

National Center for Advancing Translational Sciences

Improving Health Through Smarter Science



2017—2018 Report



National Center
for Advancing
Translational Sciences



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NCATS Director's Introduction

The National Center for Advancing Translational Sciences (NCATS) works to get more treatments to more patients more quickly by improving the science of translating scientific discoveries into improvements in human health.

Two years ago, we released our ambitious [Strategic Plan](#), which set the course for NCATS' future and explored the enormous opportunities and challenges in our young field of translational science. To help facilitate a review of our progress, we have structured this first Biennial Report around the same four strategic goals described in that plan: *advancing translational science, fostering innovative partnerships, developing the translational workforce and enhancing stewardship.*

The NCATS approach of team-based technology and model development has yielded exciting progress that has exceeded our expectations in all four strategic areas. This success has not only driven science, health and process improvements, but it also has made me even more optimistic about our ability to accelerate system-wide translation, now and in the future. This progress helps fulfill the potential of science to benefit the public and all patients.

In this report, you will read about how NCATS-supported translational science has advanced across the [translational spectrum](#) in truly remarkable and diverse ways in the past two years. Our [Clinical and Translational Science Awards \(CTSA\) Program](#) has produced breakthrough innovations in how researchers study diseases; the design, recruitment for and conduct of clinical trials; the use of informatics to advance research and health; and the inclusion of community partners as members of the research team, ensuring that health advances benefit all those who need them. Read more on [page 7](#).



Christopher P. Austin, M.D.

Rare diseases are a particular focus of NCATS, since they present both a disproportionate public health need and a research opportunity. Gene therapy for rare diseases has undergone a renaissance in the past several years, and NCATS is leading the way in developing gene therapy technologies and clinical strategies, using new approaches to bring treatments to more patients more efficiently. For example, scientists in our [Therapeutics for Rare and Neglected Diseases](#) program have helped move a gene therapy for a rare and devastating pediatric disease closer to reaching U.S. patients. (Read more on [page 24](#).) NCATS also is working closely with the Food and Drug Administration (FDA) to address regulatory science needs in this rapidly evolving field, including hosting a [joint workshop in August 2018](#) with NIH and FDA staff; academic, biotechnology and pharmaceutical researchers; and patient group representatives.

Gene editing is a particular form of gene therapy that has grown rapidly in the past two years, with enormous potential but also substantial questions concerning safety and efficiency. To address these critical questions and accelerate the translation

of gene-editing technologies to the clinic, NCATS is leading an NIH Common Fund program on [Somatic Cell Genome Editing](#). (See [page 15](#) to learn more.) And through studies supported by NCATS' [Rare Diseases Clinical Research Network](#), we helped move the first gene-editing therapy into patients at the end of 2017 (highlighted on [page 11](#)).

The focus, relevance and urgency that patients bring to research can be a uniquely powerful and positive “disruptive technology” to make translation more efficient and effective. As in most areas of translation, however, the science of patient engagement is in its infancy and is thus an area of focus for innovation. Beginning in 2017, we launched an annual NCATS Day event for NIH staff, patients and advocates, community health engagement professionals, and researchers to discuss strategies for optimally involving patients and communities in translational science. In 2017, we also launched the [Toolkit for Patient-Focused Therapy Development](#), which was created in close collaboration with the rare diseases patient advocacy community. More details about these and other ways we are partnering with patients throughout the translational process can be found on [page 17](#).

Along with these achievements, the past two years also have brought to light the public health crisis that is the opioid epidemic. As part of NIH's [HEAL \(Helping to End Addiction Long-termSM\) Initiative](#) launched in 2018, NCATS is applying innovative translational science approaches to accelerate the pre-clinical testing and development of new medicines for addiction, pain and overdose. NCATS is using an unmatched national resource — our CTSA Program — to carry out innovative “real world” clinical studies of pain therapies, while reducing the risk of addiction, to empower health care professionals to treat pain more effectively. Read more on [page 13](#).

Innovation in training and workforce development is central to NCATS' mission. Translational science is a young and rapidly developing field that requires knowledge, skills and attitudes that are distinct from other areas of science. In the past two years, the CTSA Program has inaugurated “mini-sabbatical” and pharmaceutical company externship programs to give trainees experience in different translational environments. And the field-leading [Assay Guidance Manual](#) resource has expanded in subject areas along with in-person workshops nationwide. Read about these and other training innovations on [page 30](#). In addition, NCATS has led the development of comprehensive [maps of translation](#) to assist researchers, patients, students and policymakers in understanding this confusing process and ways to improve it. Learn more on [page 5](#).

Stewardship of our human and financial resources is an integral part of every NCATS initiative: “Advancing” efficiency and effectiveness in translational science is literally in our name. In just the past two years, we have implemented a new Other Transactions Authority funding approach that has produced breakthrough productivity. We also have created leading “cloud” and data security and privacy programs and implemented small business outreach to women- and minority-owned companies that has dramatically increased participation of these important communities of innovation in NCATS programs. Read more on [page 32](#).

I am enormously proud of the creativity, dedication and success of NCATS-supported researchers and staff in our work to transform the translational process for the benefit of science, medicine and patients. As you will read in the pages of this report, this transformation is not only happening, it is accelerating, providing confidence in the NCATS mission and great optimism for its future.

Christopher P. Austin, M.D.

Director, National Center for Advancing
Translational Sciences





Strategic Goal 1: Advancing Translational Science

NCATS was created to understand — and thereby improve — translation, which is the process through which new interventions that improve human health are developed and implemented. To achieve this goal, the Center conducts and supports research to understand the fundamental principles and operational processes of translation and to uncover and solve system-wide bottlenecks that delay or prevent getting new treatments to patients.

NCATS researchers, grantees and partners develop and disseminate data and innovations, thus empowering the entire biomedical research community to conduct translation more efficiently. We do this through our own work, but even more importantly, we catalyze the work of others who are developing and deploying new and better treatments.

Creating Tools and Technologies to Accelerate Translational Research

NCATS accelerates translational research by developing cutting-edge tools and technologies aimed at overcoming scientific and operational limitations to efficiency, demonstrating their usefulness, and disseminating them to the entire research community.

A Map Through the Translational Process:

The common analogy of a drug development “pipeline” is misleading, implying a simple and inevitably successful path from a laboratory observation to a therapy in the hands of clinicians and patients. To more easily identify inefficiencies and integrate efforts to speed new therapies,

NCATS catalyzed the development of the [Drug Discovery, Development and Deployment Maps \(4DM\)](#). These maps illustrate the complexities associated with the therapeutics development process, including known roadblocks. They were created to facilitate discussions and collaborations aimed at overcoming barriers and to accelerate new therapeutic discovery.

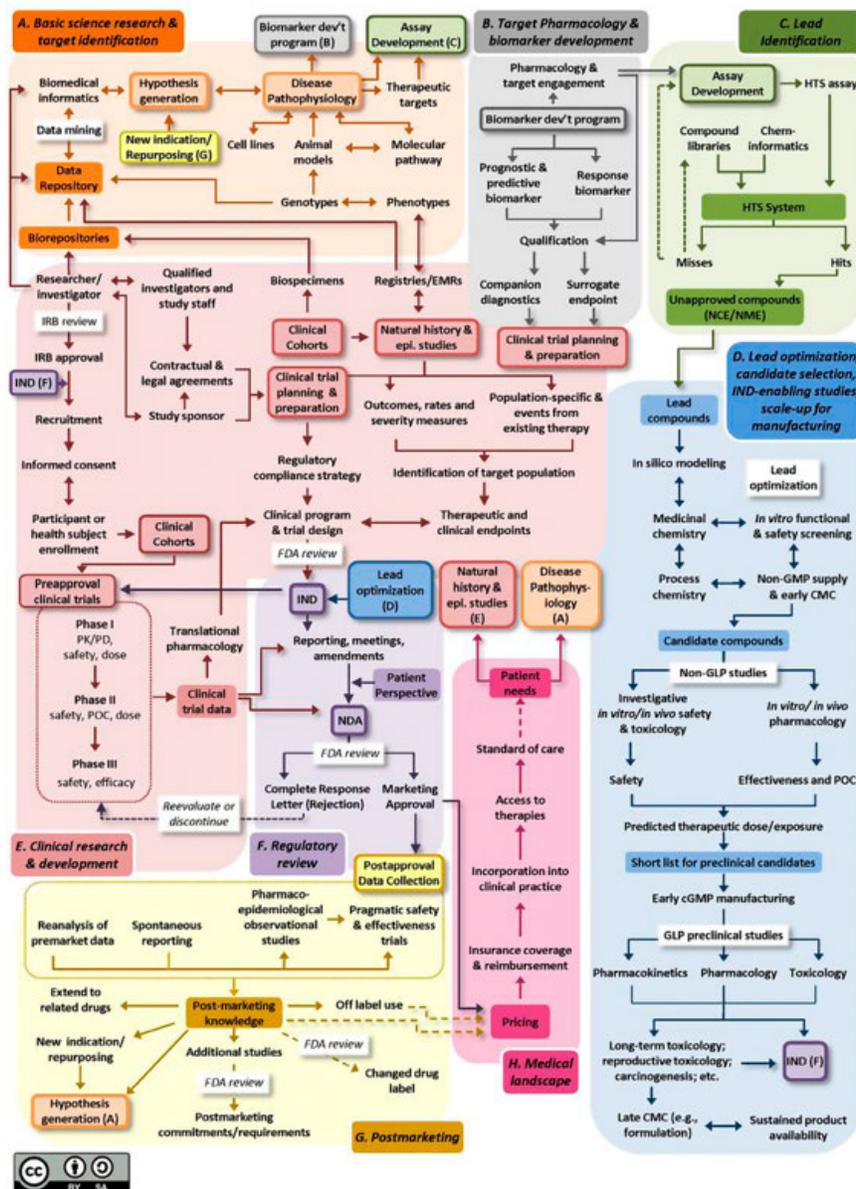
NCATS partnered with academics, pharmaceutical and biotechnology companies, regulators, foundations and patient groups to create the maps through an Action Collaborative of the Forum on Drug Discovery, Development and Translation, part of the National Academies of Sciences, Engineering and Medicine. The 4DMs are available for public use under a Creative Commons license. More detailed information on the maps was published in the [February 2018 issue of *Nature Reviews Drug Discovery*](#) and the [March 2018 issue of *Clinical and Translational Science*](#).

A Catalogue of Pathways in Health and Disease:

The [Toxicology in the 21st Century \(Tox21\)](#) program is a multi-agency effort to improve how chemicals are tested for possible toxic effects in humans (see [page 5](#)). To assist in these efforts, NCATS researchers developed [BioPlanet](#), a catalogue of human genes and pathways that helps researchers map relationships among those pathways. This information assists Tox21 scientists in understanding how chemicals may affect genes and pathways and in discovering new connections among them.

BioPlanet is more comprehensive than existing databases; it currently includes about 1,700

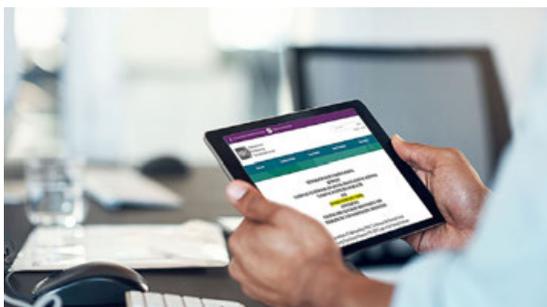
4DM Small Molecule Sample Map



4DM Small Molecule Map. This map depicts the interconnected nature of key steps in the drug development lifecycle for small molecules. The steps are grouped into eight identified neighborhoods, each depicting the steps and processes necessary to advance within a particular stage of development. Steps within each individual neighborhood are frequently dependent upon both other steps within that neighborhood and steps in other neighborhoods, resulting in a complex and nonlinear development process. This figure is attributed to: Wagner JA, Dahlem AM, Hudson LD, Terry SF, Altman RB, Gilliland CT, DeFeo C, Austin CP. Drug Discovery, Development and Deployment Map (4DM): Small Molecules. <https://ncats.nih.gov/translation/maps>. Last updated November 2017.

unique human pathways encompassing nearly 10,000 human genes. Staff carefully curate BioPlanet data from multiple publicly available sources to minimize redundancy and enhance accuracy. This powerful public resource of shared information is helping researchers identify new targets for drug development and improve safety evaluations of environmental chemicals. A web browser enables users to visualize and analyze pathways in an integrated platform that supports systematic analysis and modeling of toxicity responses.

Shortly after BioPlanet launched, Tox21 researchers used the database in a study, published in the [Feb. 20, 2018, issue of PLoS ONE](#), to demonstrate its utility. In the study, investigators recommended a list of 1,500 genes to check in toxicity tests of potentially harmful



New Therapeutic Uses template agreements are free and publicly available for researchers or companies to adapt to their own needs.

chemicals, which can lead to changes in how cells produce different genes. The investigators used BioPlanet to ensure that their list of genes sufficiently covered the known pathways involved in disease and toxicity.

A Template for Forming Public-Private

Partnerships: Public-private partnerships can accelerate translational research by bringing

each party's unique expertise and assets to the table to solve a common challenge. But lengthy negotiations to establish collaborative research agreements can be a bottleneck in public-private collaborations, significantly delaying research progress. This type of legal agreement describes how intellectual property, such as patents, will be handled in a collaborative project.

To speed the negotiation process, NCATS' [Discovering New Therapeutic Uses for Existing Molecules](#) (New Therapeutic Uses) program created template legal agreements that academic institutions and pharmaceutical companies could use as a launching point for negotiations. The templates have been so successful that other NIH Institutes and Centers (ICs) and NCATS' pharmaceutical partners have adopted the templates and adapted them to [jumpstart their innovative research initiatives](#), including the NIH Common Fund's [Stimulating Peripheral Activity to Relieve Conditions](#) program and the NIH BRAIN Initiative.

The New Therapeutic Uses template agreements demonstrate the kind of operational research hurdles NCATS is addressing. Because the templates are [free and publicly available](#) for researchers or companies to adapt to their own needs, this tool has been adopted by the wider research community to make a broader impact for patients' benefit.

Transforming Clinical Translation

NCATS' [Clinical and Translational Science Awards \(CTSA\) Program](#) supports innovation in our nation's clinical and translational research enterprise. CTSA Program-supported institutions are "hubs" of translational science innovation that provide expertise, resources, training and mentoring, and technologies to make all phases of clinical research more efficient and effective locally, regionally and nationally. Collaborative initiatives

support innovations that integrate expertise from multiple hubs and implement innovations across other hubs, greatly increasing the impact of the program to improve the quality, safety, efficiency and speed of clinical and translational research.

NCATS Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Platform:

Delays in beginning multisite clinical trials can occur when each site must have a study evaluated for risks and safety by its local institutional review board (IRB). This requirement can lead to inefficiency that results in lost opportunities for both the patients in need of new treatments and the clinical investigators developing them. Through a collaborative effort across the CTSA Program, NCATS created the [SMART IRB Platform](#) to harmonize and streamline these ethics reviews for multisite studies. SMART IRB enables all participating study sites to rely on the review of one “IRB of record” for each study, which can decrease approval times.

SMART IRB launched in March 2017 with all CTSA Program hubs participating, and NCATS has made the platform available to all biomedical research institutions that wish to join. The number of institutions participating in SMART IRB has since grown to more than 500 hospitals and medical centers across the country. The platform helps investigators implement the [NIH policy](#) that went into effect in early 2018 requiring all NIH-funded multisite clinical studies to use a single IRB.

On Sept. 12, 2018, NIH led a [public workshop](#) on successful strategies and lessons learned for modifying and enhancing infrastructure for single IRB review of multisite studies. Researchers from across the CTSA Program discussed their experiences serving as and relying on a single IRB and their work on technologies to facilitate the process.

CTSA Program Trial Innovation Network

(TIN): Launched in 2016, [TIN](#) serves as a national laboratory to study, understand and innovate on the process of conducting multisite clinical trials.

A major barrier to testing potential new treatments in clinical trials is recruiting enough participants in a timely fashion. TIN’s [Recruitment Innovation Center](#) is transforming recruitment methods to enroll participants in clinical trials more quickly. For example, investigators supported by NIH’s National Institute of Arthritis and Musculoskeletal and Skin Diseases approached TIN for help after falling behind on their recruitment schedule for a clinical trial on rheumatoid arthritis. TIN staff created more effective recruitment materials and designed a smartphone app to help clinicians identify and notify eligible participants.

An investigator also can request that one of TIN’s three [Trial Innovation Centers](#) (TICs) provide advice on the design or feasibility of a clinical trial. Through SMART IRB, TICs have served as a single IRB for more than 37 multisite trials. TIC investigators are also addressing challenges around informed consent documents. For example, consent documents for a single study may need to be translated into multiple languages, with different versions for children or other vulnerable populations. This requirement results in hundreds of different versions of what is essentially the same consent form. To address this challenge, investigators at the University of Utah TIC developed an automated consent builder that quickly updates changes to the consent form for each site, transforming hours of work into minutes or even seconds.

CTSA Program Collaborative Innovation Awards (CCIAs):

From January 2017 to September 2018, NCATS funded 17 [CCIA](#) projects, which stimulate team-based research across the CTSA Program to overcome roadblocks in translation that cannot be resolved

by any one hub working alone. The funded projects reflect the spectrum of CTSA Program goals, from integrating underserved populations in translational research to innovation in training (see “mini-sabbaticals” information on [page 28](#)).

For example, beginning in 2016, scientists established Early Check, a [voluntary newborn screening research program for rare genetic diseases](#). Genetic tests cannot be added to standard newborn screening without strong evidence of benefit. But for many rare disorders, this evidence is difficult to gather because of the challenge of identifying enough cases, especially before symptoms appear. Through Early Check, a collaboration among RTI International and three CTSA Program hubs in North Carolina, researchers are studying the benefits of screening for rare disorders so that policymakers will have the evidence they need to make decisions about newborn screening policy.

In October 2018, Early Check scientists began screening for [spinal muscular atrophy](#), which leads to progressive muscle weakness, and for [fragile X syndrome](#), the most common cause of inherited intellectual disability. A first treatment for spinal muscular atrophy was approved in December 2016, and while there is no drug treatment approved for fragile X syndrome, early intervention can help children achieve their potential. Without newborn screening, diagnosis and subsequent treatment usually occur around age 3. Early Check will enable researchers to follow children with these conditions and determine whether early intervention strategies, initiated well before they are traditionally provided, can improve children’s developmental outcomes.

Patient-Reported Outcomes: The [Patient-Reported Outcomes Measurement Information System \(PROMIS\)](#), originally developed through the NIH Common Fund, provides a standardized and efficient way to measure patient-reported

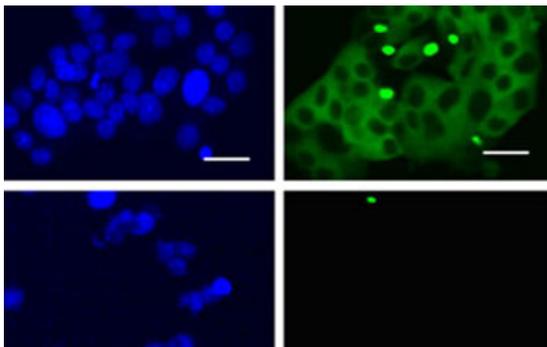


When babies are born in North Carolina, they receive a heel prick test for certain health conditions. Early Check is a research study that screens for fragile X syndrome and spinal muscular atrophy.

outcomes for a variety of chronic diseases. Northwestern University researchers successfully [integrated the PROMIS toolset](#) into the university’s local electronic health record system and are working with nine other CTSA Program hubs to do the same. This effort will help researchers across the CTSA Program capture the patient perspective, with the goal of improving diagnosis and treatment for patients.

Identifying Commonalities Across Diseases

Efforts to understand and find cures for diseases traditionally focus on one disease at a time. While this approach has produced a wealth of information and treatments for approximately 500 diseases to date, there are still more than 6,000 diseases without approved treatments. New approaches are urgently needed to increase the pace of progress, so NCATS is taking an alternative approach, identifying commonalities across diseases and developing treatments and intervention strategies that address multiple diseases at the same time. This approach, combined with NCATS’ other efforts to increase the speed and effectiveness of



In a cell model of Huntington's disease, the compound NCT-504 lowers the amount of toxic protein in the cell by inhibiting the enzyme PIP4Ky. Here, the panels show cells before (top) and after treatment (bottom) with NCT-504. The right column indicates the abundance of the toxic protein. The cells after treatment with NCT-504 show a significant decrease in toxic protein accumulation.

therapy development, has the potential to greatly accelerate new therapy development.

Many neurodegenerative diseases, such as Huntington's, Alzheimer's and Parkinson's diseases, share a common feature of protein buildup inside brain cells that is thought to cause cell death. Researchers in the NCATS Division of Pre-Clinical Innovation collaborated with researchers at the University of Michigan and Baylor College of Medicine to test thousands of molecules from the Center's [compound libraries](#) on cells from patients with Huntington's disease, an inherited, fatal neurodegenerative disorder that has no cure. Several [molecules were successfully identified](#) that decreased the levels of the toxic protein in Huntington's cells and increased survival in cell and animal models of Huntington's disease. Importantly, since these molecules work by revving up the cell's "recycling" system that rids cells of many different toxic proteins, they are being tested as potential treatments not only for Huntington's,

but also for other neurodegenerative diseases. The findings were published [Dec. 19, 2017, in eLife](#).

Accelerating Research on Rare Diseases

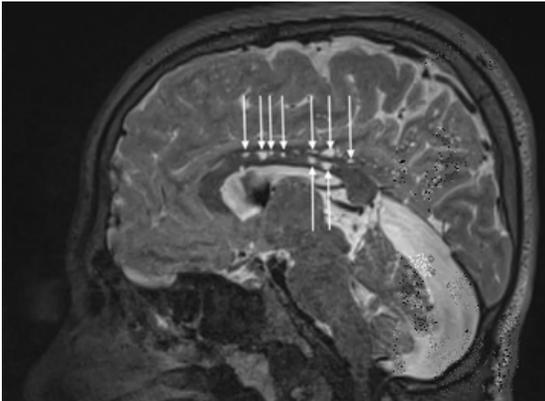
More than 7,000 diseases are officially defined as "rare," or affecting fewer than 200,000 people in the United States. Added together, these disorders are anything but rare: They affect an estimated 25 million people across the nation, yet only a few hundred have any approved treatment. NCATS is advancing systematic progress on rare diseases by working to identify what is common among them and partnering with academia, government, industry and patient advocacy groups to share resources, including knowledge and expertise.

Rare Diseases Clinical Research Network

(RDCRN): NCATS is advancing rare diseases research through clinical research approaches and facilitating collaboration, study enrollment and data sharing. In partnership with nine NIH ICs, NCATS' [RDCRN](#) supports more than 20 clinical research consortia and scientists at hundreds of clinical sites, working collaboratively to study more than 200 rare diseases. Each consortium focuses on at least three related rare diseases, participates in multisite studies and actively embraces patient advocacy groups as research partners. RDCRN consortia have a long history of accomplishments, including two recent examples:

- **Paving the Way for New Treatments for Lysosomal Diseases.** Lysosomal diseases are characterized by an abnormal buildup of various toxic materials in the body's cells due to improper functioning of lysosomes, compartments within cells that are designed to break down and eliminate waste.

Scientists supported through RDCRN's Lysosomal Disease Network (LDN) — which also receives support from NIH's National



Magnetic resonance imaging reveals the brain's structure. In this image, enlarged spaces (arrows) around blood vessels in the brain of a patient with Hunter syndrome, a neurodegenerative disease, show a physical effect of the disorder. (University of Minnesota Photo/Igor Nestrasil, M.D., Ph.D., and Carol Nguyen)

Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Diabetes and Digestive and Kidney Diseases — conducted clinical studies of children and adults affected by several types of lysosomal diseases. The studies revealed how these diseases affect the brain and progress over time, and they [paved the way for a first-in-human gene-editing clinical trial](#) that began in November 2017 for patients with one type of lysosomal disease called Hunter syndrome.

LDN researchers worked with Sangamo Therapeutics, Inc., to develop the current clinical trial and recruit participants. Together, these academic and industry scientists will gauge the safety of the gene-editing technique in patients and look for signs of effectiveness using LDN-developed tools, including brain imaging. In addition, LDN investigators will help study and evaluate the effects of the gene-editing therapy on patients' thinking and learning abilities.

- **Charting a New Course for Severe Combined Immunodeficiency (SCID).**

Babies with SCID, an inherited disorder that prevents the immune system from fighting infections, often die before age 2 unless they receive gene therapy, enzyme replacement treatment or a bone marrow stem cell transplant. For nearly 50 years, clinicians

have been using transplants — designed to help re-establish the patient's ability to create blood cells and restore the immune system — to treat children with SCID. When deciding on treatment, clinicians generally must rely on limited information from small numbers of patients seen at individual institutions.

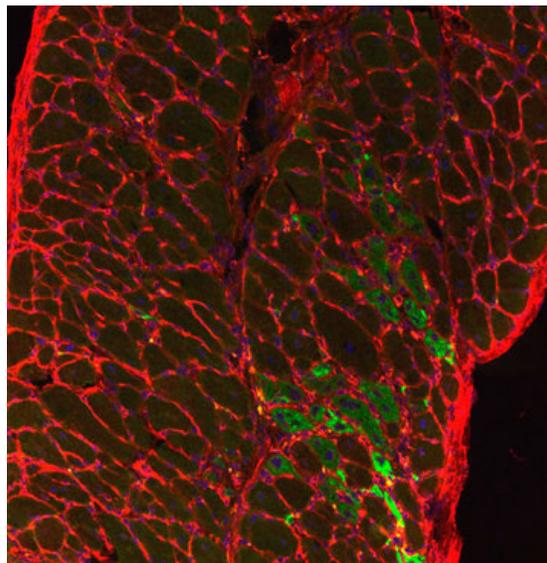
The RDCRN Primary Immune Deficiency Treatment Consortium (PIDTC) is [supporting a large, retrospective study](#) on the health of nearly 600 SCID patients who have received a stem cell transplant since 1982. The study focuses on long-term effects resulting from transplants, such as mental impairment, lung disease, and fertility and hearing problems. Such studies also have revealed more about how the specific genetic form of SCID affects the disease's progression and about which therapy to use.

Another treatment for SCID is gene therapy, in which a specially modified virus delivers a correct copy of a damaged gene to the patient. SCID was the first disease treated with gene therapy, and some patients unexpectedly developed cancer following treatment. Other PIDTC-led studies focus on improving this treatment for SCID and studying its long-term effects.

NIH reinforced its support for rare diseases research with the [2018 RDCRN funding opportunity announcements](#) made possible via NCATS' partnership with eight NIH ICs and Offices. A key component of the network's success will be to ensure that data standards such as collection and analysis are uniform, of high quality and shared across the network. This effort will lead to better understanding across rare diseases, which can contribute to knowledge for improving diagnosis and treatment. To support this effort, NCATS will provide centralized "cloud" computing services for RDCRN and its Data Management and Coordinating Center (DMCC) to facilitate data accessibility and use. DMCC researchers will provide expertise and consulting to the consortia in several areas, such as the development and management of research study protocols, biostatistics and study design.

Drug Repurposing for Rare Disorders: One approach to accelerating the development of treatments is to find new uses for drugs that already have been approved or have cleared several regulatory review steps; this approach is called drug repurposing. One NCATS drug repurposing project led to the identification of a small molecule that [may improve muscle function in patients with Duchenne muscular dystrophy](#) (DMD). Researchers from NCATS and the University of Nevada, Reno, screened more than 350,000 compounds to find SU9516, which had been previously developed as a treatment for leukemia.

SU9516 represents a different kind of approach for treating DMD, a rare muscle disease that usually begins in childhood and has no known cure. Rather than trying to fix or replace the faulty gene, SU9516 ramps up the muscle repair process, helping to reinforce muscle structure. The research team demonstrated that this compound improved muscle function in laboratory and animal



Diaphragm muscle from SU9516-treated dystrophin-deficient mouse showing nuclei (blue), myofibers (outlined in red) and regenerating muscle fibers (green). (University of Nevada, Reno School of Medicine Photo/Burkin Laboratory)

models for DMD. The results, published in the [June 7, 2017, issue of *Molecular Therapy*](#), may provide a promising approach against DMD and other muscle-wasting conditions.

See [page 16](#) to learn about ways NCATS is partnering with patients and advocacy groups to advance rare diseases research. Examples of how NCATS' Therapeutics for Rare and Neglected Diseases program is supporting progress in this field can be found on [page 24](#).

Addressing New Areas of Need and Opportunity

Through work to identify and overcome scientific and operational roadblocks in translation, NCATS is positioned to address new areas of opportunity and need, such as public health crises. NCATS resources and expertise can be put into action

when epidemics emerge. Additionally, institutions funded through NCATS' CTSA Program can apply their capabilities to respond quickly to broadly recognized health problems and to leverage their resources by partnering with institutions locally, regionally and nationally.

Following are examples of NCATS' work to address public health concerns in 2017 and 2018:

- Fighting Infectious Diseases.** NCATS researchers have quickly adapted their [high-throughput screening assay](#) (test) technologies to address public health emergencies. During the 2015–2016 Zika virus epidemic, NCATS scientists screened 2,800 drugs from the [NCATS Pharmaceutical Collection](#) of approved and investigational medicines to identify molecules that interfere with the virus' ability to make more copies of itself. The assay identified several promising molecules, including emetine, a drug approved to treat certain parasite infections. Because emetine is already approved by the Food and Drug Administration (FDA), the path to clinical trials is shorter than for newly identified chemical compounds.

Taking advantage of commonalities between Zika and Ebola infections, NCATS scientists worked with a large team of collaborators, including Florida State University and Johns Hopkins University, to find emetine and related molecules that helped mice survive both infections. The results, published in the [June 5, 2018, issue of Cell Discovery](#), demonstrate how NCATS leverages resources, expertise and collaborations to make rapid pre-clinical progress.

- Combating the Opioid Crisis.** Nearly 50,000 Americans died of opioid overdose in 2017, and more than 2 million Americans currently live with addiction to opioids. More than 25 million Americans live with daily

chronic pain, making them susceptible to risks associated with opioid use, and there are few effective and safe non-opioid options for pain management. To address the opioid epidemic, new, safe interventions are needed to combat misuse and addiction and to treat pain. Not only are more accurate research models needed to determine how potential new drugs will affect humans, but scientists also must identify existing drugs or develop new therapies that have potential as effective treatments.

In April 2018, NIH launched the [HEAL \(Helping to End Addiction Long-termSM\) Initiative](#) to advance national priorities in addressing the opioid crisis. As part of HEAL, NCATS is marshaling its resources and expertise to accelerate both pre-clinical and clinical translation of new and promising therapeutics.

Previous efforts to develop therapies for addiction, overdose and pain have often failed because animal-based testing systems cannot accurately predict the effects of these potential therapies in humans. NCATS' pre-clinical initiatives for HEAL are focused on developing human cell-based models as platforms to identify potential therapies. These platforms include induced pluripotent stem cells (iPSCs); 3-D bioprinted tissues; and "organs-on-chips" that model human addiction, overdose and pain pathways. New chemical structures must be quickly



developed and tested for new therapies. Therefore, NCATS is building a revolutionary new platform called [ASPIRE \(A Specialized Platform for Innovative Research Exploration\)](#), which will integrate automated chemical synthesis, high-throughput biological screening and machine learning to rapidly explore new chemical structures that can address targets of pain, addiction and overdose.

Led by NCATS and NINDS, the [NIH HEAL Pain Management Effectiveness Research Network \(ERN\)](#) will support studies to compare the effectiveness of existing pain treatments and new approaches to prevent and manage pain while reducing the risk of addiction. The network will leverage NCATS' CTSA Program hubs and TIN to implement clinical trials and studies of interest to multiple NIH ICs and Offices and to support studies that provide evidence to inform practice-based guidelines.

In addition to HEAL, NCATS has provided resources and encouraged CTSA Program hubs to apply their expertise to address the opioid epidemic. NCATS awarded funding to CTSA Program investigators to develop and disseminate a model for community pharmacists to dispense the drug naloxone to patients and their caregivers to counter the deadly effects of overdoses. Another award enables CTSA Program researchers to create a patient registry to identify best practices for prescribing pain relief for burn and trauma patients to reduce addiction to opioids.

In June 2018, the CTSA Program Center for Leading Innovation & Collaboration convened an "Un-Meeting" dedicated to [addressing the opioid crisis through translational science](#). Researchers, clinicians and policymakers came together to foster new, collaborative

teams and generate ideas to advance research to reduce the misuse and abuse of opioids while exploring innovative approaches to improve outcomes for those already affected.

Advancing the Promise of Regenerative

Medicine: iPSCs have the potential to generate all human body cell types. Most commonly made from the skin or blood cells of a patient, iPSCs can be turned into relevant cells to repair or replace tissues lost during disease, injury or aging. But there are major limitations that slow the use of these cells in regenerative medicine, including creating high-quality iPSCs and coaxing them into becoming specialized cell types in a reproducible and efficient way that also meets regulatory and clinical standards. Such issues were discussed at the NCATS-hosted Workshop on Translational Challenges of Induced Pluripotent Stem Cells on Sept. 26, 2017.

To address these challenges, the NIH Common Fund's Regenerative Medicine Program supported the creation of the NCATS [Stem Cell Translation Laboratory](#) (SCTL) that opened in July 2017. Take a [virtual tour of the laboratory](#).

In the past 18 months, SCTL investigators have made significant progress on several key projects targeting translational challenges, including the following:

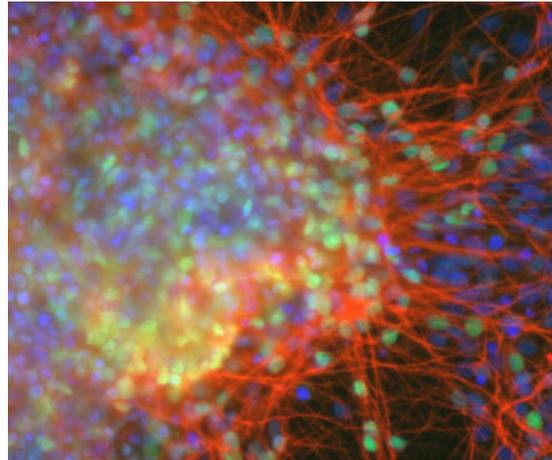
- **Improving Standardized Stem Cell Growth and Differentiation.** Taking advantage of NCATS' molecule screening

NIH Common Fund programs address scientific needs and opportunities that are of interest to all NIH ICs. NCATS has led several Common Fund programs that complement the Center's efforts to transform the translational science process so that more treatments can reach more patients more quickly.

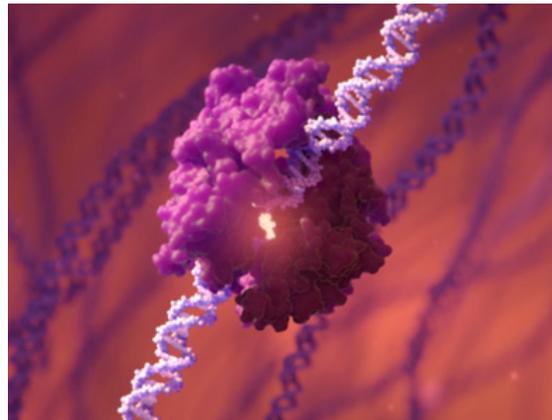
capabilities, researchers discovered a combination of four molecules that drastically improved survival of iPSCs. The combination also improved other processes needed for clinical application, including cell freezing for storage and on-demand use, gene editing, and unlimited production of cellular material. The advance has the potential to make the process of working with iPSCs more efficient and controlled.

- Making the Process Scalable and Reproducible.** Keeping iPSCs alive and growing — called cell culturing — is a labor-intensive process. NCATS staff have fully automated the process of growing and differentiating iPSCs into brain, heart or liver cells, using and modifying the robotic stem cell culture system called Select. This advance makes the process more reproducible and scalable, both of which are needed for pre-clinical research and regenerative medicine applications. And with the capacity to grow nearly 100 different types of iPSCs at the same time, SCTL serves as a resource for other groups within NIH. For example, SCTL researchers are providing different types of specialized cells created from patient-derived iPSCs to NCATS scientists studying new treatments for rare diseases, such as Gaucher disease.

Developing Genome-Editing Tools to Treat Disease: In genetic diseases, a problem with a particular gene means that a protein is made incorrectly or not at all. Genome editing, which makes precise changes to a person's DNA, has the potential to correct damaged genes and holds promise for treating thousands of genetic diseases. Recognizing the potential of this technology, the NIH Common Fund launched the [Somatic Cell Genome Editing](#) program in January 2018. Led by NCATS, funded investigators will pursue the development of high-quality tools for performing safe and effective genome editing



Cortical neurons derived from induced pluripotent stem cells. Red: neuronal marker TuJ1 (class III beta tubulin). Green: cortical marker CUX1. Blue: nuclear marker DAPI.



An illustration depicts a genome editing tool bound to a DNA helix. New genome editing tools can substitute single “letters” in the DNA code without changing the surrounding DNA structure.

within non-reproductive (somatic) cells. Limiting genome editing to somatic cells ensures that changes to DNA cannot be passed down to future generations. Once developed, these tools will be widely available to the research community to reduce the time and cost of developing new therapies.

Strategic Goal 2: Fostering Innovative Partnerships

The expertise, capabilities and resources required to successfully advance a drug, device or intervention reside in different groups as efforts progress through the [translational science spectrum](#). Partnerships and collaborations across individuals, organizations and sectors are essential to efficient progress. The creation of productive and mutually beneficial collaborations depends not only on individual excellence but also on teamwork, coordination, cooperation and communication.

Traditional professional incentive structures focus on individual accomplishment and make teamwork difficult to navigate. Embracing patients and communities as research partners also holds great potential for the development of treatments with meaningful outcomes for the populations affected by disease. With these needs in mind, NCATS tests innovative partnership structures that cut across traditionally separate scientific disciplines, organizations and sectors.

The [NCATS Office of Strategic Alliances](#) aims to make it easy for industry, small businesses and academia to interact and partner with NCATS scientists. Staff help develop formal partnerships that proactively address complex issues, such as intellectual property and project management roles, to make for smoother, more effective collaborations. Many projects in this report would not have been possible without the Office of Strategic Alliances:

- Speeding the Formation of Public-Private Partnerships on [page 16](#)
- Blocking Cancer Metastasis on [page 21](#)

- Moving Gene Therapies Closer to U.S. Patients on [page 24](#)
- Supporting an Award-Winning Technology for Drug Development on [page 25](#)
- Testing New Approaches on [page 24](#)

Enhancing Patient and Community Engagement

The ultimate goal of translation is a tangible improvement in health, so perspectives from and partnerships with patients are crucial. NCATS works to involve patients, caregivers, advocates and their communities in all stages of translational research and includes representation of these groups on its [Advisory Council](#).

Partnering with Patients for Smarter

Science: On June 30, 2017, NCATS convened the [first NCATS Day](#) on the NIH campus. At the event, NCATS staff and researchers described their programs and initiatives and received



During the breakout discussion at NCATS Day: Partnering with Patients for Smarter Science on June 30, 2017, participants discuss topics such as how to improve patient outreach and engagement. (Daniel Soñé Photography)



Taj Neaz Powell (right), a patient at The Children's Inn at NIH, talks about the challenges of living with sickle cell anemia at Rare Disease Day at NIH on March 1, 2018. Pictured on the left is Eric Sid, M.D., M.H.A., of NCATS' Office of Rare Diseases Research. (Daniel Soñé Photography)

feedback from participants about community needs and ways to enhance patient participation in translational research. More than 150 people attended, including patients, their families and other caregivers, and representatives of more than 75 patient and disease advocacy groups. The [second NCATS Day](#) was held Sept. 28, 2018. Patient organizations and researchers shared examples of successful patient and community engagement and discussed the foundations for productive partnerships. A “community engagement studio” demonstration illustrated how patients can provide valuable input for a research protocol, providing feedback to an NIH investigator that will support better research participation. The lively and informative discussion helped advance ideas for more collaboration and innovation in this critical area.

Patients and Researchers – Partners

for Life: As part of the global observance of Rare Disease Day, NCATS and the NIH Clinical Center co-sponsor [Rare Disease Day at NIH](#) on the campus in Bethesda, Maryland. The [10th annual event](#), held March 1, 2018, with the theme “Patients and Researchers, Partners for Life,” brought together a record-breaking 700 participants — patients and their support groups, scientists, clinicians, and policymakers — to discuss collaborative research efforts. Participants learned about translating the technique of gene editing into new treatments, how patient groups

can help advance research progress, some of the challenges presented by gene therapy, and the experiences of young adults living with rare diseases.

A “How-to” Guide to Patient-Focused Research: NCATS worked with members of the rare diseases community to create the [NCATS Toolkit for Patient-Focused Therapy Development](#).

Launched in September 2017, the Toolkit is a collection of online resources, created by and for patients, intended to help patient groups advance through the complex process of therapy research and development. The tools address a range of topics, including how to establish a patient registry, work with NIH and the FDA, and



Sarah Hogate Bacon asks panel members a question at the Toolkit Demonstration and Dissemination meeting. (Daniel Soñé Photography)

conduct post-market surveillance after a drug is approved. More than 230 patients, caregivers and other community members participated in the [unveiling of the Toolkit portal](#) at an event on the NIH campus. NCATS will continue to partner with the patient community to add new tools; ensure that existing content is accurate, timely and relevant; and identify gaps so that new tools can be developed.

Genetic and Rare Diseases Information Center (GARD): An important part of NCATS' patient and community engagement involves making research information available to the public. Through the Rare Diseases Act of 2002, Congress authorized the creation of [GARD](#), an online database of up-to-date, easy-to-understand information about rare and genetic diseases, including symptoms, treatment options, research, patient organizations and other resources. In addition to the online database, GARD information specialists can discuss questions by phone or in writing in English and Spanish. A professional translation service assists with translations of requests and responses in other languages.

This collaborative effort with NIH's National Human Genome Research Institute provides crucial information to patients, their families and caregivers, other members of the public, and researchers. GARD is being used now more than ever: Every month, the GARD website receives more than 1 million visits, and GARD staff handle about 900 additional information requests submitted by email or received during discussions with information specialists.

Tackling Health Disparities: NCATS supports robust patient and community engagement through its CTSA Program. Funded institutions have community advisory boards to help promote patient engagement and provide feedback to researchers, and many hubs employ patient engagement specialists.

Forming Innovative Collaborations with Academic Partners

Academic researchers are typically experts in particular fields of basic or clinical science, including specific diseases or organ systems. In contrast, NCATS researchers are experts in translational science, supporting the development and deployment of interventions to prevent or treat diseases more efficiently and effectively. NCATS programs are designed to complement basic and clinical research discoveries with [translational pre-clinical resources and expertise](#) to collaboratively accelerate candidate drugs for first-in-human testing.

Tissue Chips for Drug Screening and Disease Modeling: Most investigational drugs fail in human clinical trials due to a lack of effectiveness or safety, despite promising pre-clinical studies using cell and animal models. One reason for this high rate of failure is that traditional models cannot closely mimic the structure and function of the human body.

One NCATS approach to this challenge involves tissue chips, which consist of live human tissues on small plastic chips that can be used in pre-clinical testing to more closely model human organs. In collaboration with multiple NIH ICs, the FDA, and the International Consortium for Innovation and Quality in Pharmaceutical Development, NCATS leads the [Tissue Chip for Drug Screening](#) program. The program supports academic researchers in developing tissue chips of different organs and systems, such as the heart, lung, nervous system, female reproductive tract and liver.

- **Modeling the Heart.** In 2018, Columbia University investigators [overcame a key obstacle to accurately modeling the heart](#) and blood vessel system on a tissue chip. Researchers can convert adult human skin



Barbershop owner Eric Muhammad (left) takes the blood pressure of customer Marc Sims (right). (Smidt Heart Institute at Cedars-Sinai Medical Center Photo)

Black men are more likely to die from complications of high blood pressure than any other group in the United States. Many of these men could be treated with medications to lower their blood pressure. But overwhelmed primary care offices, patients' hesitation to take a new medication, and other barriers prevent many men from getting this beneficial treatment.

To tackle this disparity, researchers from the Smidt Heart Institute at Cedars-Sinai and the University of California, Los Angeles (UCLA), [paired pharmacists with barbershops](#) to offer high blood pressure care for customers. Instead

of sending patients to pharmacists, the research team sent pharmacists to the patients in their neighborhood — specifically, to barbershops. The goal was to overcome yet another obstacle for black men: They are less likely than other groups to visit a doctor. Barbershops are often a cornerstone of African American communities, and because men tend to visit the same barber every couple of weeks for years, barbers and patrons can develop a trusting relationship.

The Community Engagement Unit at UCLA's Clinical and Translational Science Institute helped the research team recruit the first few barbershop owners, who then reached out to other colleagues to recruit a total of 52 barbershops for the study. Barbers encouraged patrons with high blood pressure to meet with a pharmacist at the shop, and the pharmacists prescribed high blood pressure medications as appropriate and then followed up with the participants at future haircut appointments.

This intervention resulted in dramatically lower blood pressure for participants after six months, compared to a group of patrons who were encouraged to meet with a doctor and adopt lifestyle changes but were not prescribed medications by the pharmacist. The findings, published in the [April 5, 2018, issue of the *New England Journal of Medicine*](#) (updated in the [January 2, 2019, issue of *Circulation*](#)), offer valuable lessons on the potential impact and sustainability of directly engaging communities and using alternative health care delivery, through pharmacists, in nontraditional settings.

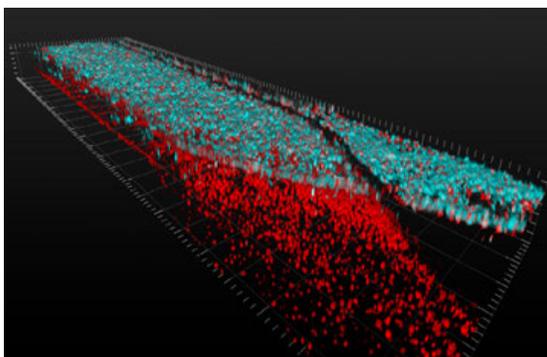
cells into iPSCs, which have the potential to become any type of cell. But heart muscle cells made from iPSCs do not fully mature and therefore do not mimic all the complexities of adult human heart cells. Supported by NCATS and NIH's National Institute of Biomedical Imaging and Bioengineering, Tissue Chip investigators developed a reliable way to grow adult-like human heart tissue in the lab. They tested different physical stimuli at different times to make the young heart cells contract and then increased the frequency of the contractions slowly each day. The results,

reported in the [April 4, 2018, issue of *Nature*](#), set the stage for a better model to predict the effects of potential new therapies on patients' hearts.

- **Studying the Spinal Cord.** Researchers at Cedars-Sinai [can now mimic conditions in the early human spinal cord](#). To understand how the spinal cord develops in the early brain, investigators used iPSCs to create early-stage spinal cord nerve cells, called neurons, and blood vessel cells. The team grew these cells in separate but porous chambers of a tissue

chip. The blood vessel cells reached out and created network-like connections with the neurons, which triggered the neurons to grow and mature. These mature neurons showed better signaling and function than typical spinal cord neurons grown in the lab. The study, supported by NCATS and NINDS, was published in the [April 10, 2018, issue of *Stem Cell Reports*](#).

The insights gained from the initial Tissue Chip for Drug Screening program created an opportunity for tissue chip technology to build upon and inform basic and mechanistic biomedical research. Through the [Tissue Chips for Disease Modeling and Efficacy Testing](#) initiative, NCATS collaborated with nine other NIH ICs and the FDA to award 14 grants in 2017 and 2018 to further develop tissue chips as models of both rare and common human diseases. For example, Northwestern University researchers will use their [female reproductive tract platform](#) to study polycystic ovary syndrome. The platform, described in the [March 28, 2017, issue of *Nature Communications*](#), mimics a 28-day menstrual cycle. It will be adapted to test drugs that AstraZeneca is developing to treat the syndrome.

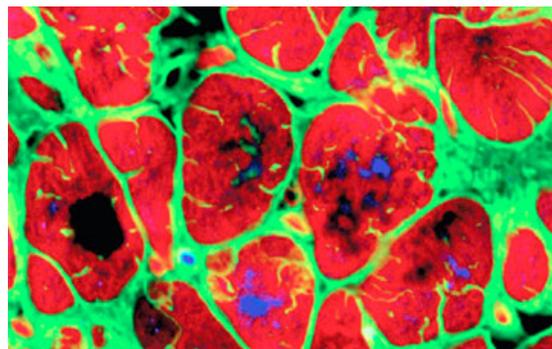


Layers of spinal cord motor nerve cells (top, in blue) and blood vessel cells (bottom, in red) are shown interacting on a tissue chip, a 3-D platform that supports living tissue and cells. (Cedars-Sinai Board of Governors Regenerative Medicine Institute Photo)

See [page 26](#) to learn more about Tissue Chip–supported technology that is advancing pre-clinical testing of potential new drugs.

Working in Three Dimensions: Another promising approach to pre-clinical testing that better mimics how cells grow in the body is modeling tissues in 3-D, which could help researchers better predict how patients will respond to potential new therapies. NCATS launched the [3-D Tissue Bioprinting](#) program in 2018 to use the techniques of 3-D printing to combine living cells with a manmade scaffold, creating laboratory-grown human tissues that more closely model natural tissues in human organs.

NCATS is collaborating with Rockefeller University and Columbia University to [provide 3-D printed skin tissues to investigate therapies for skin cancer and psoriasis](#). Rockefeller researchers have access to patient-derived cancer cells, which they grew into spheres in the printed skin in a way that models how these cells grow in patients. Once a model for melanoma is honed, the research team can use it to screen for new therapies. Rockefeller researchers also are using these skin constructs to fine-tune an innovative imaging technique for skin. The technique enables investigators to get



The iPS-derived cardiomyocytes have formed heart tissue that closely mimics human heart functionality at more than four weeks of maturation. (Columbia University)

a clearer picture of thicker tissues, such as a cancer sphere, while also keeping the tissue alive for experiments.

A challenge in using 3-D tissue models as a drug screening platform is producing tissues that look the same, function consistently and are reproducible from assay to assay in a multi-well plate format. This consistency helps ensure that screening results are reliable. With the use of 3-D bioprinters, NCATS can begin to industrialize production of 3-D tissues in an efficient, reproducible and scalable manner. Bioprinted tissues and their associated technologies have promise for civilian and military research applications, such as pandemic diseases, biodefense and national security. For example, cell and tissue replacement for injured soldiers and development of new medicines for field use — such as antibiotics and drugs for mental illness, trauma and surgery — are areas of huge potential. The closer the testing platforms are to mimicking humans, the better scientists will be at discovering new drugs for the patients who need them.

Driving Federal Collaborations

NCATS serves as a partner, convener and expert on translational science and shares its expertise and resources with colleagues at other NIH ICs and across the federal government. Collaborating with federal researchers and regulators who have knowledge of particular disease areas is essential to demonstrating the utility of translational technologies and strategies developed by NCATS.

Blocking Cancer Metastasis: When cancer spreads from one part of the body to another, it can eventually grow beyond the reach of effective therapies. By leveraging the unique expertise of NCATS and NIH's National Cancer Institute (NCI), [researchers have identified a potential therapy to stop this deadly process](#) known as metastasis.

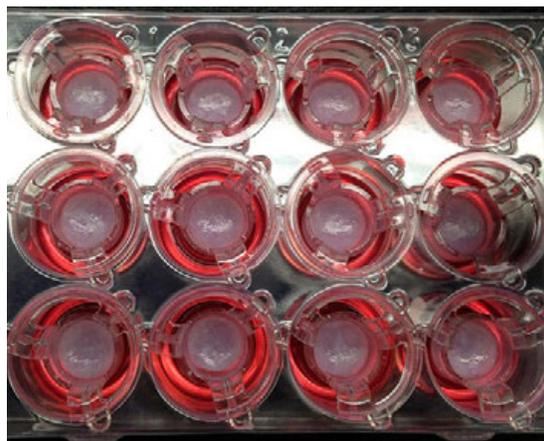
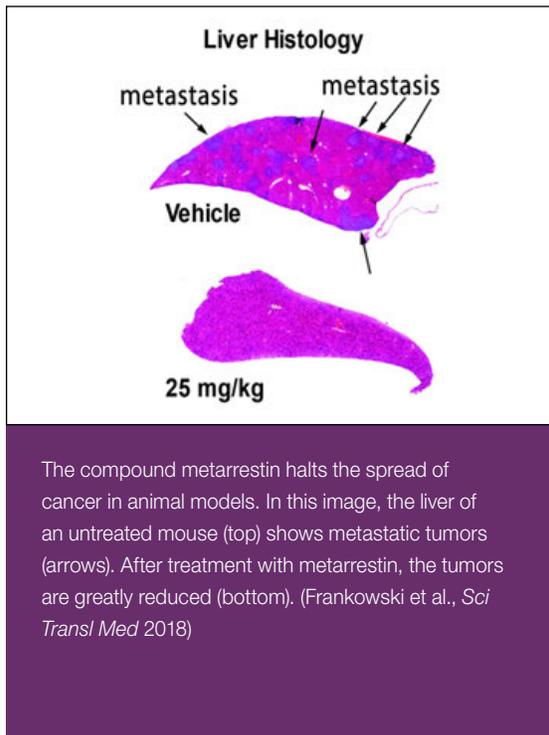


Photo of 3-D bioprinted tissues in a 12-well plate showing a reproducible tissue shape from well to well. (Paige Derr and Kristy Derr, NCATS)

Northwestern University researchers initially found a special compartment inside cancer cells that is related to cancer spread. They approached NCATS scientists to collaborate on screening more than 140,000 compounds and identified one that broke down the compartment in pancreatic cancer cells. The team then partnered with University of Kansas investigators to modify the molecule — metarrestin — to work better as a potential drug and tested it in cancer cells in the lab.

To move the project forward, the team partnered with an NCI researcher who had experience with testing new therapies for pancreatic cancer in pre-clinical and clinical studies. Together, they demonstrated that metarrestin helped mice with pancreatic cancer live longer and with fewer tumors.

Based on these promising results, published in the [May 16, 2018, issue of *Science Translational Medicine*](#), NCI is preparing to run a clinical trial of metarrestin in patients at the NIH Clinical Center. To clear the final hurdles in pre-clinical development, the NCI team is working with NCATS scientists from the [Bridging Interventional](#)



[Development Gaps](#) (BrIDGs) program. Through BrIDGs, NCATS provides project management and access to contracting services to collect pre-clinical data on candidate drugs needed by the FDA before the drugs can be tested in patients.

A System to Better Track Drug Safety: NCATS [engages with the FDA](#) on a number of training, tool development and joint research projects, including the [Global Ingredient Archival System \(ginas\)](#) developed by NCATS scientists. The system uses standardized scientific descriptions for naming ingredients in medical products as a solution to a translational science challenge: A chemical may have one name when used as a drug, a different name in cosmetics, yet another name in foods and something else entirely in another country. For example, in the United States, the active ingredient in Tylenol is called acetaminophen, but most countries refer to it as paracetamol. In fact, the ginas system currently

has 119 names for acetaminophen. Unfortunately, inconsistent naming for the same chemical means that side effects are tracked separately, preventing regulators from getting a complete picture of safety data.

NCATS, the FDA and several international regulatory agencies collaborated on software called G-SRS to implement ginas worldwide. By establishing a system of standard names, ginas and G-SRS are helping regulators more efficiently identify safety concerns and exchange information about substances in medicines throughout the global health community. The FDA deployed G-SRS software in 2017 as a replacement for the agency's previous registration system.

Accelerating Chemical Testing for Harmful

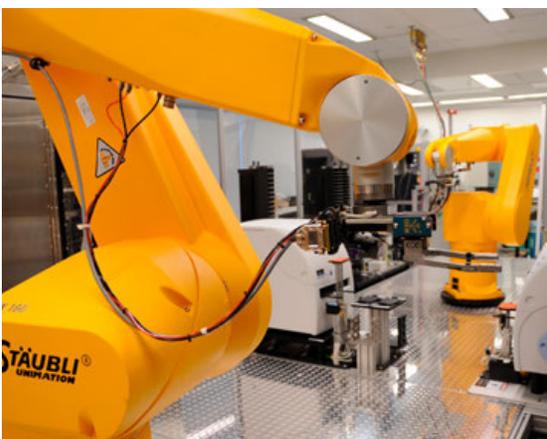
Effects: The Tox21 program is a long-standing federal collaboration among NCATS, the National Toxicology Program (NTP) at NIH's National Institute of Environmental Health Sciences, the Environmental Protection Agency (EPA) and the FDA to improve testing and predictability of chemicals for harmful effects. During the first 10 years of the program, Tox21 scientists developed and validated new high-throughput screening assays and generated data on tens of thousands of chemicals. The publicly available data are now beginning to inform regulatory decisions about safety.

These successes have enabled a greater understanding of key obstacles that remain in toxicity testing. To address these challenges, Tox21 partners [released a new strategic and operational plan](#) in March 2018. The plan features a shift in focus from screening libraries of chemicals to follow-up studies that will more fully integrate Tox21 partner expertise and resources.

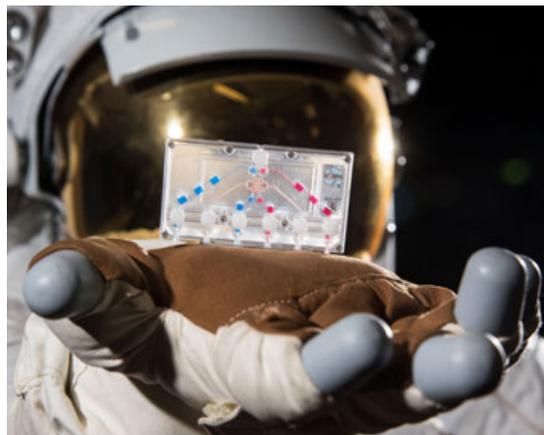
Tox21 projects exemplify successful collaboration. For example, NCATS scientists wanted to find

more efficient, reproducible ways to evaluate thousands of chemicals that could potentially damage mitochondria, which produce energy for cells. Based on their early work of previously identifying 622 chemical compounds that appeared to disrupt mitochondria, the Tox21 team of NTP, FDA, EPA and NCATS scientists developed an operational strategy for characterizing and prioritizing which compounds should be further examined. The strategy consists of a series of tests that narrowed the list down to four compounds that had not been extensively studied before and that should be tested for toxicity in animals. The approach, published in the [July 26, 2018, issue of *Environmental Health Perspectives*](#), can be used to guide strategies for other types of large-scale toxicity studies.

Using Space to Understand Disease: One of NCATS' collaborations is out of this world, literally! Since 2016, NCATS has partnered with the International Space Station U.S. National Laboratory to refine tissue chip technology for research conducted in space. Through NCATS' [Tissue Chips in Space](#) initiative, NCATS and



Using NCATS' state-of-the-art robotic screening system, Tox21 scientists have produced more than 120 million data points on approximately 8,500 chemicals since 2008.



NCATS is collaborating with the ISS U.S. National Laboratory to conduct tissue chip research in space. (NASA Photo)

the Center for the Advancement of Science in Space funded nine research teams in 2017 and 2018 to create tissue chip platforms that mimic human physiology under the extreme low-gravity environment of space. The first chips were [launched into space on Dec. 5, 2018](#), and two additional launches are scheduled for 2019.

Through this initiative, NCATS will help scientists better understand the impact of microgravity on human health and translate those findings to improve prevention, treatments and cures for diseases on Earth. Funded Tissue Chip projects are supporting research on the effects of reduced gravity on organ models for lung infection, the blood-brain barrier, osteoarthritis and bone loss, immune system aging, and kidney function.

In 2018, NCATS' Director Christopher Austin, M.D., was named as both NIH liaison to NASA and the Department of Health and Human Services (HHS) liaison to NASA. In these roles, he is reaching out to and assisting other NIH ICs and HHS agencies in developing relationships and collaborations with NASA to drive progress in their mission areas.

Engaging Private-Sector Partners

Through its [Therapeutics for Rare and Neglected Diseases](#) (TRND) and BRIDGs programs, NCATS establishes strategic partnerships to advance therapeutics development into clinical testing for rare and common diseases. These include collaborations with NIH and academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies. Rather than funding, NCATS provides expertise and resources, working with research partners to move therapeutics through pre-clinical testing, including plans for clinical trials and submission of Investigational New Drug (IND) applications to the FDA. These efforts effectively “de-risk” therapeutic candidates and make them more attractive for adoption by outside business partners for commercialization.

Moving Gene Therapies Closer to U.S.

Patients: In late 2015, the small biopharmaceutical company Agilis Biotherapeutics, Inc., licensed a gene therapy for the rare disease aromatic L-amino acid decarboxylase (AADC) deficiency. The disease currently has no treatment, and patients with severe forms usually die within their first decade of life.

Agilis licensed the gene therapy from National Taiwan University after investigators there demonstrated that a single dose led to drastic improvements in children. Despite these promising results, the investigators needed to provide the FDA with a comprehensive pre-clinical data package for U.S. market approval. The small market for this rare disease and the need to conduct additional studies threatened to stall the project.

Many private companies stop development of, or will not invest in, promising therapeutics in the pre-clinical and early clinical testing stages, finding it difficult to justify the costs for small rare disease markets. This “valley of death” in

drug development is where NCATS strategically positioned its TRND program to provide pre-clinical expertise and resources to catalyze the development of therapeutic candidates for rare disorders with unmet medical needs. In 2016, [Agilis partnered with NCATS through TRND](#) to develop a manufacturing process and produce the gene therapy to meet FDA requirements, conduct essential pre-clinical safety studies, and complete statistical analysis of available clinical data in preparation for discussions with the FDA.

These efforts led to a successful meeting with the FDA in fall 2017 to review the pre-clinical, clinical and manufacturing data. In an unusual step, FDA reviewers determined that Agilis did not have to repeat clinical trials in the United States, clearing the path to file a Biologics Licensing Application (BLA). If approved, this would accelerate the pace at which the company can market the gene therapy to patients by years. PTC Therapeutics, Inc., which acquired Agilis in 2018 based on the successful FDA meeting, is preparing to submit the BLA in 2019.

This therapy is poised to be among the first FDA-approved gene therapies for treating a central nervous system disorder. Moreover, it could be the first therapy supported through NCATS’ TRND program to receive marketing approval from the FDA and become available to patients.

Testing New Approaches: More than 10,000 Americans suffer spinal cord injuries each year, often leaving the patient permanently paralyzed. Such injuries are often permanent because damage to the nerve tissues causes the body to produce “inhibitory” substances that block regrowth of damaged spinal cord nerve fibers (axons) and prevent the signals of pain, heat and body position from reaching the brain.

To address this challenge, Yale University researchers and the biotechnology startup

ReNetX Bio developed a “decoy” molecule that blocks these inhibitory molecules. The therapy led to the growth of axons in the spinal cord and recovery in injured rats. ReNetX Bio partnered with NCATS through its BrIDGs program in 2012 to develop and manufacture the drug and conduct pre-clinical safety and toxicity studies and other steps needed for an IND. Based on the promising pre-clinical studies, the foundation Wings for Life committed \$7 million to support the clinical studies. The therapy is expected to move into clinical trials in 2019.

Supporting Innovative Entrepreneurs

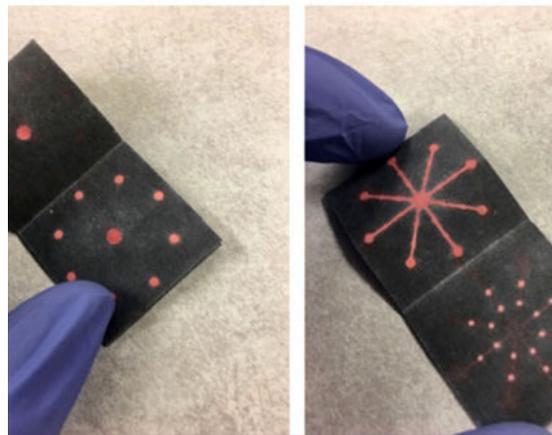
Through its [Small Business Innovation Research \(SBIR\)](#) and [Small Business Technology Transfer \(STTR\)](#) programs, NCATS provides opportunities for grants, contracts and technical assistance to move a small business or research organization innovation from proof of concept to early technology development and initial uptake by industry. In 2017 and 2018, NCATS increased efforts to reach more women- and minority-owned small businesses through outreach activities that included several interactive [webinars](#), including one in collaboration with the Association of Women in Science.

NCATS’ overarching goal for these programs is to advance translational research and technologies that will improve disease prevention, detection and treatment. See [page 32](#) for updates about the SBIR-supported IonField plate-washing technology — featured in the [2016 NCATS Annual Report](#) — which is helping reduce plastic waste and save money in drug development. In addition, the following examples demonstrate recent SBIR/STTR-supported advances:

Supporting Cost-Effective, Faster Diagnostic Tests: Diarrheal diseases kill more than 1 million people every year, mostly affecting children in

developing countries. Currently, a diagnosis requires sending a stool sample to a lab for testing, then waiting to find out if the patient has a bacterial or viral infection, a parasite, or some other problem. By the time the results come back, the patient has missed days of potentially lifesaving treatment.

GoDx is a biotechnology company founded [to develop a simple paper test for diarrheal disease](#). The test does not need electricity for processing and can detect seven common causes of diarrhea in less than 30 minutes. GoDx has a clinical cooperative research and development agreement to develop the test with a digestive diseases researcher at NIH’s National Institute of Nursing Research (NINR). Data generated through that collaboration made it possible for GoDx to apply for and receive a Phase I SBIR grant from NCATS in 2017.



The GoDx test has four paper layers. From left to right: First the stool sample (red dye) is loaded into the central dot. Next, the paper disperses the sample into eight tiny wells, arranged in a circle. In the third layer, the sample spreads along straight lines, which cross over a probe that detects each potential cause of the patient’s symptoms. At the bottom right is the final stage; if a dot lights up green, the sample contains that cause of diarrhea. (GoDx Photo)

NCATS' SBIR funding helped GoDx's founder participate in the [I-Corps™ at NIH](#) program, which provides mentoring and training for entrepreneurs. As part of I-Corps, GoDx colleagues interviewed 130 patients, doctors and others about the test and received input about improving and distributing it.

In July 2018, GoDx received Phase II SBIR funding from NCATS to continue the test's development. NINR is sponsoring a clinical study at the NIH Clinical Center to demonstrate the accuracy of the new test.

NCATS is supporting GoDx and the diarrheal test's development as a platform technology that could be used to diagnose many different diseases. GoDx plans to apply the technology to urinary tract infections, sepsis and sexually transmitted infections.

Supporting an Award-Winning Technology for Drug Development: Through both its Tissue Chip for Drug Screening and SBIR programs, NCATS has [supported development of a technology](#) that is adaptable to solve numerous challenges in translational research. The inventor, a Vanderbilt University researcher, was among the first grantees funded in 2012 through the Tissue Chip program.

Organs in the body do not work in isolation but receive chemical signals, called hormones, from other organs. While Tissue Chip program researchers are working to connect different tissues and organs on a chip to model a whole system, it is not yet feasible to model and connect every organ in the body. The Vanderbilt investigator realized that he could engineer a series of pumps, valves and tubing to deliver hormones or nutrients to a tissue chip, essentially standing in for a missing organ. This approach sparked the idea for the MicroFormulator, which enables researchers to mix and deliver small

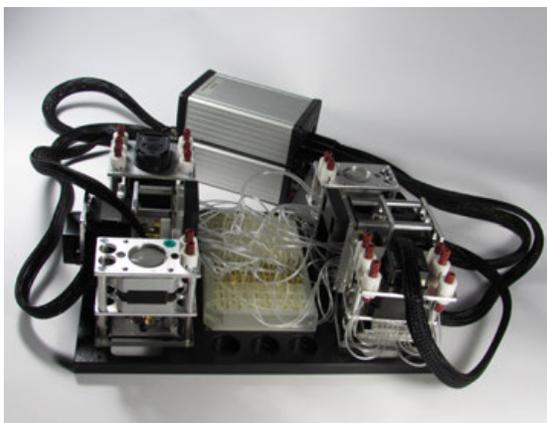
amounts of drugs or other solutions to laboratory cell models quickly and automatically.

After hearing about the MicroFormulator at a conference, AstraZeneca became interested in adapting the device to address another challenge in drug development: accurately mimicking, in a laboratory testing dish, how drug concentrations rise and fall in the bloodstream (also known as a pharmacokinetic profile). AstraZeneca realized the MicroFormulator could raise or lower a cell's exposure to a drug in a timed fashion, simulating a real-world pharmacokinetic profile. But the company wanted the device adapted to a standard 96-well high-throughput screening plate so that multiple profiles could be tested at the same time.

In 2016, NCATS awarded SBIR funding to the CFD Research Corporation in Huntsville, Alabama, to adapt the screening plate. This award supported hardware development as well as a computer programmer who created the software to control the pumps and valves. The resulting MultiWell MicroFormulator enables researchers to independently add and remove solution in each well so that 96 experiments can run at the same time. The transformative potential of the new device was acknowledged with an R&D 100 Award, commonly referred to as the "Oscars of Innovation," from *R&D Magazine* in late 2017. What's more, the MultiWell MicroFormulator project soon achieved the ultimate goal for SBIR awards: commercialization. In 2017, the U.K. biotechnology company CN Bio Innovations licensed the device.

NCATS provided additional SBIR support in 2017 for the same Vanderbilt investigator to adapt the technology for better care and maintenance of 3-D bioprinted tissues. The NCATS 3-D Tissue Bioprinting team creates human tissue from cells, printing them on standard cell plates to use for drug screening. But growing tissues in plates

rather than on chips has challenges. Tissue thickness requires laboratory staff to repeatedly change the solution in which the cells grow to supply the tissue with fresh nutrients and remove waste. The process is time-consuming, and removing the cells from the incubator exposes the tissues to stressful changes in temperature. These stresses affect how well the cells mature into the desired tissue. The new SmartLid device changes the tissue's nutrient liquid environment automatically and continuously and keeps the tissues at their preferred temperature and oxygen level without the stress of removal from the incubator, which saves researchers time and leads to a more reproducible, consistent process.



The SmartLid device, created through a Small Business Innovation Research award and delivered to NCATS' 3-D Tissue Bioprinting Laboratory, automatically and continuously changes the solution in which bioprinted cells grow in the incubator, which enables better cell growth. (Vanderbilt University Photo)

Igniting International Collaborations

Recognizing that translation is a global effort, NCATS partners with organizations worldwide across scientific sectors, as demonstrated in these examples:

- **Rare Disease Research as a Global Imperative.** Rare diseases are estimated to affect more than 350 million people worldwide, making understanding and treating these disorders a global imperative. The International Rare Diseases Research Consortium (IRDiRC) brings together national and international government and nonprofit agencies, patient advocacy organizations, companies (including pharmaceutical and biotechnology enterprises), and scientific researchers to promote international coordination, enhance collaboration and advance rare diseases research on a global scale. During his three years as chair of IRDiRC, the NCATS director led the development and release of an ambitious vision for the field and a [new set of goals](#) for the consortium for the next decade.
- **New Approaches to Fight Disease-Causing Parasites and Bacteria.** NCATS and University of Tokyo scientists have [identified the first molecule](#) that blocks the activity of an enzyme common to certain parasites and bacteria that can cause devastating infectious diseases, such as river blindness. Previous approaches to finding a drug or molecule that would react or bind to the enzyme had repeatedly failed, leading to the conclusion that the target enzyme was “undruggable.” To overcome this challenge, the Tokyo team created a library of more than 1 trillion small protein fragments (peptides) that NCATS scientists reasoned would better fit the enzyme's unusual shape. After the researchers sorted through the vast library to find a small number of candidate peptides, scientists in NCATS' [Assay Development and Screening Technology](#) laboratory identified two that could shut down the enzyme. The finding, reported in the [April 3, 2017, issue of Nature Communications](#), could set the stage for new types of antimicrobial drugs.

Strategic Goal 3: Developing the Translational Workforce

NCATS supports training and career development programs that provide the skills, knowledge and perspectives critical for the success of tomorrow's translational science workforce. For example, through NCATS' CTSA Program, biomedical research institutions support training opportunities for new and established researchers. They also provide other innovative types of training opportunities, such as "externships" or sabbaticals, where investigators experience a different research environment, either at another CTSA Program hub or at a pharmaceutical company.

Offering Industry Externships: The NCATS-Eli Lilly and Company externship program pairs CTSA Program scholars, trainees and investigators with a mentor at the pharmaceutical company Eli Lilly. There, externs are fully embedded in a project team to enhance academic translational researchers' skills in drug development. [One such extern is Josephine Taverna, M.D.](#), a clinical breast cancer researcher at the University of Texas Health Science Center at San Antonio.

Taverna worked with a team at Eli Lilly to develop a computer model simulating how tau, a key protein in the brain, behaves — and misbehaves — in people with Alzheimer's disease. The technique, called quantitative systems pharmacology, uses large amounts of data from cell and animal studies and from patients to build a mathematical model of a disease system. Once researchers complete a computer model, they can use it to show the effects of using a drug to target a specific part of a disease system. The goal is to find an effective therapy for Alzheimer's disease.



Josephine Taverna, M.D., presented on her externship project to NCATS staff and leadership in February 2018. From left to right: Christopher P. Austin, M.D., director of NCATS; Joan Davis Nagel, M.D., M.P.H., medical officer in the NCATS Division of Clinical Innovation (DCI); Danise Subramaniam, Ph.D., senior director of global regulatory affairs at Eli Lilly; Taverna; and Michael G. Kurilla, M.D., Ph.D., director of DCI.

Supporting Mini-Sabbaticals: Some CTSA Program hubs offer "mini-sabbaticals," short career development experiences at other partnering institutions that can be completed in as little as a week. These experiences are designed to complement the training that scholars and trainees receive at their home institutions. In 2018, NCATS awarded administrative supplements to the University of Alabama at Birmingham, University of Massachusetts Amherst and New York University, with the goal of determining best practices for these sabbaticals and to expand their use across the CTSA Program.

Cultivating the Translational Workforce: The CTSA Program supports longer training opportunities for early-stage investigators through the [KL2 Mentored Clinical Research Scholar awards](#), which combine formal coursework with

a rich research experience in a multidisciplinary setting. KL2 scholars come from a range of backgrounds; many are clinicians interested in pursuing research but who do not have sufficient training or the time to devote to such endeavors.

For example, Faheem Guirgis, M.D., an emergency department physician at the University of Florida (UF), was fascinated with the science underlying sepsis — an illness resulting from bloodstream infections — during his medical residency. Guirgis [became the first recipient of a KL2 award](#) at the UF College of Medicine at Jacksonville. Through the program, he connected with mentors among the faculty at the UF Sepsis and Critical Illness Research Center in Gainesville, more than 70 miles away. The KL2 award provided dedicated time for research and enabled Guirgis to take advantage of distance-learning opportunities covering topics such as research methods and laboratory techniques.

With his mentor's guidance and his pilot data from the program, Guirgis developed a sophisticated, successful application for an NIH Mentored Patient-Oriented Research Career Development award. With that support, Guirgis has now made the leap from clinician to clinician-scientist.

NIH's National Institute of Dental and Craniofacial Research (NIDCR) also collaborated with NCATS to expand the CTSA Program KL2 training opportunities to investigators interested in conducting research relevant to oral, dental and craniofacial research. NIDCR provided supplemental funding to [support KL2 awards for five investigators](#) in 2017.

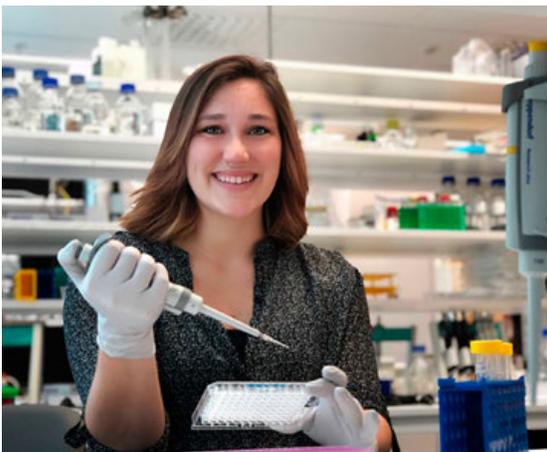
Igniting the Translational Spark for New Investigators: NCATS offers a range of training opportunities for research in its own laboratories, such as sponsoring talented Ph.D. students through the [NIH Graduate Partnerships Program](#). These exceptional students split their time



University of Florida (UF) Assistant Professor of Emergency Medicine Faheem Guirgis, M.D., FACEP, and Scientific Research Manager Ricardo Ungaro work with samples in the UF Sepsis and Critical Illness Research Center. (University of Florida Photo)

between an NIH intramural laboratory and a host university, receiving mentorship and guidance from researchers at both locations to [accelerate their training and benefit from international collaborations](#). For example:

- **Dorian Cheff** is working to find molecules that block an enzyme known to help cancers survive drug or radiation treatment. The goal is to find a treatment to make brain and other cancers more sensitive to existing drugs. At her Karolinska Institutet laboratory in Sweden, she is creating an assay (test) to identify molecules that stop the enzyme glutathione peroxidase from working. Once she has refined the test, she will bring it back to her mentor's laboratory at NCATS, using the Center's collections of chemicals and molecules and high-throughput screening resources to rapidly identify potential therapies.
- **David Morse, M.Phil.**, is developing new techniques to study what genes are turned on in individual tumor cells. Using the technique



Dorian Cheff is a graduate student in a collaborative doctoral program between NCATS and the Karolinska Institutet in Sweden. (Karolinska Institutet/Qing Cheng)

that he helped develop through his work at Cambridge University and at NCATS, along with collaborators at the Broad Institute and Harvard University, Morse found that tumor cells in the center of an ovarian tumor are different from those on the tumor's surface. Because the surface cells are more accessible to potential treatments, these results could help researchers design better drugs or ways to deliver existing drugs to ovarian tumors. Morse is now working to improve the new technique to track and pinpoint precisely where each cell was in the tumor at the time of data collection.

- **Kimberly Breglio, D.Phil.**, worked with mentors at NCATS and the University of Oxford to determine possible ways the malaria parasite becomes resistant to drugs. She found a gene, *ATG18*, that seemed to be

altered in many resistant parasites. Breglio used gene-editing tools to create malaria parasites that had an altered *ATG18* gene so she could study them in the lab. She screened the parasites against NCATS' [compound collections](#) to try to understand why the altered gene seems to be beneficial to the parasite. Her work will help researchers understand how malaria parasites survive stress, such as exposure to a drug. Breglio is now completing her medical degree and plans to use her research skills as a clinical investigator to study how tropical diseases affect the skin.

Sharing Knowledge: NCATS places great emphasis on knowledge dissemination and education as well as on creating a community that welcomes new investigators who learn from each other to advance the field. A principal resource in NCATS' educational toolbox is the [Assay Guidance Manual](#) (AGM), a free online guide for developing robust tests for drug discovery. More than 100 scientists have contributed to the 46 chapters currently included in the AGM. The resource is widely accessed by scientists in the pharmaceutical and biotechnology sectors, government and academic research laboratories: Use of the AGM has risen steadily from about 4,000 visits per month in 2012 to more than 30,000 visits per month in 2017.

NCATS also led six AGM training workshops around the country in 2017 and 2018. High attendance by industry, academic and government scientists demonstrated the desire for such in-person, hands-on training, which [NCATS now makes available online](#). The history, progress and future of the AGM were discussed in an article in the [Sept. 11, 2018, issue of *Clinical and Translational Science*](#).

Strategic Goal 4: Enhancing Stewardship

NCATS is a steward of public resources and, as such, has the responsibility to deploy those resources in the most effective manner. This requires not only supporting innovative research but also fostering continuous improvement in operations to enhance scientific stewardship. NCATS works with employees, awardees and partners throughout the government and beyond to leverage available resources toward the development, demonstration and dissemination of medical interventions.

Optimizing Internal Operations and Business Practices

NCATS fosters an open and collaborative working environment with flexible approaches to best address and manage scientific, operational and administrative change. This approach includes optimizing internal organization and infrastructure, including technology systems, and encouraging innovative approaches to internal operating procedures.

Responding Nimblely: The Cures Acceleration Network (CAN) is an authority created by Congress to advance the development of high-need cures and to address significant barriers between research discovery and clinical trials. The NIH Office of the Director transferred CAN to NCATS when the Center was established in late 2011. CAN includes Other Transaction Authority (OTA), a research support mechanism that provides flexibilities that significantly improve stewardship compared to NIH's traditional business transactions associated with grants, contracts or cooperative agreements.

Currently, NCATS uses OTA to support its [Biomedical Data Translator](#) program. With CAN and OTA, NCATS is supporting research to develop a groundbreaking computational tool that enables connections among conventionally separate data types. Once completed, Translator will be able to draw on data sources ranging from air quality measurements to electronic health records. Translator not only needs to be able to comprehend a user's query, but it must then be able to find the relevant knowledge sources, extract the right information and piece the information together into a narrative that the user can understand. Each of those tasks is a difficult problem on its own, and creating such a reasoning tool requires bringing together people with diverse expertise.

NCATS' use of OTA has been highly effective for nimble management of awards. Using the flexibilities afforded by this mechanism, NCATS was able to guide groups of scientists who submitted independent applications to work together as a unified team. In addition, the Center was able to invest quickly in a new scientific opportunity that arose in the program by taking unspent funds from one OTA award and moving them to another award.

In August 2017, to find the right teams to work on the reasoning tool prototype, NCATS used an unusual funding approach enabled by OTA. Candidates interested in applying for Translator funding first had to complete a series of computational tasks before they could access the application instructions. The tasks were designed to provide important background and insights



Scientists collaborate at the January 2018 NCATS Translator Data Hackathon. From left to right: Greg McInnes, Stefano Rensi, Margaret Guo, Adam Lavertu, Matt Brush, and Tyler Peryea. (Oregon Health & Science University Photo)

for building the tool prototype. Completing the tasks required candidates to pull together relevant expertise, and, at the same time, familiarize themselves with the Translator program. The tasks also enabled NCATS to determine whether applicants had the required skills to build a reasoning tool.

Managing Data and Protecting Privacy:

A single experiment by NCATS scientists can generate terabytes of data. In 2016, most of the vast amounts of data NCATS maintained was housed on servers at the Center. But as the amount of data grew, NCATS staff undertook a focused review of data management strategies. This effort included performing cost-benefit analyses and looking at use cases to determine which data to move to the cloud. As a result, NCATS moved much of its data to cloud services in 2017 and 2018, with more planned for 2019, saving the Center money and making more effective use of public resources.

Privacy and security are front and center to NCATS' data strategy. In 2017, NCATS underwent its first official security assessment since the

Center was established. The assessment helped determine whether there were sufficient hardware, software and personnel security safeguards and whether a particular system meets Department of Homeland Security requirements. Often, assessments result in an authorization to operate for a year, but based on the thoroughness of NCATS' security strategy, it received authorization for the maximum of three years. The NCATS Chief Information Officer discussed NCATS' data strategy in an [Aug. 28, 2018, interview on Federal News Radio](#).

Reducing Costs and Waste: Back in 2010, staff at what is now the NCATS high-throughput screening facility noticed how quickly plastic plates were piling up in the waste bin. These plates are used to test thousands of drugs and chemical compounds to gain insights about a range of human diseases. The [team developed a method to clean and re-use the plates](#), demonstrating value by saving NCATS nearly half a million dollars and keeping nearly 50,000 plates out of landfills.

In 2013, NCATS awarded a Phase I SBIR contract to IonField Systems in Moorestown, New Jersey, to develop and commercialize an automated plate cleaner based on technology initially developed at NCATS. With a follow-on Phase II award, IonField built on the process, creating an automated plate-washing system. In January 2018, AstraZeneca and IonField Systems announced the successful completion of the PlasmaKnife Microplate Cleaning System beta test and the first installation of a commercial release. The PlasmaKnife is being used at the company's Alderley Park Research Facility and will later be used at a new Cambridge Research Facility.

The creation of the plate-cleaning technology aligns perfectly with the NCATS "3 Ds" approach to translational science: NCATS **developed** an innovative solution to address a translational problem and then **demonstrated** that the

approach worked and could save time, money and environmental waste. In a short amount of time, the technology has been **disseminated** to benefit the larger scientific community.

Fostering Complementary Connections

NCATS strives to eliminate redundancy where possible to streamline the translational process. This includes identifying and taking advantage of complementary NCATS resources and programs to advance a project in which the Center has invested. For example, a project funded through NCATS' CTSA Program also received support through the Center's New Therapeutic Uses program for pre-clinical development to more efficiently move a new approach to treating infection into clinical trials.

The bacterium *Clostridium difficile* is a major cause of antibiotic-associated diarrhea and a leading infectious disease in U.S. hospitals. The infection, which can be fatal, recurs in around a quarter of people following treatment. Many of these people, especially older adults who are at the greatest risk of dying from the infection, undergo cycles of treatment and infection for months or years.

In 2015, a Vanderbilt University Medical Center researcher suspected that the drug misoprostol, approved by the FDA to prevent stomach ulcers, also could help prevent recurrence of *C. difficile* infection. Through the Vanderbilt Institute for Clinical and Translational Research (VICTR), a CTSA Program hub, the researcher and his team accessed a biobank of patient samples and health information that researchers can use to look for links between certain genes and diseases or conditions. People with variants in genes that are the targets of misoprostol were more likely to have intestinal disorders similar to *C. difficile* infection, which indicated that misoprostol may help prevent recurrence of the infection.

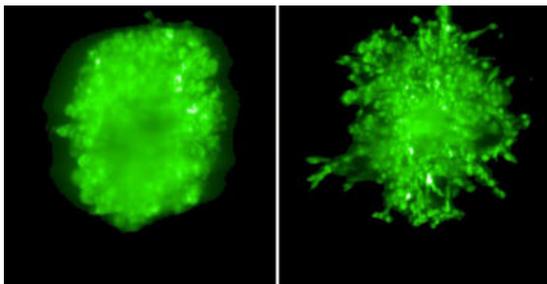
The Vanderbilt team received funding through NCATS' New Therapeutic Uses program in 2016 to test the new idea in a mouse model of *C. difficile*. And it worked: Misoprostol dramatically reduced the severity of *C. difficile* colitis in mice, suggesting it might be beneficial in people. With NCATS support, the team began work to determine the optimal amount and timing of the drug. Based on these pre-clinical studies and the drug's existing safety data, the FDA gave the green light for a clinical trial on misoprostol to prevent recurrent infections in patients with *C. difficile*.

The Vanderbilt team reached out to two other CTSA Program hubs — the University of North Carolina at Chapel Hill and Washington University in St. Louis — to conduct a multisite trial. To design the study, the team took advantage of the VICTR studio program, which brings together diverse perspectives to discuss anything from a grant application to community engagement. During the studio, the research team heard from biostatisticians, bioinformaticians and clinicians with decades of experience designing and running clinical trials.

Supported through a [second award from the New Therapeutic Uses program](#), the multisite trial began in fall 2018. The objective is to test whether giving misoprostol to patients after they are treated for their initial attack of *C. difficile* colitis prevents the infection from coming back. If successful, the repurposed drug represents a cost-effective strategy to treating a life-threatening disease. Best of all, because the drug does not target the bacteria but instead makes the intestine more resistant to infection, it could be repurposed for other diarrheal infections.

Sharing Data and Disseminating Knowledge

NCATS expands the reach of its efforts by proactively creating and sharing resources,



RNAi screening of 3-D breast cancer cells. After different genes are turned off — or “silenced” — cancer cells are placed in a gel that mimics the extracellular matrix, which surrounds and supports cells in the body, to see whether the cancer cells can still invade the matrix. The right panel shows that silencing a gene that chews up the matrix prevents the cells from invading. The left panel shows that silencing another gene has no effect on the cells’ ability to invade.

methodologies, operational models, tools and data as well as new approaches to facilitate sharing and collaboration.

Finding New Targets for Therapeutics

Development: One approach to finding new treatments to diseases is to first identify a drug target, which is a vulnerability in the disease that scientists can exploit. To find new drug targets, researchers can use a biological process called RNA interference (RNAi) that turns off, or silences, a gene. Researchers can then see how silencing the gene affects the diseased cells. Investigators can conduct RNAi experiments on hundreds of different genes at a time using high-throughput screening available at NCATS’ [Trans-NIH RNAi Facility](#) (TNRf). NCATS scientists help other NIH researchers use this type of screening approach to better understand gene function and identify new drug targets.

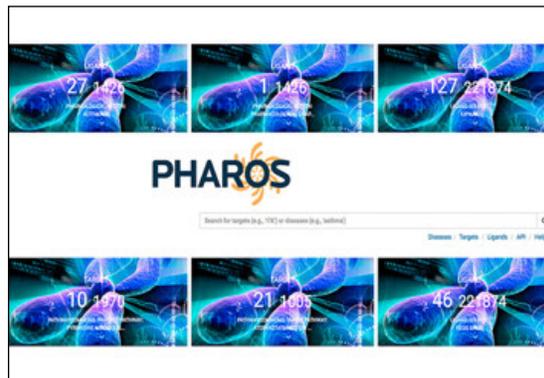
NCATS scientists have also developed complementary screening approaches that can be used with the RNAi screening platform. For

example, they recognized that the typical 2-D cancer cells that are screened may not accurately model a tumor and its microenvironment. This limits how useful RNAi screens are for finding new cancer drugs. To address this challenge, the facility team developed methods to turn off genes in 3-D cancer cells, which are essentially a ball of cells. They then compared what happens when genes are turned off in 2-D cells versus 3-D cells for colorectal and breast cancer. The study, published in the [June 2017 issue of *SLAS Discovery*](#), showed differences in which drug targets were identified and suggested that 3-D cells may be more accurate.

In 2017 and 2018, TNRf researchers received NIH Deputy Director of Intramural Research Innovation Awards to incorporate a newer gene-editing tool called CRISPR into the facility and make it available to the scientific community. Researchers can use CRISPR genome editing to completely remove a gene from a cell, ensuring it has no activity. In contrast, RNAi may enable a little of the gene product to be made. The TNRf team is also using the awards to conduct pilot studies and to develop methods to overcome technical challenges to running CRISPR screens, especially in 3-D spheroids. By piloting studies on methods and sharing best practices for RNAi and CRISPR screens, NCATS is promoting adoption of these cutting-edge techniques by the wider scientific community.

Closing the Protein Knowledge Gap: About 3,000 of the approximately 20,000 genes in the human genome encode proteins that scientists can manipulate or “drug” with small molecules or biologics, making these proteins potential therapeutic targets. However, only a small fraction of these targets has been well-studied with findings that resulted in FDA-approved drugs. Clearly, an opportunity exists to shed more light on these other druggable proteins.

The NIH Common Fund's [Illuminating the Druggable Genome](#) (IDG) program is designed to improve scientific understanding of understudied protein families in the druggable genome. To facilitate progress, NCATS scientists developed [Pharos](#), an online interface that provides access to the protein information collected by IDG investigators. The interface is designed to be easily accessible and promote discovery, helping the entire research community make progress on unstudied or understudied drug targets, with the ultimate goal of closing the protein knowledge gap and finding new therapies. Pharos was described in the [Jan. 4, 2017, issue of *Nucleic Acids Research*](#). In recognition of its pioneering potential, Pharos was selected as a finalist for the 2018 Society for Laboratory Automation and Screening Innovation Awards.





Appendix: Statutory Language on Biennial Report

Public Health Service Act

Section 479 NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

(c) BIENNIAL REPORT.—The Center shall publish a report on a biennial basis that, with respect to all research supported by the Center, includes a complete list of—

- (1) the molecules being studied;
- (2) clinical trial activities being conducted;
- (3) the methods and tools in development;
- (4) ongoing partnerships, including—
 - (A) the rationale for each partnership;
 - (B) the status of each partnership;
 - (C) the funding provided by the Center to other entities pursuant to each partnership, and
 - (D) the activities which have been transferred to industry pursuant to each partnership;
- (5) known research activity of other entities that is or will expand upon research activity of the Center;
- (6) the methods and tools, if any, that have been developed since the last biennial report was prepared; and
- (7) the methods and tools, if any, that have been developed and are being utilized by the Food and Drug Administration to support medical product reviews.

(d) INCLUSION OF LIST.—The first biennial report submitted under this section after the date of enactment of the 21st Century Cures Act shall include a complete list of all of the methods and tools, if any, which have been developed by research supported by the Center.

(e) RULE OF CONSTRUCTION.—Nothing in this section shall be construed as authorizing the Secretary to disclose any information that is a trade secret, or other privileged or confidential information subject to section 552(b)(4) of title 5, United States Code, or section 1905 of title 18, United States Code.

Responses to Required Information

<p>(1) the molecules being studied</p>	<p>The NCATS Pharmaceutical Collection is a comprehensive collection of approved and investigational drugs for high-throughput screening that provides a valuable resource for both validating new models of disease and better understanding the molecular basis of disease pathology and intervention. The resource consists of a physical collection of drugs and an information browser and database. Access to the collection is provided through the Therapeutics for Rare and Neglected Diseases program and Toxicology in the 21st Century initiative, and instructions are available. Sources for the current collection include traditional chemical suppliers, specialty collections, pharmacies and custom synthesis.</p> <p>All data generated by the NCATS Chemical Genomics Center are deposited in PubChem, supported by NIH's National Library of Medicine. PubChem consists of three dynamically growing databases. Please select a link below to view a current list:</p> <ol style="list-style-type: none"> 1. PubChem Compound: Contains pure and characterized chemical compounds. 2. PubChem Substance: Contains mixtures, extracts, complexes and uncharacterized substances. 3. PubChem BioAssay: Contains database results from high-throughput screening programs with several million values.
<p>(2) clinical trial activities being conducted</p>	<p>ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.</p> <p>View studies for which NCATS is a sponsor/collaborator.</p> <p>View a list of clinical research studies being supported by NCATS' Rare Diseases Clinical Research Network.</p>
<p>(3) the methods and tools in development</p>	<p>This report highlights many of NCATS' ongoing efforts to develop methods and tools that will improve the translational research process. View a complete list of all active projects funded by NCATS.</p>
<p>(4) ongoing partnerships, including—</p> <p>(A) the rationale for each partnership;</p> <p>(B) the status of each partnership;</p>	<p>(A and B) The Therapeutics for Rare and Neglected Diseases (TRND) program stimulates therapeutic development research collaborations among NIH and academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies working on rare and neglected illnesses. The program provides expertise and resources, working with research partners to move therapeutics through pre-clinical testing, including plans for clinical trials and submission of an Investigational New Drug (IND) application to the Food and Drug Administration (FDA). These efforts effectively “de-risk” therapeutic candidates and make them more attractive for adoption by outside business partners. View a description of each project, including the partners.</p>

<p>(C) the funding provided by the Center to other entities pursuant to each partnership, and</p> <p>(D) the activities which have been transferred to industry pursuant to each partnership;</p>	<p>The Bridging Interventional Development Gaps (BrIDGs) program enables research collaborations to advance candidate therapeutics for both common and rare diseases into clinical testing. View a description of each project, including the partners.</p> <p>(C) Investigators do not receive grant funds through the TRND or BrIDGs programs. Instead, selected researchers partner with NCATS experts to generate pre-clinical data and clinical-grade material through government contracts for use in IND applications to a regulatory authority such as the FDA.</p> <p>(D) Details regarding completed TRND and BrIDGs projects, including those which have been transferred to industry, are available. Review the Outcomes sections of completed TRND projects and completed BrIDGs projects.</p>
<p>(5) known research activity of other entities that is or will expand upon research activity of the Center</p>	<p>NIH investigators frequently conduct PubMed searches on areas of research interest. However, NIH does not conduct competitive intelligence on for-profit entities.</p>
<p>(6) the methods and tools, if any, that have been developed since the last biennial report was prepared</p>	<p>Small molecule chemical compounds, which can be used to test or “probe” the effects of increasing or decreasing the activity of a biological target in cells or animals, are some of the most powerful tools for target validation, which is the process of demonstrating that engaging a target provides meaningful therapeutic benefit. Probes enable researchers to investigate protein and cell functions and biological processes. If appropriate, probes can be optimized to become potential drug candidates. Generating these chemical probes requires specialized expertise and facilities, and the NCATS Chemical Genomics Center (NCGC) provides world-leading collaborative services to meet these needs. Collaborators work with NCATS scientists in NCGC to develop screens against promising drug targets and to refine these results into small molecule probes and potential therapies.</p> <p>View a list and descriptions of the assays (tests) developed through NCGC.</p>
<p>(7) the methods and tools, if any, that have been developed and are being utilized by the Food and Drug Administration to support medical product reviews.</p>	<p>The Global Ingredient Archival System (ginas) resource is a registration system for the ingredients in medicinal products. This project, developed by NCATS scientists, makes it easier for regulators and other stakeholders to exchange information about substances in medicines, supporting scientific research on the use and safety of these products.</p> <p>The main goal of ginas is the production of software, called G-SRS, to assist agencies in registering and documenting information about substances found in medicines.</p> <p>Staff from the Food and Drug Administration (FDA) and regulatory authorities from several other countries work together with NCATS on G-SRS software development. FDA deployed G-SRS software in 2017 as a replacement for the agency’s previous registration system. In addition, the European Medical Agency has committed to using the G-SRS software.</p> <p>View the ginas resource.</p>

