NCGC)	4
Bridging Interventional Development Gaps (BrIDGs)	8
Clinical Research	9
Clinical and Translational Science Awards (CTSA) Program	9
Focus on Rare Diseases	13
Office of Rare Diseases Research (ORDR)	13
Therapeutics for Rare and Neglected Diseases (TRND)	16
Special Initiatives	17
Discovering New Therapeutic Uses for Existing Molecules....	17
Tissue Chip for Drug Screening	17
Extracellular RNA (exRNA) Communication.....	19
Illuminating the Druggable Genome (IDG).....	19
Strategic Alliances and Partnerships	20
Fostering Partnerships Across the Spectrum of Research	20
Increasing Collaboration Efficiencies.....	20
Resources for Small Businesses.....	21
Making NCATS Technologies Accessible	21
Policy Issues	22
References	23
For More Information	23

This report reflects activities of the National Center for Advancing Translational Sciences during the Center's first 2 years, from Dec. 23, 2011, through Dec. 31, 2013.

Director's Message



Christopher P. Austin, M.D.

On Sept. 23, 2012, I was privileged to become the first permanent director of the National Center for Advancing Translational Sciences (NCATS). During the past 15 months, I have discussed the needs and opportunities in translational science with constituents across the National Institutes of Health (NIH), Food and Drug Administration (FDA), and other government agencies; academic institutions; patient organizations and nonprofits; and pharmaceutical, biotechnology and venture capital firms. These stakeholders are both optimistic that scientific advances will lead to improved human health and frustrated by the difficulty in realizing that promise. All are aware of the paradox that though each part of the research enterprise is more productive than ever, the whole is currently less than the sum of its parts. NCATS, the newest component of the NIH research ecosystem, aims to help resolve this paradox. In this first report of NCATS activities, we convey the excitement and uniqueness of the Center's mission, operations and accomplishments.

Put simply, "translation" is the process by which scientists convert a basic discovery in a research laboratory or a clinical observation with a patient into an intervention that is developed and shown to be safe, effective and useful to prevent, diagnose or treat a health problem in people.

Though many research organizations, including most NIH Institutes and Centers, do translational work on a specific disease or condition, NCATS focuses on translational innovation *as a scientific and organizational problem*. The science underlying the translational process is poorly understood, leading to the current high failure rate of translational projects. But roadblocks also are caused by organizational, educational, incentive and policy issues that often thwart success. NCATS works on both kinds of translational problems with the goal of creating a robust, science-based translational ecosystem that will deliver more health improvements to more people more rapidly.

NCATS is distinct in many ways. It serves as an "adaptor" to connect basic, clinical and public health research and as a convener for disparate organizations that play roles in the long, complex process from discovery to health improvement. The Center focuses not on what is *different* about diseases but on what is common to them and the translational process. Because successful translation requires teamwork, every NCATS initiative is a collaboration with

partners in the public, private, government or nonprofit sector. And every project is designed to address what I call the “3Ds of NCATS”: **Develop** new approaches, technologies, resources and models; **demonstrate** their usefulness; and proactively **disseminate** the data, analysis and methodologies so that other scientists can implement them. In this way, NCATS serves as a catalyst, both leveraging others’ work and enabling their work with new technologies, insights and approaches.

These principles are well illustrated in the story on p. 7 about the discovery of a compound that prevents the death of cells in the eye from glaucoma, a disease that can lead to blindness. The research team for this promising new therapeutic approach included experts in a wide variety of disciplines from the Johns Hopkins School of Medicine in Baltimore and NCATS’ Assay Development and Screening Technology Laboratory and RNA interference (RNAi) program. Together, the collaborators were able to solve a problem that none of them could address alone.

In another example of the 3Ds at work, through the Therapeutics for Rare and Neglected Diseases program, we catalyzed the development of a treatment for a rare, devastating childhood neurological disorder called Niemann-Pick disease type C1 (see p. 15). This treatment moved rapidly from the laboratory to the clinic thanks to an unprecedented collaboration among researchers in 10 different disciplines, from genetics to neurosurgery, from four NIH Institutes and Centers, three academic institutions, a pharmaceutical company, and several patient groups. The treatment entered its first clinical trial in January 2013, and *The Wall Street Journal* featured this research on the front page of its Nov. 15, 2013, print edition, and produced a more [in-depth e-book](#) about the effort.

Both of these stories illustrate NCATS’ “dual purpose” approach to its projects, which not only produce potential

new treatments for previously untreatable and devastating illnesses, but also lead to new scientific and collaborative paradigms that researchers can use to advance translation in many other diseases.

At the same time, NCATS-supported research teams are creating new ways to make the therapeutic development process faster, cheaper and more accurate. For example, NCATS’ Tissue Chip for Drug Screening program is a collaboration with the Defense Advanced Research Projects Agency and FDA to develop 3-D human tissue chips that accurately model the structure and function of human organs, such as the lung, liver and heart. These devices will enable researchers to predict harmful health effects of new drugs more accurately, thus addressing one of the main reasons that drug studies so often fail.

The past 2 years also have brought important successes in the evolution of the Clinical and Translational Science Awards program, which works to improve the efficiency of the clinical phases of translation. The Institute of Medicine delivered a milestone report on the program in June 2013, and since then, NCATS has moved expeditiously on its recommendations, including creating a high-level working group of the NCATS Advisory Council to help guide implementation.

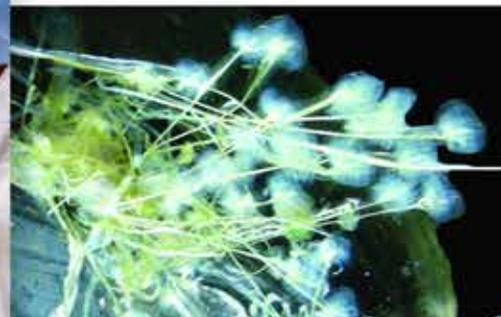
These projects are just a few examples of the exciting and innovative efforts underway at NCATS. Though the Center is still relatively new, early successes demonstrate how its distinctive approaches can help solve some of the most challenging problems in translational science. I look forward to sharing more of NCATS’ achievements with you as the Center continues to evolve in the years to come.

Christopher P. Austin, M.D.

Director

National Center for Advancing Translational Sciences

Introduction



The National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) was established on Dec. 23, 2011, with the mission “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 human diseases and conditions.” Advances from NCATS will enable researchers across the public and private sectors to more efficiently develop treatments for diseases, demonstrate the treatments’ effectiveness in improving health, and accelerate the pace at which new treatments are delivered to patients. By creating new technologies and improving the process by which medicines and other treatments are developed, NCATS aims to make translational science more efficient, less expensive and less risky.

Rapid progress in scientific research and increased availability of innovative technologies have generated unprecedented potential for advancing the translation

of basic discoveries into new or more effective medical treatments. At the same time, the process of developing new diagnostics and therapeutics is widely recognized as a complex, costly and risk-laden endeavor: For every 5,000 to 10,000 compounds that enter the development pipeline, only one makes it into the nation’s medicine chest. Not only is the process of developing new treatments poorly understood and therefore failure-prone, but the system for clinical testing of disease interventions is equally inefficient, as is our ability to deliver the right treatments to the right patients at the right time.¹

NCATS, NIH’s newest Center, was founded to address these critical problems by serving as a unique resource for transforming the translational process to benefit science and patients. It emphasizes innovation and deliverables, relying on the power of data to develop, demonstrate and disseminate improvements in translational science.

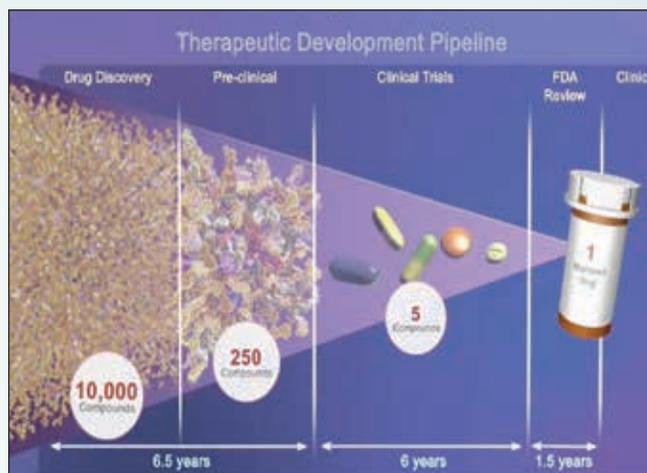
NCATS was created by the Consolidated Appropriations Act, 2012 (P.L. 112-74). In the short time since it was established, the Center has launched several major research initiatives, cultivated effective strategic partnerships, and established a presence at NIH and in the

Left: An investigator at Children’s Hospital Boston conducts stem cell research inside a clean room (Harvard University Photo/Justin Ide).
Right: A protein produced by the common mussel is being studied to develop synthetic materials for a variety of medical applications.

The Therapeutic Development Pipeline

In recent years, researchers have identified the molecular causes of more than 5,000 diseases and conditions,² most of which are rare diseases. Finding the molecular basis of rare diseases is much easier than finding the basis of common diseases because most are single-gene disorders. Common diseases tend to be more complex, involving many pathways and genes.

Turning knowledge into new therapies, however, has proved to be difficult, time-consuming and costly: Only about 400 orphan products have been approved for treating 250 rare diseases, according to data from the [Online Mendelian Inheritance in Man](#) database, [Orphanet](#) and the U.S. Food and Drug Administration (FDA).³ Bottlenecks in the process mean that translation of a promising molecule into an approved therapeutic takes, on average, more than 13 years.⁴



NCATS aims to overcome barriers in therapeutics development, helping researchers more quickly translate discoveries into devices and therapeutics to improve human health.

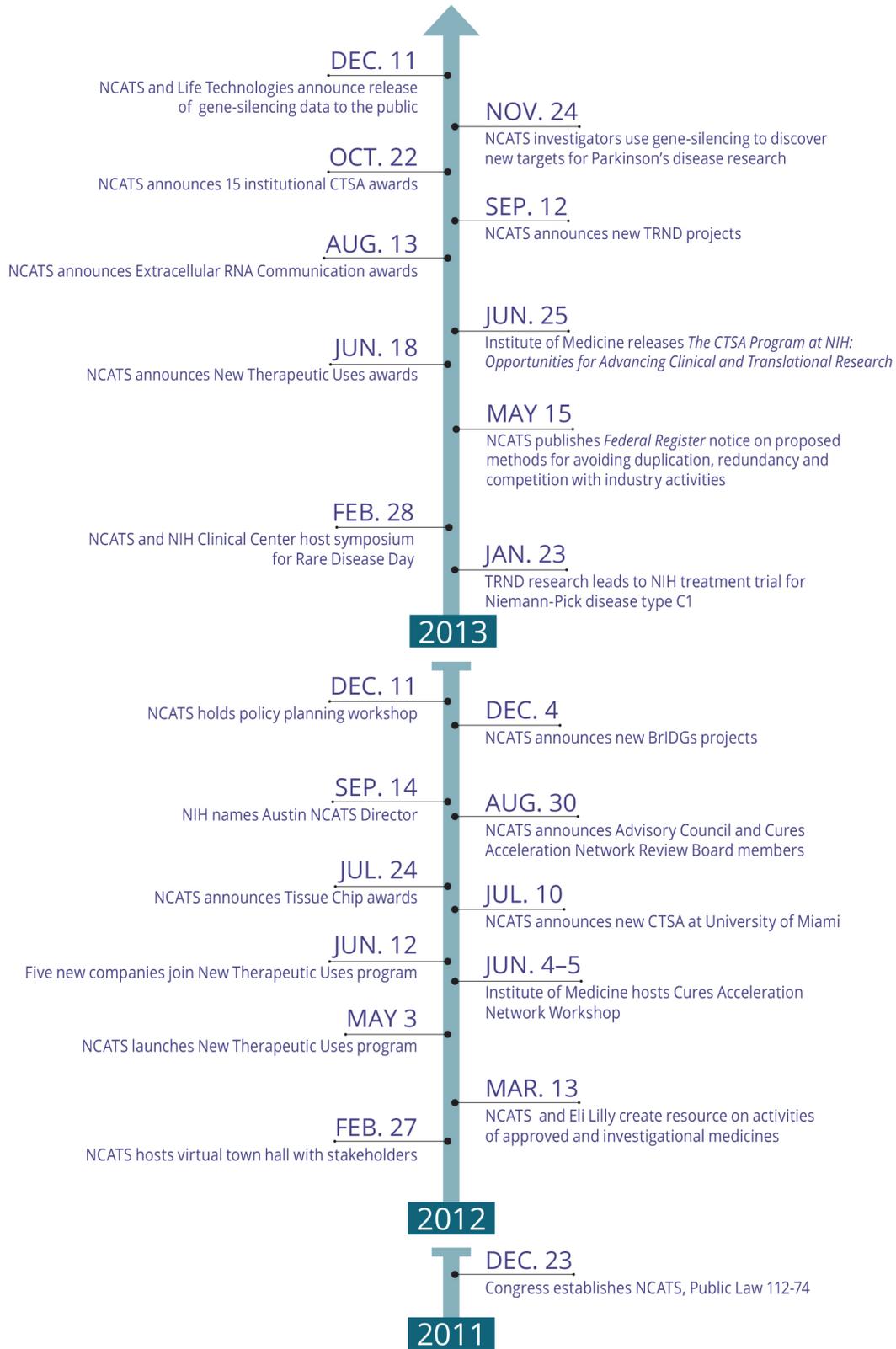
community — all while standing up a brand-new organization. Milestones NCATS achieved in its first 2 years include:

- Supported Clinical and Translational Science Awards (CTSA) at 62 grantee institutions and began implementing Institute of Medicine (IOM) recommendations to improve the efficiency and effectiveness of the CTSA program to benefit human health
- Granted awards to help scientists create new tools for predicting drug toxicity, such as 3-D human tissues on chips that mimic the physiology of the human body
- Inaugurated the Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) pilot program and made nine awards through this initiative that employed a novel crowdsourcing approach to match researchers with a selection of investigational agents from industry
- Launched Bridging Interventional Development Gaps (BriDGs) studies to advance therapeutics that target cancers, spinal cord injury and a rare disease

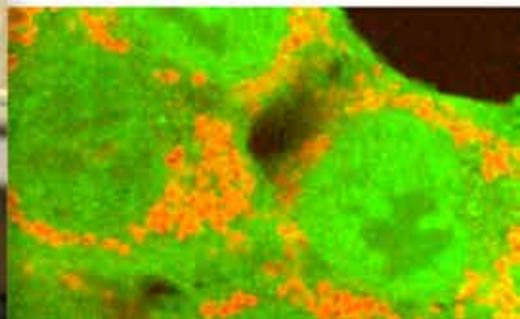
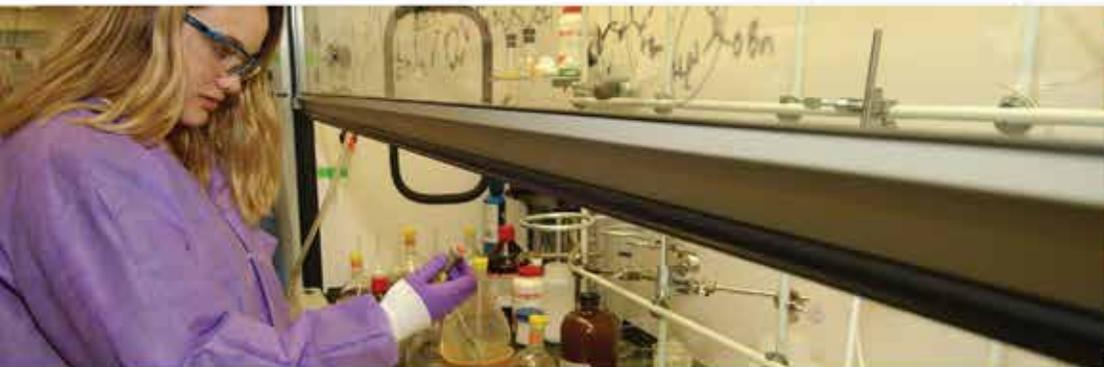
- Initiated collaborative Therapeutics for Rare and Neglected Diseases (TRND) research projects that marked the program's first use of a cell-based therapy and a new partnership with a large pharmaceutical company
- Created a new public database for RNA interference (RNAi) information in collaboration with a major life sciences company
- Embarked on a trans-NIH initiative to study extracellular RNA (exRNA) communication, a recently discovered cell-to-cell signaling process that holds enormous promise for improving our understanding of a wide variety of diseases

NCATS receives important input from a national Advisory Council and the Cures Acceleration Network (CAN) Review Board, both of which include representatives from academia, industry, health advocacy groups and other government agencies. In addition, the Center continually engages other diverse stakeholders and receives expert advice on setting policies and making the best use of budgeted resources.

NCATS Timeline



Pre-Clinical Research



Pre-clinical research, the bridge between basic scientific discoveries and initial development of human therapies, is the most failure-prone stage of translation. (See box for key definitions.) NCATS' pre-clinical programs are designed both to develop new technologies to make this stage more predictive and efficient, and to "de-risk" novel targets and disease projects so that they will be attractive for commercial investment. The Center works with academic, nonprofit and industry investigators, providing molecules and tools to advance their research, and hands off promising potential therapeutics to biopharmaceutical companies who perform the clinical trials required for regulatory approval. NCATS collaborates and shares research resources with hundreds of nonprofit and for-profit institutions each year using a variety of agreements and mechanisms.

NIH Chemical Genomics Center (NCGC)

The goal of NCGC is to create and disseminate tools and technologies that (1) validate new therapeutic targets for untreatable diseases and (2) improve the efficiency and

Left: A technician in an NCATS chemistry laboratory works with a chemical probe. Right: RNAi is used to study a mutated protein (green) and damaged mitochondria (red) that are linked to Parkinson's disease.

The Research Spectrum

- The therapeutics development pipeline begins with **basic research** — the study of the fundamental mechanisms of disease and behavior. Basic research discoveries are a major force for progress in the biomedical and behavioral sciences and can lead to insights essential to understanding basic human biology and behavior in both normal and diseased states. Basic research is fueled by dramatic technological advances and new insights into disease mechanisms.
- **Pre-clinical research** serves as a bridge between basic science and human medicine. In this stage, scientists apply fundamental laboratory discoveries to translational studies, which often are carried out using cell or animal models; samples of human or animal tissues; or computer-assisted modeling of drug, device or diagnostic interactions with living systems.
- **Clinical research** is patient-oriented research that is conducted with human participants. Clinical research includes clinical trials, behavioral and observational studies, and outcomes and health services research as well as the testing and refinement of new technologies.

NCATS Probe Development Leads to Promising New Class of Drug Aimed at Chronic Heart Failure

In 2013, NCATS scientists in its Probe Development Branch developed the first small molecule capable of activating a cell receptor known as RXFP1. Modulation of the activity of this important receptor might provide a new therapeutic approach to cardiovascular disease, including heart failure. Although scientists already knew that the hormone relaxin, which activates RXFP1, could provide benefit for patients with heart failure, relaxin does not last very long in the body, and it must be given intravenously, making it unsuitable for long-term use.

The scientists collaborated with Alexander Agoulnik, Ph.D., of Florida International University, a grantee of the NIH Common Fund's [Molecular Libraries Program](#). Together, they developed a new molecule called ML290 that, like relaxin hormone, activates the RXFP1 receptor but with improved pharmacological

and drug-like properties, making it a better candidate for treating chronic diseases.

This groundbreaking work was recently published in the highly regarded journal [Nature Communications](#) and has piqued the interest of both public and private research communities. In early 2013, NCATS' solicitation for Cooperative Research and Development Agreement (CRADA) proposals for the development of ML290 elicited numerous responses from pharmaceutical companies as well as biotechnology firms. NCATS' Strategic Alliances group is currently working closely with a large U.S. pharmaceutical company to develop a research plan and finalize details of a joint agreement. The aim of this public-private collaboration is to complete the necessary studies with ML290 to produce the first small-molecule drug that activates the RXFP1 receptor to treat chronic heart failure and fibrotic disorders.

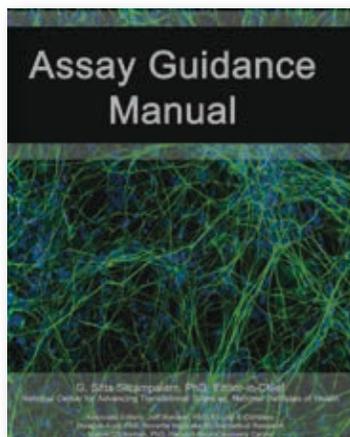
effectiveness of the earliest stages of the translational process. The NCGC was established in 2004 through the NIH Common Fund. Now part of NCATS' Division of Pre-Clinical Innovation, NCGC is a collaborative resource with more than 200 active collaborations with researchers in academia, industry, nonprofit organizations and disease foundations on projects across the full spectrum of biology and disease.

NCGC programs include [Chemical Probe Development](#), [Assay Development and High-Throughput Screening](#), [NCATS Pharmaceutical Collection \(NPC\)](#), [Chemistry Technology](#), [Toxicology in the 21st Century \(Tox21\)](#), and [RNAi](#). Through these programs, NCGC produces a variety of [pre-clinical research tools](#), from chemical probes that elucidate novel biology and approaches to disease, to broadly enabling informatics and software tools, to educational materials, including an Assay Guidance Manual for investigators new to translation. By providing investigators with these tools, programs and collaborative resources, NCGC accelerates the pace of new translational approaches to disease and the quest for new therapeutics.

Chemical Probe Development

Small molecule chemical compounds, which can be used to probe the effects of increasing or decreasing the activity of a target in cells or animals, are some of the most useful tools for target validation (the process of demonstrating that engaging the target provides meaningful therapeutic benefit). Generating these chemical probes requires specialized expertise and facilities, and NCATS has built a world-leading collaborative chemical probe development program to meet these needs. Initially established via the Molecular Libraries Common Fund Program, NCATS' chemical probe development group is working with more than 200 investigators in the NIH extramural, intramural, biopharmaceutical and nonprofit communities to generate probes for studying a diverse cross-section of human biology, focusing specifically on novel targets and untreatable diseases. Probes are used to investigate protein and cell functions and biological processes and, if appropriate, can be further optimized to become potential drug candidates in the development pipeline. NCATS' probe development activities also focus on finding new, more

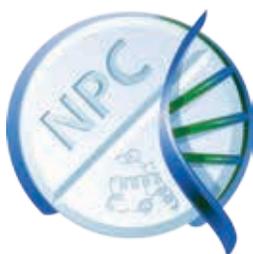
efficient ways to make probes, using probes to understand diseases, and validating targets to treat diseases.



NIH and Eli Lilly publish a guide to help researchers develop therapeutic screening tests.

with colleagues at Eli Lilly and Company and an international editorial board, is a how-to guide for researchers on how to develop and use assays in [high-throughput screening projects](#).

NCATS Pharmaceutical Collection (NPC)

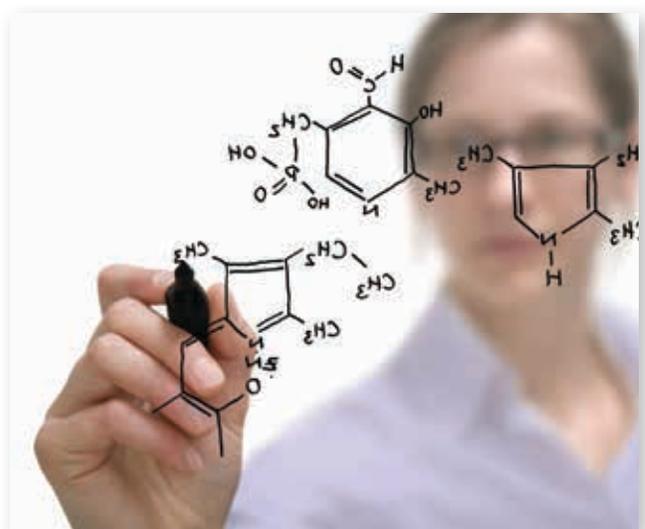


Often, the shortest path to a new drug is to find a new use for an old one. To enable such “repurposing” on a broad scale, NCATS created the NPC, a comprehensive database and compound screening library of drugs approved for clinical use by regulatory authorities in

the United States, Europe, Canada and Japan.⁵ The NPC is available in two forms: as a free electronic resource that lists the drugs and their regulatory status, and as a compound library that is used in high-throughput screening assays at NCGC.

Testing of NPC drugs has already generated many new potential treatments. Cyclodextrin, currently in a first-in-human study for the treatment of the rare genetic disorder Niemann-Pick disease type C1, was discovered in an NPC screen (see box on p. 15), as was auranofin, which is in a

Information is the most catalytic of all translational tools. Therefore, via publications and NIH’s [PubChem database](#), NCATS makes all of the probes and the high-throughput screening and chemistry data generated publicly available for any researcher to use. The [NCGC Assay Guidance Manual](#), developed



Researcher illustrates the chemical structure of a molecule.

clinical trial for the treatment of treatment-resistant chronic lymphocytic leukemia (see box on p. 16).

In addition to being used in many repurposing projects, the NPC provides a valuable avenue for understanding the molecular basis of disease pathology and possible routes for treatment. For example, scientists from NCATS and the Wilmer Eye Institute at Johns Hopkins University combined their diverse expertise to identify a new treatment target for glaucoma — the second-leading cause of blindness in the world. These researchers combined a new way of culturing cells from the eye with screening of the NPC and large-scale RNAi (see p. 7) to identify both a drug (tozasertib) and its target — a gene called *DLK*. Because the side effects of tozasertib are too serious for clinical use in glaucoma, the team is now busy searching for new, safer compounds with the same anti-*DLK* activity.

High-throughput screening uses robotics; data processing and control software; liquid handling devices; and sensitive detectors to enable scientists to quickly conduct millions of chemical, genetic or pharmacological tests. The results of such experiments provide starting points for drug design and for understanding the interaction or role of a particular biochemical process in biology.

Tox21 Leads to New Thinking about Antioxidants

Collaborating with NCATS' Tox21 initiative researchers, an investigator from the National Human Genome Research Institute (NHGRI) developed a test, or assay, that demonstrated that some antioxidants damage DNA and kill cells instead of protecting them. This surprising finding may open up several new lines of research and lead to improved cancer treatments. The researchers identified 22 antioxidants that damage DNA. Three of these — resveratrol, genistein and baicalein —

are currently being used or studied to treat several disorders, including heart disease, type 2 diabetes and chronic hepatitis, and as an anti-aging treatment. Not only did the antioxidants damage DNA; they also could kill dividing cells that cause disease (such as in tumors). The Tox21 team has added the test to its standard screens for biological harm produced by environmental chemicals.



Tox21 robot for high-throughput screening of chemicals for toxic effects

Chemistry Technology

Biomedical research functions most efficiently when the disciplines of chemistry and biology intertwine with a common focus and goals. Novel chemistry technologies can add unique dimensions to drug discovery paradigms by advancing nontraditional clinical tools and cutting-edge reagents for studying cellular and biological processes. NCGC's Chemistry Technology Group works to solve fundamental limitations in probe and drug development via [chemistry technology projects](#) ranging from novel library design to inventive bioanalytical techniques.

Toxicology in the 21st Century (Tox21)

A unique collaboration among NCATS, the National Institute of Environmental Health Sciences, the U.S.



Environmental Protection Agency, and the FDA, [Tox21](#) is aimed at developing better methods of assessing the potential toxicity of drugs and environmental chemicals. The initiative adapted high-throughput screening technologies developed in

NCATS' Chemical Probe Development program. Tox21 is measuring the effects of more than 10,000 different drugs and chemicals on a wide variety of cellular pathways and functions that may lead to adverse health effects. These data are being used to identify chemicals in need of more in-depth study, develop computational programs that will better predict toxicity of new drugs and chemicals, and improve the efficiency and accuracy of new drug and chemical development.

RNA interference (RNAi)

RNAi, an important pathway that is used in many different organisms to regulate gene expression, has emerged as a powerful tool used in thousands of labs worldwide to understand gene function. However, its potential for improving understanding of disease pathways and identifying new drug targets has been limited by the dearth of technologies that can perform RNAi reliably across the entire genome, the lack of collaborative expertise to perform genome-wide RNAi screens, and the absence of comprehensive RNAi data in public databases for researchers to use. To solve these problems, NCATS has established a state-of-the-art trans-NIH [RNAi screening facility](#).

Collaborative projects supported by NCATS identify genes that control critical processes and pathways and find new targets for therapeutic intervention. For example, a team

BrIDGing the Gap in Parkinson's Research

Support from the BrIDGs program has contributed to successful translation of a candidate drug for treating Parkinson's disease, a disorder that affects nerve cells, or neurons, in a part of the brain that controls muscle movement. About 50,000 Americans are diagnosed with Parkinson's disease each year. As symptoms get worse, people with the disease have trouble walking, talking and doing simple tasks. There is no cure.

Over the last decade, researchers have discovered a protein that supports the growth and health of the neurons that produce dopamine, which is lacking or malfunctioning in the brains of patients with Parkinson's disease. This protein, glia-derived growth factor (GDNF), is considered to be a promising candidate for treating the disease. BrIDGs supported the pre-clinical

development of GDNF, delivered by a virus engineered to have no disease-carrying components. This virus delivers GDNF to the regions of the brain where the malfunctioning neurons reside. BrIDGs provided resources for the pre-clinical studies that researchers at the University of California, San Francisco (UCSF), needed to file an IND application with the FDA. The first clinical study, funded by NIH and conducted by a NINDS investigator at the NIH Clinical Center, is currently enrolling patients.

UCSF leveraged the data generated by BrIDGs and the pending clinical trial to enter into a collaborative agreement with uniQure, a leading gene therapy company. uniQure has accepted responsibility for the continued development of GDNF if early clinical trials are successful.

of researchers from NCATS and the National Institute of Neurological Disorders and Stroke (NINDS) identified dozens of genes that may represent new therapeutic targets for Parkinson's disease and improve understanding of related mitochondrial disorders. These findings were published on Nov. 24, 2013, in *Nature*.

NCATS researchers have developed and published several new techniques that enable reliable genome-wide RNAi screens. In December 2013, for the first time, NCATS RNAi researchers and Life Technologies Corporation publicly released information on the chemical makeup of the small interfering RNA molecules used in NCATS' RNAi experiments. The broad availability of this information will be catalytic to scientists studying gene functions in health and disease, accelerating the pace of therapeutic development.

Bridging Interventional Development Gaps (BrIDGs)

The BrIDGs program makes available, on a competitive basis, resources that investigators need to develop new therapeutic agents, including small molecule drugs, biologics and gene therapy. Investigators do not receive grant funds through this program. Instead, successful

applicants receive access to NCATS expertise and contract resources to conduct key pre-clinical studies necessary for regulatory approval of first-in-human trials. BrIDGs provides access to a range of services, including compound synthesis, formulation, and pharmacokinetic and toxicology studies in support of investigator-held Investigational New Drug (IND) applications to the FDA.

In 2012 and 2013, BrIDGs actively supported 23 projects, initiated 11 new projects (7 in 2012 and 4 in 2013), and successfully completed 2 projects. During this period, BrIDGs support enabled one IND filing with the FDA and three phase I human clinical trials. In addition, one therapeutic agent in the program was licensed by a pharmaceutical company in 2012.

Gene silencing through RNAi is a natural process that cells use to turn down, or silence, the activity of specific genes. It works by destroying the molecular messengers that carry information coded in genes to the cell's protein factories. These messengers, called messenger RNAs, carry out a critical function, without which a gene is essentially inactive.

Clinical Research



In the clinical translational process, medications, devices, diagnostic products and treatment regimens developed in the pre-clinical stage are tested for safety and effectiveness in humans, disseminated to broader patient populations, and studied for their benefit in improving public health. The clinical stage, like those before it, is fraught with scientific uncertainties and operational inefficiencies that limit the ability to test new treatments and deliver them to the people who need them. NCATS' clinical programs are directed at developing, demonstrating and disseminating new approaches that will increase the efficiency and effectiveness of research involving human subjects.

Clinical and Translational Science Awards (CTSA) Program

The CTSA program works to improve the efficiency and effectiveness of clinical research by developing and providing to the research community improved tools, operational models, and training of investigators. Under NCATS leadership, the program supports a [national consortium of 62 medical research institutions](#) that work together to transform how translational research is conducted.

Left: Staff at the University of Kentucky obtain a muscle biopsy for histochemistry and measurement of gene expression (Kristi Lopez Photo). Right: A researcher at Oregon Health & Science University obtains information from a museum visitor who agreed to participate in a nutrition study.

Examples of program success stories include developing a single institutional review board (IRB) model for multisite studies; enabling more efficient data collection and the use of tools for sharing and mining data; developing innovative methods for enhancing patient recruitment; facilitating engagement of communities; and forming efficient and effective strategic alliances.

NIH launched the CTSA program in 2006 to help strengthen the full spectrum of biomedical research. Under NCATS, the program continues to evolve and transform research across the nation through the initiatives and support described below.

CTSAs and Clinical Research

The CTSA program provides resources that support clinical research, including assistance with study design, biostatistics, IRB approval and expedited contracting. In addition, the CTSAs develop and deploy to the research community a broad range of [clinical research tools](#) that facilitate human subjects research. Many of these resources enable and accelerate research collaborations, particularly for multisite studies. Examples include:

- **ResearchMatch** is a free, secure national registry aimed at improving research participant recruitment. It connects people who are looking for research studies with researchers who are seeking people to participate in their studies.

University of Pittsburgh Researchers Work to Restore Function in Paralysis Patients

Five years ago, a CTSA-supported multidisciplinary team of researchers — neurologists, neurosurgeons, neurobiologists, bioengineers and physicians at the University of Pittsburgh (Pitt) and its medical center — set out to tackle an important translational research goal: restoring function for those who cannot move. As a result, breakthrough brain-computer-interface research published in *The Lancet* in February 2013 provides hope to nearly 6 million paralyzed individuals and another 1.7 million amputees nationwide. As explained in the *Lancet* article, the Pitt team implanted electrodes into a paralyzed patient's brain so that the team could pick up her brain signals while she imagined moving her hand and arm. A computer interface translated the signals, allowing her to use her mind to control a prosthetic arm and hand in a full range of motion, even grasping objects. The study volunteer was able to move the robotic arm with only her thoughts less than 1 week after surgery. After 13 weeks of controlling the arm with her thoughts, she was able to use the process to take a bite of chocolate. This success was featured on *60 Minutes*.



The collaboration relied on help from four federal agencies — NIH, the Department of Defense, the Department of Veterans Affairs and the FDA — along with support from a private foundation, two academic research centers and a private company. Pitt's Clinical and Translational Science Institute (CTSI), which is supported through the CTSA program, paved the road to this accomplishment by providing initial research funding and helping to assemble the diverse team required. Help from regulatory experts at the Pitt CTSI and the Defense Advanced Research Projects Agency (DARPA) helped fast-track FDA approval of a clinical trial.

- **REDCap** is an easy-to-use, freely available tool for clinical study management and data capture that allows investigators to build and manage online surveys and databases.
- **CTSA-IP** is a Web-based intellectual property search engine that aggregates and promotes technologies from CTSA institutions and NIH.
- **CTSpedia**, a national effort to collect wisdom, tools, educational materials and other resources useful for clinical and translational researchers, features information on biostatistics, ethics, research design, data management, grants and recruitment.

Specific clinical studies are supported through pilot projects and within training programs, restricted by **NCATS' authorizing statute** to trials only through the end of the pilot study phase.

CTSA Consortium

Through the CTSA Consortium, which at the end of 2013 comprised **62 CTSA sites** located in 31 states and the District of Columbia, investigators work together on data sharing, multisite trial regulatory hurdles, patient recruitment, communication and other functional areas of research to enhance the efficiency and quality of clinical and translational research. In addition, many CTSA institutions have formed regional connections to address common scientific interests and capitalize on complementary strengths. For example, the University of California Research eXchange (UC ReX) Data Explorer is a secure, online system that enables cross-institution queries of clinical aggregate data from 12 million de-identified patient records derived from patient care activities at five University of California medical campuses: Davis, Irvine, Los Angeles, San Diego and San Francisco. Search criteria can include demographics, diagnosis and procedure codes, the

Collaborative CTSA Effort Enables First Newborn Screening Study of Fragile X Syndrome

In the first such study in the United States, researchers at the University of California, Davis (UC Davis); the University of North Carolina Hospital in Chapel Hill; and the Rush University Medical Center in Chicago collaborated to explore the use of newborn screening to diagnose fragile X syndrome and to determine how often any form of its underlying genetic mutation occurs in infants.

This cooperative initiative was made possible by NCATS resources, provided through the UC Davis Clinical and Translational Science Center with funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and additional funding from the Centers for Disease Control and Prevention and the Association for Prevention Teaching and Research.

Fragile X is the most common inherited cause of cognitive disabilities. It stems from a mutation in the *FMR1* gene, located on the X chromosome. Affected male children typically have worse disabilities and symptoms than females.

Testing 14,207 male and female infants revealed that many more than previously known carried the



“premutation,” a milder form of the genetic change that causes fragile X syndrome. A much larger sample than was possible in this pilot study will be needed to determine how often the full fragile X mutation occurs, but the investigators found one male infant with it in this study.

The UC Davis Clinical and Translational Science Center allows researchers to follow these infants and their families and document the clinical outcomes associated with the premutation. The researchers also plan a much larger study to estimate how often the full mutation occurs.

top 150+ lab orders, and a proof of concept for four medications. The output of each query from the UC ReX Data Explorer is a numeric count of patients by site that match the criteria identified in the query. The numeric count helps investigators assess the feasibility of their study ideas by identifying whether there are sufficient numbers of prospective subjects from the queried sites. The sources of information for the Data Explorer are de-identified datasets that are extracted from each institution’s clinical data warehouse, transformed into a common data representation and stored in a separate, dedicated data repository at each institution. The system uses recognized best practices to de-identify the patient information.

CTSA Support for NIH-Funded Research

NIH-funded investigators regularly use CTSA facilities, core resources and equipment, staff expertise, and

administrative services for their research. The CTSA program provides centralized support to many NIH-funded research projects to help increase efficiencies and expand the flexibility and reach of NIH’s Institutes and Centers (ICs). Recognizing the value that CTSA institutions bring to their research priorities, many NIH ICs now encourage applicants to collaborate with the CTSA institutions.

CTSAs and Pediatric Research

Eight CTSAs are headed by principal investigators who are also pediatricians; 57 support one or more pediatric investigators’ participation in the CTSA Consortium Child Health Oversight Committee, a consortium-wide leadership committee charged with sharing best practices and facilitating collaborative activities; and 51 included children’s hospitals conducting pediatric research as partners in their CTSA applications.

CTSA Training and Career Development

To prepare future generations of clinician-scientists and to build the clinical and translational research workforce, the CTSA program supports hundreds of trainees and early-stage clinical investigators, develops courses on a wide variety of translational topics, and provides open access to [training resources and educational materials](#) created by CTSA-supported institutions and NIH. Trainees learn to work and communicate in interdisciplinary teams guided by experienced mentors. Effective translation requires scientists from many disciplines to work together, and this team science approach prepares trainees to address today's complex translational research challenges.

NCATS' ongoing efforts in [research training](#) and career development are helping to ensure that our nation will have a cadre of trained research team members who have the skills and knowledge to develop and deploy new interventions that improve human health.

Networking and Partnership Development

CTSA grantees work with industry, manufacturers, patient groups and nonprofit organizations to ensure that potentially lifesaving new drugs and devices reach the public faster. Here are two examples:

- The Scripps Translational Science Institute received a grant from the Qualcomm Foundation to create a

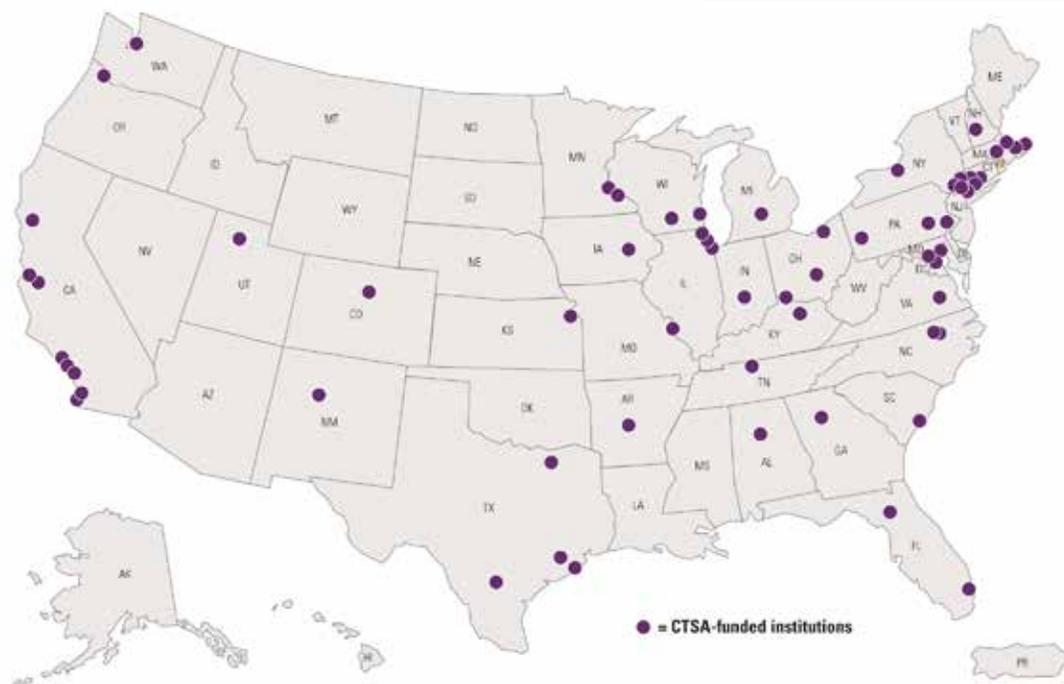
[digital medicine program](#). The program aims to advance clinical trials of wireless biosensor systems, rapid pharmacogenomic diagnostic tests, various software applications and embedded sensors for tracking and predicting disease.

- A [diabetes program](#) for the South Side of Chicago is a collaboration of the University of Chicago CTSA, the Merck Foundation, the American Diabetes Association, the American Heart Association, and other partners.

Institute of Medicine (IOM) Evaluation

In NCATS' fiscal year 2012 appropriation, Congress requested a study by the IOM "that would evaluate the CTSA program and recommend whether changes to the current mission are needed." In response, the IOM convened an independent committee of experts in August 2012. The committee released its report, *The CTSA Program at NIH: Opportunities for Advancing Clinical and Translational Research*, which articulated seven [broad recommendations](#), in June 2013. NCATS is committed to implementing the IOM's recommendations and has formed a working group of the NCATS Advisory Council with key stakeholders to provide advice. The working group will focus on measurable goals and objectives for the program.

CTSA Sites



Focus on Rare Diseases



NCATS conducts and supports research aimed at accelerating new treatments for rare diseases. The amendments to the Orphan Drug Act of 1983, P.L. 97-414, and the Rare Diseases Act of 2002, P.L. 107, define a rare disease as one affecting fewer than 200,000 persons in the United States. About 6,000 to 7,000 rare conditions⁶ affect an estimated 25 million Americans and their families.⁷ However, according to the FDA's Office of Orphan Products Development, only about 5 percent of these diseases have an FDA-approved treatment.

Although all diseases can inflict tremendous suffering on patients and their families, rare diseases can pose even greater challenges than more common disorders, including difficulty obtaining an accurate diagnosis and support. These diseases often involve severe, progressive illness and disability, and many lead to premature death. In addition, rare diseases frequently affect more than one organ system, require collaborative research structures, and have a low potential return on investment for industry. For all of these reasons, rare diseases research would benefit greatly from improvements in the translational process.

New discoveries about the molecular basis of rare diseases offer unprecedented opportunities to improve the diagnosis

and treatment of these diseases. New scientific insights, genetic bases, modeling, and the development of experimental therapeutics for rare diseases also promise to shed light on more common diseases. NCATS is capitalizing on these opportunities in its rare diseases research programs.

Because translational science is a team effort, NCATS develops novel collaborative models for rapidly advancing translational research on rare diseases, creating partnerships among government, industry, academia and patient advocacy groups. These partners work together to advance the process of discovering specific new therapies, while they develop scientific and technological innovations to improve success rates at each stage of the drug development pipeline.

Office of Rare Diseases Research (ORDR)

NCATS' ORDR coordinates rare diseases research across NIH and supports a number of collaborative programs addressing systematic barriers to the understanding, diagnosis and treatment of rare diseases.

Genetic and Rare Diseases Information Center (GARD)

Through GARD, NCATS assists in the dissemination of research findings — a key part of the translational process — by helping patients, their families, health care providers, researchers and the public find information on thousands of rare diseases via the GARD website, email, telephone

Left: A patient with the rare disease Niemann-Pick type C1 visits with his doctor at the NIH Clinical Center. Right: DNA illustration.

Rare Diseases: A Special Niche for NCATS

The Human Genome Project catalyzed the discovery of the molecular basis of thousands of rare diseases, providing an unprecedented opportunity to understand and develop therapeutics for the millions of Americans affected by untreatable rare diseases. Given the large number of individual rare diseases, the current “one disease at a time” paradigm simply is not working to deliver treatments that are so desperately needed. Further, because rare diseases tend to affect multiple organs, they do not fit neatly into the missions of disease-specific research institutions. Private companies often do not pursue new therapies for rare diseases due to the low anticipated return on investment.

NCATS’ unique role in the research ecosystem enables it to address these gaps and make a meaningful differ-

ence in the study of rare diseases and the development of interventions to improve the lives of people affected by rare conditions. By applying a holistic, “systems” approach to rare diseases, NCATS is developing approaches to characterizing, diagnosing and treating rare diseases based on a modern understanding of relationships among disease mechanisms, genomics and drug action. NCATS can both address enormous unmet medical needs and add to our understanding of commonalities among diseases to improve the translational process.

In addition to groundbreaking science, NCATS seeks to develop new collaborative models of rare disease research by facilitating interactions among government, industry, academia and patient constituency groups.

and traditional mail. Each month, approximately 180,000 unique visitors view GARD Web pages, and GARD information specialists respond to an average of 475 inquiries per month. In the past 11 years, GARD has responded to questions about 5,400 different rare or genetic diseases. In addition, GARD staff:

- Dynamically maintain a list of approximately 6,500 terms related to rare and genetic diseases
- Provide access to NIH and other information resources, FDA-approved medical products for rare diseases, ongoing rare disease research, and patient registries on the GARD disease-specific pages
- Develop patient-friendly guides, such as “How to Find a Disease Specialist” and “Tips for the Undiagnosed,” to address frequently asked questions

Rare Diseases Clinical Research Network (RDCRN)

The RDCRN facilitates rare diseases understanding and treatment through support for (1) collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies and clinical trials; (2) training of clinical investigators in rare diseases research; (3) pilot/demonstration clinical research projects; and (4) access to information related to rare diseases for basic and clinical researchers, academic and practicing physicians, health care professionals, patients and the public.

The RDCRN currently supports **natural history studies** (see box below), clinical trials and other clinical studies on more than 100 rare diseases at more than 200 clinical centers across the United States and in other countries. Twenty-five of the participating clinical centers are located outside of the United States.

Between 2009 and the end of September 2013, the RDCRN enrolled 18,000 participants in 84 multisite clinical research studies. One of the RDCRN’s successes is an early-stage clinical trial of a heart drug that was repurposed for treating nondystrophic myotonia, a rare muscle disorder (see box on p. 15). In addition, researchers have

Natural history studies follow a group of people with a specific medical condition or disease over time. They collect health information to understand how a medical condition or disease develops and progresses. These studies also can help establish registries of patient data and biobanks (samples of tissue or DNA) to be used in future research. In addition, information collected from natural history studies about disease signs, symptoms and outcomes can inform the design of clinical trials of possible therapies.



TRND Research Leads to NIH Trial to Test Drug for Rare Neurological Disease

Niemann-Pick disease type C1 is a rare, inherited and invariably fatal disease characterized by progressive impairment of brain functions in early childhood. Life expectancy often does not exceed an individual's teenage years. No FDA-approved drugs are available to treat the disease. Today, a new treatment may be on the horizon, thanks to the collaborative efforts of an award-winning, multidisciplinary team of experts from NCATS; three other NIH Institutes (NICHD, NINDS and NHGRI); Janssen Research & Development, LLC; Washington University School of Medicine in St. Louis; Albert Einstein College of Medicine in New York City; University of Pennsylvania; and a number of Niemann-Pick disease type C1 patient groups.

The TRND-led team has repurposed the chemical sugar cyclodextrin, normally used as an inactive ingredient in

certain formulated drug products, as a potential therapeutic for Niemann-Pick disease type C1. Cyclodextrin was selected because studies in Niemann-Pick disease type C1 patient cells and animals showed that it can reduce the disease-related cholesterol storage in cells and improve nerve and liver function. The TRND team completed a highly innovative pre-clinical development program, enabled the development of a blood biomarker test to track the drug's effects in participants in human studies, and, in close consultation with the FDA, launched a first-in-human trial of cyclodextrin in Niemann-Pick disease type C1 patients in 2012. This remarkable story was reported in a multi-part front-page feature in *The Wall Street Journal* print and online editions in November 2013.

finished following patients in 10 studies and are in the final analysis phase. Since the inception of the RDCRN, investigators have made progress in many aspects of clinical and translational research on rare diseases. The RDCRN website is a resource for health care providers, researchers, patients and caregivers, and the general public. It also includes a novel Web-based contact registry for patients who are considering participating in RDCRN clinical studies.

In the fall of 2013, NCATS, in collaboration with 10 other NIH components, reissued a funding opportunity announcement (FOA) for consortia for the RDCRN. In addition, NCATS and NINDS reissued a FOA for a data management and coordinating center for the RDCRN. The purpose of the center is to develop innovative ways to provide infrastructure and support to the individual RDCRN consortia sites.

Repurposing an Approved Drug for a Rare Disorder

Patients with a rare genetic muscle disorder called nondystrophic myotonia have new help: a drug called mexiletine, which normally is prescribed to treat heart disorders. With assistance from NCATS' RDCRN, researchers at seven institutions in four countries were able to recruit enough patients with this rare disease for a clinical trial to test this drug. One young patient was frustrated because the disease affected his ability to participate in physical activity. When playing baseball, he could not even make it to first base unless he took extra measures to get warmed up. Mexiletine has made it possible for him to play the game without any special preparation.

Aes-103 for Sickle Cell Disease (SCD)

SCD is a genetic blood disorder that affects millions worldwide and approximately 100,000 in the United States, including one in every 500 African-American births. A defect in hemoglobin causes red blood cells to become rigid and sickle-shaped, blocking small blood vessels and causing decreased blood flow, inflammation, pain and strokes in children. To date, the only drug approved by the FDA to treat SCD is hydroxyurea, an anticancer drug that is indicated for use only in adults, has modest efficacy and has undesirable side effects that severely limit its use. The novel compound Aes-103 is the first disease-modifying drug candidate for SCD. An NCATS-supported project aims to develop Aes-103 as an effective treatment for both adults and children with SCD.

Despite the public health need SCD represents and early promising data on Aes-103, the biopharmaceutical company AesRx was unable to garner financial or

scientific partners to develop the molecule because safety and efficacy in human patients had not been demonstrated. TRND signed a collaborative agreement with AesRx to study the molecule and established a project team that included NCATS and AesRx staff and a leading SCD clinical researcher at the National Heart, Lung, and Blood Institute (NHLBI). In less than 1 year, the team completed the pre-clinical toxicology, chemistry, manufacturing, controls and regulatory studies necessary to support IND application, and filed an application with the FDA. Upon clearance from the FDA, Aes-103 moved into [phase I clinical trials](#) in healthy volunteers and SCD patients in 2011 and into a phase II trial in SCD patients in 2013. After TRND's involvement with the project, AesRx was able to obtain a Massachusetts Life Science Accelerator Grant to support additional studies necessary to complete clinical development of Aes-103.

Therapeutics for Rare and Neglected Diseases (TRND)

The TRND program's goal is to speed the development of treatments for rare and neglected diseases. The program operates via collaborative research partnerships with public and private entities, which leverage the unique strengths and capabilities of each party to develop new technologies and collaborative models that improve the efficiency of therapeutic development.

At the end of 2013, TRND had a portfolio of 20 projects targeting drug development for some of the most devastating diseases afflicting either small populations in the United States or large populations in the developing world. Four projects, targeting chronic lymphocytic leukemia (CLL), Niemann-Pick disease type C1, sickle cell disease (SCD) and hereditary inclusion body myopathy (see box on p. 15 and box above), already have yielded successful IND applications to the FDA and are currently in first-in-human clinical trials. Two additional projects are on schedule for IND submission in 2014.

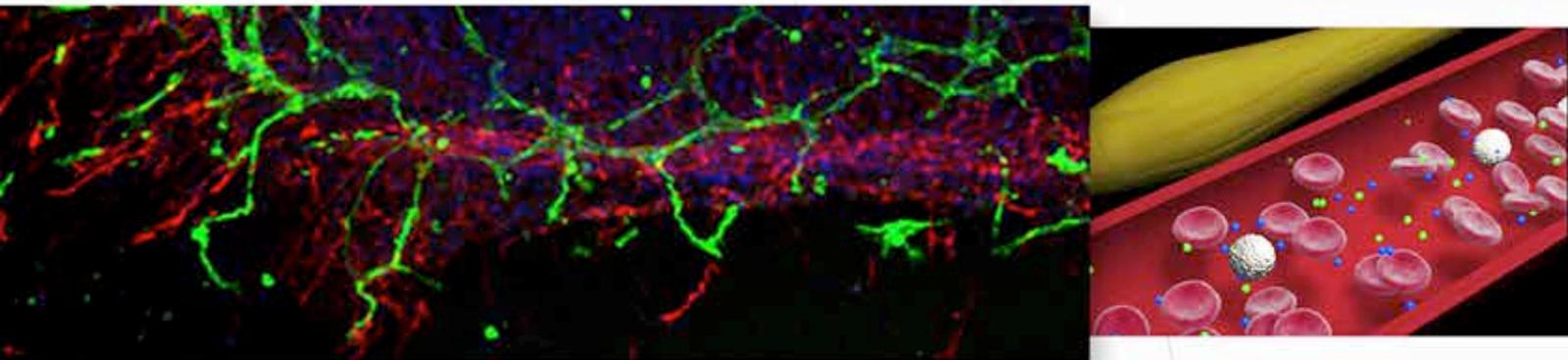
In addition to meeting project-specific goals, TRND researchers develop novel technologies and collaborations that improve the efficiency of the translation process. For example, two projects are building novel platform

technologies that can be used to develop therapeutics to treat a variety of human disorders. In addition, TRND is a founding partner in The Learning Collaborative (TLC; see box below), which develops novel collaborative structures to speed the development of new drugs for blood cancers. The clinical trials TRND supports can be found at clinicaltrials.gov.

The Learning Collaborative (TLC)

Through the TLC public-private partnership, NCATS contributes expertise to accelerate novel therapies into action. TLC is an alliance of the University of Kansas Institute for Advancing Medical Innovation, The Leukemia & Lymphoma Society, and NCATS' TRND program. The alliance aims to identify novel and repurposed drugs for the treatment of rare blood cancers and to find industry partners to develop them. One example of a TLC success story involves the progression of the rheumatoid arthritis drug auranofin into clinical testing for the treatment of chronic lymphocytic leukemia (CLL). CLL is diagnosed in 15,000 U.S. adults each year. Patients eventually become resistant to the chemotherapy used to treat CLL. The TLC team is conducting [a clinical trial](#) to examine auranofin's safety and effectiveness against treatment-resistant CLL and will initiate a second trial in another blood cancer, mantle cell lymphoma, in 2014.

Special Initiatives



Discovering New Therapeutic Uses for Existing Molecules

Drugs may be effective in treating several distinct disorders. “[Repurposing](#)” refers to studying drugs that are already approved to treat a disease or condition to see if they are safe and effective for treating other diseases. Also, for every drug that is approved by the FDA, many others are abandoned after initial clinical testing but before FDA approval because of lack of effectiveness or for business reasons. Drug “rescue” refers to research involving such partially developed molecules. NCATS focuses on drug rescue and repurposing because of their potential for rapid therapeutic advances and lower costs.

In May 2012, NCATS launched the [Discovering New Therapeutic Uses for Existing Molecules](#) (New Therapeutic Uses) collaborative pilot program to catalyze new mechanisms for drug rescue, pairing pharmaceutical companies that had partially developed drugs with academic investigators who had new ideas for disease indications in which the drugs could be tested. The

program included a “crowdsourcing” mechanism (see box on p. 18) to obtain the best ideas from the research community. It also featured a streamlined template for collaboration agreements to speed negotiation time. Eight pharmaceutical companies (AbbVie [formerly Abbott]; AstraZeneca; Bristol-Myers Squibb; Eli Lilly and Company; GlaxoSmithKline; Janssen Research & Development, LLC; Pfizer; and Sanofi) made 58 molecules available that had undergone significant research and development, including safety testing in humans. Almost 160 different ideas were submitted for consideration, and, in June 2013, [NIH announced nine projects](#) that matched academic research groups with companies to study compounds in eight disease areas, including two rare diseases. Through New Therapeutic Uses, NCATS is re-engineering how the public and private sectors collaborate and is creating new and rapid ways to test novel treatments for underserved diseases.

Tissue Chip for Drug Screening

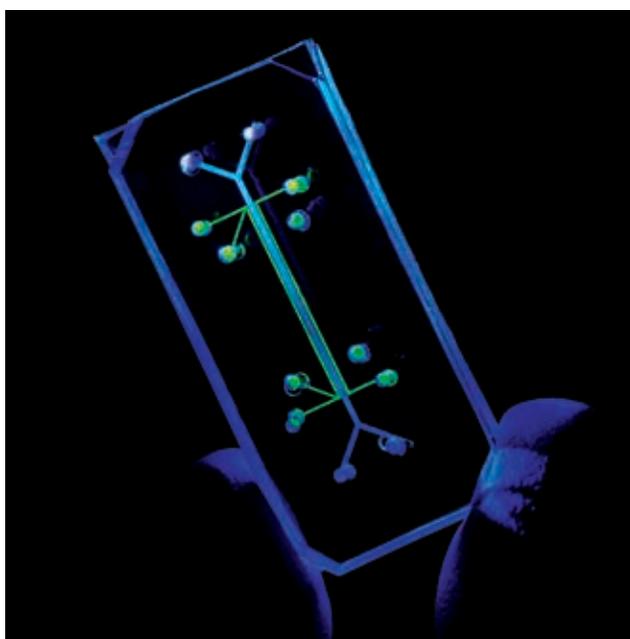
More than 30 percent of promising medications have failed in human clinical trials because they are determined to be toxic despite promising and costly pre-clinical studies in animal models. In an effort to overcome this major translational roadblock, NCATS, DARPA and the FDA are leading the [Tissue Chip for Drug Screening](#) program, an initiative to revolutionize the process for predicting drug

Left: Neural tissue with blood vessels derived from human induced pluripotent stem cells cultured on a laboratory-engineered extracellular matrix (University of Wisconsin–Madison Photo). Right: Artistic illustration of extracellular RNAs (blue and green) traveling through the bloodstream.

The Power of Crowdsourcing

One of the unique strategies being tested in the [New Therapeutic Uses](#) program is crowdsourcing — the practice of soliciting ideas from a large group of people, often an online community. The pharmaceutical companies that partnered with NCATS provided a set of compounds for study, enabling biomedical researchers across the country to propose ideas for new therapeutic uses of those agents. The

program's FOA included information about each compound, giving scientists an unprecedented opportunity to identify potential new uses for the agents. Interested researchers submitted pre-applications; each one identified an agent and proposed a new use. For all but one agent, when five or more applications were submitted for an agent, the applications proposed treatment of at least three distinct diseases.



Chip developed by Wyss Institute at Harvard. *Wyss Institute*

safety. The program aims to develop 3-D human “tissue chips” that accurately model the structure and function of human organs, such as the lung, liver and heart. The intent is for researchers to use these models to predict whether a candidate drug, vaccine or biologic agent is safe in humans faster and more cost-effectively than by using current methods.

Seeking the best ideas in engineering, biology and toxicology, NIH issued two FOAs in the fall of 2011. On July 24, 2012, NIH [issued 17 awards](#) funded by the NCATS Cures Acceleration Network (CAN) and the NIH

Common Fund. In September 2012, NIH issued two more awards that were funded by other NIH ICs. [Twelve of these](#) support the development of 3-D cellular microsystems that represent human organ systems. These bioengineered devices aim to be functionally relevant and accurately reflect the complexity of the tissue of origin, including genomic diversity, disease complexity and pharmacological response. [Seven awards](#) fund research to explore the potential of stem and progenitor cells to differentiate into multiple cell types that represent the cellular architecture within organ systems. These technologies could serve as sources of cells to populate tissue chips. In addition to organ systems, some of the awarded researchers will develop tissue microsystems that target specific health conditions, such as cardiovascular disease, cancer, degenerative arthritis and gastrointestinal disease.

Eliminating toxic and ineffective drugs earlier in the development process would save time and money and, most important, would prevent patients from being exposed to these agents in clinical studies. Use of human tissue chips also offers great promise for more relevant disease models, enabling researchers to better understand and, ultimately, diagnose and treat diseases.

DARPA is conducting a separate but parallel program in close coordination with NIH; it has entered into a Memorandum of Understanding with NIH to develop engineering platforms capable of integrating 10 or more organ systems. For its part, the FDA is exploring how this new technology might be used to assess drug safety prior to approval for first-in-human studies.

Cures Acceleration Network (CAN)

Originally authorized in the Patient Protection and Affordable Care Act of 2010 (P.L. 111-148), CAN was moved to the newly authorized NCATS by the Consolidated Appropriations Act of 2012 (P.L. 112-74). On June 4–5, 2012, the IOM held a workshop in Washington, D.C., to explore options and opportunities in NCATS' implementation of CAN. Authorized to reduce significant barriers to successful translation and accelerate the development of high-need cures, CAN provides NCATS with flexibility in how it funds projects. This authority is guided by the CAN Review Board, which advises and provides recommendations to the NCATS Director on programs to overcome significant barriers to successful translation of basic science into clinical application.

Extracellular RNA (exRNA) Communication

ExRNA communication is a recently discovered cell-to-cell signaling process that holds enormous promise for improving our understanding, diagnosis and treatment of a wide variety of diseases. Most RNA works inside of cells to help translate genes into the proteins that are necessary for organisms to function. Other types of RNA control cells' protein production. Until recently, scientists believed RNA worked mostly inside of the cell that produced it. Now, findings show cells can release RNA in the form of exRNA to travel through body fluids and affect other cells. ExRNA can act as a signaling molecule, communicating with other cells and carrying information from cell to cell throughout the body.

Scientists are beginning to understand the potential exRNA research may hold for improving diagnosis and treatment of diseases and conditions such as cancer, bone marrow disorders, heart disease, Alzheimer's disease and multiple sclerosis.

In July 2012, to advance this new field of research, NIH launched a new program called [Extracellular RNA Communication](#). The collaborative, cross-cutting program is supported by the [NIH Common Fund](#) and led by a trans-NIH

team that includes NCATS, the National Cancer Institute, the National Institute on Drug Abuse, NHLBI and NINDS. The program spans the entire spectrum of translational research from discovery to treatment, including study of:

- How cells make and release exRNA
- How exRNA travels through the body
- How exRNA targets specific cells and affects other cells
- How the amount and types of exRNA can change in disease
- How exRNA could be used to develop new therapies

In August 2013, NIH [announced \\$17 million in awards](#) for 24 milestone-driven cooperative agreement research projects in these areas. NCATS is administering [18 of the projects](#), focused on developing biomarkers from exRNA found in body fluids and designing new ways to use exRNA in treatments. The new ExRNA Consortium formed by these projects is also collaborating, sharing information and spreading knowledge of exRNA to the larger scientific community and the public.

Illuminating the Druggable Genome (IDG)

NCATS is co-leading a new NIH Common Fund program called [Illuminating the Druggable Genome \(IDG\)](#). The program focuses on increasing the understanding of the properties and functions of poorly characterized and/or unannotated proteins within four of the most commonly drug-targeted protein families. The protein families' relationships to diseases suggest that many of the as-yet-unannotated members of the druggable genome have the potential to serve as drug targets for diseases and conditions important to human health. IDG has two components. The first, the Knowledge Management Center, will feature an integrated informatics system that will enable researchers to access and query — from a single portal — data of diverse types that may illuminate the biological functions or disease relevance of members of the druggable genome. The second component is the Technology Development Initiative, through which researchers will work to establish scalable, medium- to high-throughput technology platforms to characterize large groups of proteins at the molecular and cellular levels. Applications were received in December 2013 for funding in July 2014.

Strategic Alliances and Partnerships



Virtually every stage of the translational process, from target validation through determining the public health benefits of interventions, is fraught with failure and inefficiency. Much of this is due to poor understanding of the science of translation. A primary mission of NCATS is to define these scientific principles as a precursor for improving translational practice and effectiveness. Because translational research is inherently collaborative and multidisciplinary, failures in the translational process can just as frequently be caused by organizational roadblocks, including misaligned incentives, inefficient collaboration structures and intellectual property issues. As a result, the NCATS mission also includes creating solutions to these organizational roadblocks to translation.

Fostering Partnerships Across the Spectrum of Research

Every NCATS project features collaborations with outside investigators or organizations; partnerships are integral to NCATS' work. Establishing innovative strategic alliances and partnerships with NIH-funded

investigators, other federal agencies, industry, patient groups and advocacy organizations is vital to the success of all NCATS programs. Among other benefits, this approach enables leveraging of public and private resources, the expansion of knowledge, and increased participation in clinical research. Examples of partnerships, consortia and networks facilitated with NCATS support are provided throughout this report.

Increasing Collaboration Efficiencies

NCATS is developing new ways for different components of the research ecosystem to work together more efficiently. For example, to accelerate collaborations across its programs, the Center developed [standard forms and model agreements](#) for its work with outside parties, including universities, pharmaceutical companies and biotechnology companies. With these standard template agreements, NCATS and its partners can more quickly initiate collaborative approaches, avoiding protracted negotiation and allowing important research to be conducted efficiently. These agreements help facilitate the exchange of research materials and confidential information, collaborative research conducted under cooperative research and development agreements (CRADAs), and clinical studies to determine the safety and effectiveness of new agents under clinical trial agreements.

Left: Team of NCATS, NIH and industry recipients of the 2012 Mid-Atlantic regional Federal Laboratory Consortium for Technology Transfer Award.

NCATS' Inaugural Research & Development Day Linked Investors with NIH Projects

In September 2013, NCATS held its inaugural Research & Development Day, hosted by Novartis Institutes for BioMedical Research in Cambridge, Mass. The event featured therapeutic candidates for sickle cell disease, hereditary inclusion body myopathy, Duchenne muscular dystrophy and cryptococcal meningitis. Participants from biopharmaceutical firms,

venture capital companies, nonprofits and other organizations learned about collaboration opportunities for pre-clinical drug development projects supported by NCATS' TRND and BrIDGs programs. Several potential partnerships identified at the event are being actively pursued.

Resources for Small Businesses

NCATS increases small businesses' participation in federally supported research and development as well as the private-sector commercialization of technology developed with federal support. The Center supports these aims through the federal government's [Small Business Innovation Research and Small Business Technology Transfer](#) programs.

Making NCATS Technologies Accessible

NCATS helps ensure that its new technologies are developed fully and commercialized. Working closely with the NIH Office of Technology Transfer (OTT), NCATS carefully considers instances in which patent protection is necessary to commercialize a technology and aims to remove the barriers in precompetitive research areas. With OTT, NCATS is pursuing creative licensing arrangements with a

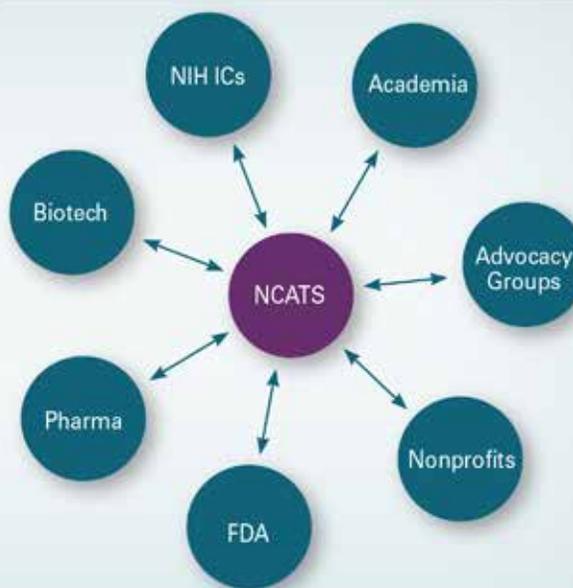
variety of partners that will develop NCATS technologies to address public health needs. NCATS' Office of Strategic Alliances has a dedicated [Web page](#) to promote projects that are available for out-licensing. A technology matrix was created to represent both the stage of development and the disease indication for these NCATS-developed technologies. Non-confidential and contact information are provided to encourage interaction with interested collaborators. This initiative has already proven to be useful by connecting potential licensees and inventors working on multiple different technologies and disease indications.

NCATS sponsors meetings and events that bring academic, nonprofit and industry researchers together. A prime example is Research & Development Day (see box above), which provides a setting for NCATS and its collaborators to showcase their therapeutic development projects for potential investment partners.

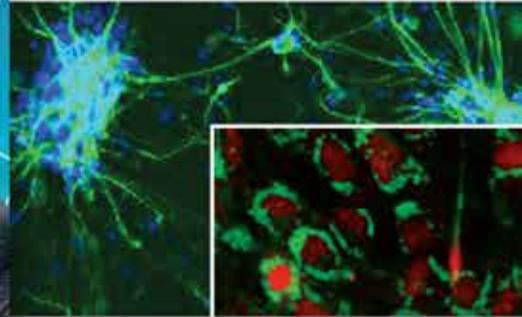
Catalyzing Collaborations

NCATS:

- Complements — does not compete with — the work of other organizations
- Revolutionizes the process of translation by targeting and overcoming barriers
- Galvanizes and supports new kinds of partnerships
- Supports and augments regulatory science and its application
- Expands the precompetitive space



Policy Issues



Accelerating the translation of biological insights into new medicines requires developing powerful new scientific knowledge, methodology and tools, as well as thoughtfully navigating translational research policy issues. NCATS is partnering with stakeholders to prioritize key issues and specific policy goals in the areas of informing regulatory science, navigating intellectual property challenges, streamlining clinical research and forming efficient strategic alliances. Given NCATS' position as a hub for catalyzing innovations and creative partnerships in translational science, its goal is to overcome hurdles that slow the development of effective treatments and cures by developing new policies as well as new science.

To demonstrate that its efforts do not create duplication, redundancy or competition with industry activities, NCATS published a notice in the *Federal Register* on May 15, 2013, delineating the different approaches it uses to ensure that its initiatives do not duplicate or compete with those of industry. The notice explained how NCATS continually seeks input from stakeholders, including industry, on its plans, priorities and programs through multiple avenues, including discussions at NCATS Advisory Council meetings and other open public meetings; publication of

Requests for Information in the *Federal Register* and NIH Guide for Grants and Contracts; and communication with the public through its website, e-newsletter and social media tools. In response to the notice, NCATS received comments from for-profit, nonprofit and academic institutions. A number of responses were supportive and affirmed that NCATS' work is not redundant, duplicative or competitive with industry. Many statements complimented NCATS' outreach efforts with industry, and several respondents urged NCATS to continue actively engaging non-industry stakeholders.

Building an NCATS Policy Research and Analysis Agenda

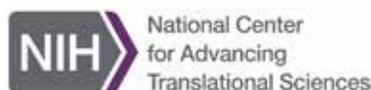
On Dec. 11, 2012, NCATS convened a workshop to discuss issues and obtain advice on building a solid policy research and analysis agenda to inform translational research within the scope of its mission. This meeting provided an opportunity to consult with key stakeholders in the regulatory, academic, nonprofit and private sectors to obtain views on how policy research and analysis can inform translational research and to identify barriers to translation that policy research and analysis could mitigate. A [summary of the workshop](#) is available on the NCATS website.

Left: Panelists at Partnering for Cures 2012 discuss "Molecule to man (and woman): Speeding translation to human trials" (FasterCures Photo). Right: Neurons derived from human induced pluripotent stem cell (larger image) stained to show cholesterol accumulation (smaller image) in Niemann-Pick disease type C1.

References

1. Pharmaceutical Research and Manufacturers of America. Figure 12: The Research and Development Process. In: *2012 profile: Pharmaceutical industry*. Washington, D.C.: PhRMA. Available at http://www.phrma.org/sites/default/files/pdf/phrma_industry_profile.pdf.
2. As of Nov. 26, 2013. Johns Hopkins University. Online Mendelian Inheritance in Man. Available at www.omim.org/statistics/geneMap.
3. Braun, M.M., Farag-El-Massah, S., Xu, K., et al. Emergence of orphan drugs in the United States: A quantitative assessment of the first 25 years. *Nat Rev Drug Discov* 9:519–522, 2010.
4. Collins, F.S. Reengineering translational science: The time is right. *Sci Transl Med* 3:90cm17, 2011. Available at www.ncats.nih.gov/files/translational_science_07062011.pdf.
5. Shukla, S.J., Huang, R., Simmons, S.O., et al. Profiling environmental chemicals for activity in the antioxidant response element signaling pathway using a high throughput screening approach. *Environ Health Perspect* 120:1150–1156, 2012.
6. Institute of Medicine. *Rare Diseases and Orphan Products: Accelerating Research and Development*. Washington, D.C.: The National Academies Press, 2010.
7. Rare Diseases Act of 2002, P.L. 107-280.

For More Information



Website: www.ncats.nih.gov



Facebook

www.facebook.com/ncats.nih.gov



Twitter

www.twitter.com/ncats_nih_gov



YouTube

www.youtube.com/user/ncatsmedia



E-Newsletter

www.ncats.nih.gov/e-news.html



For more information and to **submit comments** about NCATS, send an email to: info@ncats.nih.gov.