

Public Health



Basic Research



Patient Involvement



Clinical Implementation



Clinical Research



Pre-Clinical Research

2016 REPORT

National Center for Advancing Translational Sciences

Improving Health Through Smarter Science



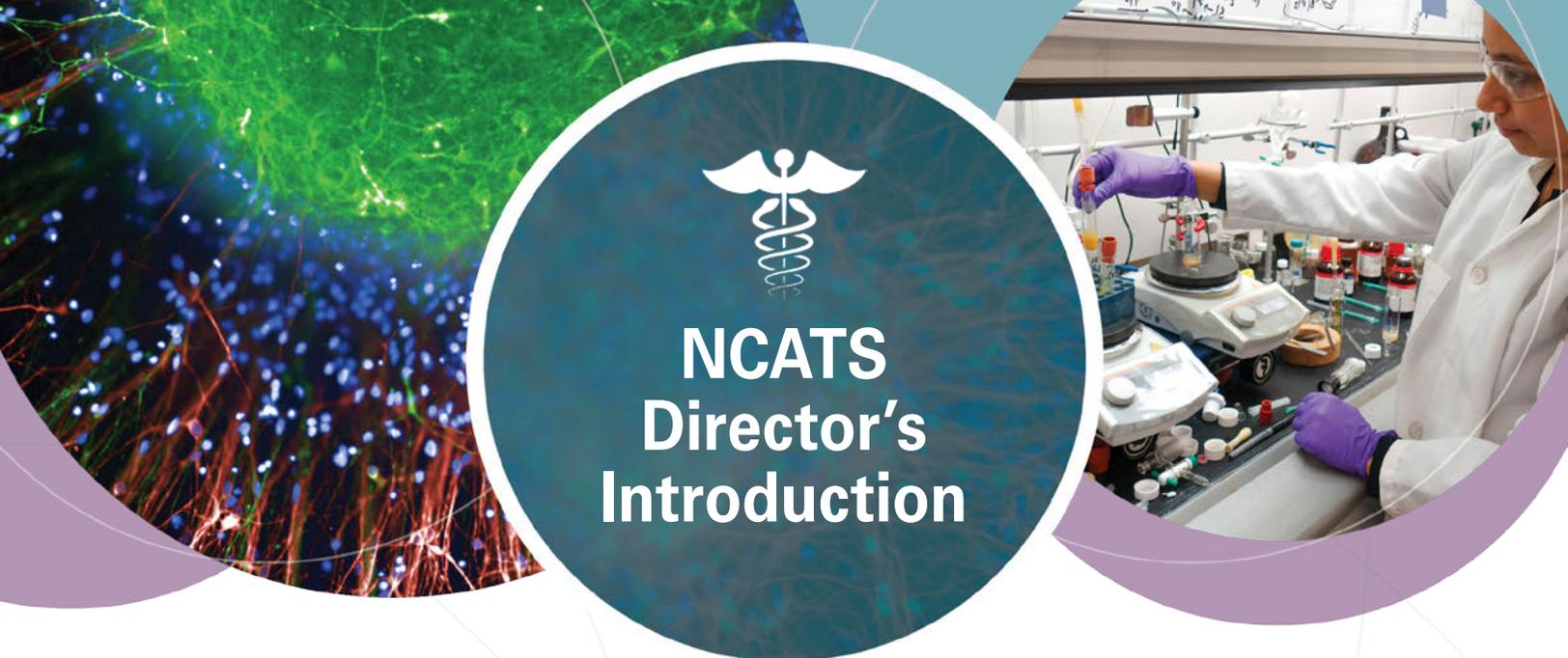


Cover Image: NCATS' **translational science spectrum** represents each stage of research along the path from the biological basis of health and disease to interventions that improve the health of individuals and the public. The spectrum is not linear or unidirectional; each stage builds upon and informs the others. At all stages of the spectrum, NCATS develops new approaches, demonstrates their usefulness and disseminates the findings. Patient involvement is a critical feature of all stages in translation.

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NCATS Director's Introduction



Christopher P. Austin, M.D.

The National Center for Advancing Translational Sciences (NCATS) conducts and supports research on the science and operation of translation — the process by which interventions to improve health are developed and implemented — to allow more treatments to get to more patients more quickly.

Since our founding five years ago, we have made enormous strides in advancing our unique mission, and this 2016 NCATS report provides a snapshot of these accomplishments.

At the time of NCATS' [fifth anniversary](#) in late 2016, I observed that the Center's team-based "3Ds" paradigm of **d**eveloping, **d**emonstrating and **d**isseminating new technologies and approaches that address major translational roadblocks has produced insights and advances well beyond what I thought would be possible five years ago. That progress set the stage for the ambitious vision portrayed in our new [Strategic Plan](#), which sets the course for NCATS' future and explores the enormous opportunities and challenges in our young field of translational science. Read more about our plan on [page 5](#).

Authorized to reduce significant barriers to successful translation and accelerate the development of high-need cures, NCATS' [Cures Acceleration Network](#) (CAN) provides the flexibility to fund truly transformational approaches to some of the most vexing problems in translational science. In spring 2016, NCATS launched its first signature program within CAN, the [Biomedical Data Translator](#) (a.k.a. "Translator"). The aim is to comprehensively connect all of the diverse data types needed to traverse the translational spectrum, from genes to organs to diseases to drugs. NCATS used the special authorities provided through CAN to assemble a team of collaborators of unprecedented expertise from two dozen institutions nationwide, including program scientists from the Center. By enabling discovery of complex relationships among currently siloed data types, Translator will help scientists better understand connections among diseases and develop new treatments for patients. Read more on [page 30](#).

Through its [Division of Pre-Clinical Innovation](#), NCATS is propelling scientific advances in the early stages of translation from target validation through first-in-human studies, and establishing and disseminating new principles of translational science that catalyze progress across target classes and diseases. On [page 6](#), read about a remarkable collaboration on Gaucher disease research, which established new ways of screening for drugs, new cellular models of human disease that are more predictive of effects in the body, and a new

type of drug mechanism — all of which led to a biotechnology company adopting the project for further development and then partnering with a larger biopharmaceutical partner to move the drug into human clinical trials.

The NCATS [Clinical and Translational Science Awards \(CTSA\) Program](#) is designed to catalyze innovation in the later stages of translation from studies on the mechanisms of human disease to clinical trials of new interventions to application and adherence of health solutions in the community. As part of this program, the [Trial Innovation Network](#) brings together diverse medical research institutions from across the country to address roadblocks in clinical translation and to develop and test innovations that will effectively turn new interventions into therapies. The goal is not only to execute trials better, faster and more cost-efficiently, but also to be a national laboratory to study, understand and innovate the processes for conducting multisite studies. The network will launch its first collaborative clinical trials with NIH Institutes and Centers (ICs) and other partners in 2017.

Also in 2016, the Center launched the [NCATS Streamlined, Multisite, Accelerated Resources for Trials \(SMART\) Institutional Review Board \(IRB\) Platform](#), which provides flexible resources to harmonize and streamline human subjects reviews for multisite studies. In addition to being a critical component of the nationwide CTSA Program Trial Innovation Network, the NCATS SMART IRB Platform is now serving as a roadmap to implementing the new [NIH-wide policy](#) that expects all NIH-funded multisite clinical studies to use a single IRB. Read more on [page 16](#).

NCATS is transforming translation into a predictive science for the benefit of patients. I hope you enjoy learning more in the following pages about the many ways NCATS is improving health through smarter science.

Christopher P. Austin, M.D.

Director
National Center for Advancing Translational Sciences
National Institutes of Health



NCATS Strategic Plan



In November 2016, NCATS released a bold new [Strategic Plan](#) organized into four overarching themes: advancing translational science, fostering innovative partnerships, developing the translational workforce and enhancing stewardship. Within these themes are NCATS' goals, specific objectives and strategies that collectively provide an overview of what the Center plans to accomplish to achieve its mission of getting more treatments to more patients more quickly. NCATS' Strategic Plan — which is closely aligned with the [NIH-Wide Strategic Plan](#) — sets the stage for the Center's future and is a living document that will be adapted over time, as relevant, to the changing needs in translational science.

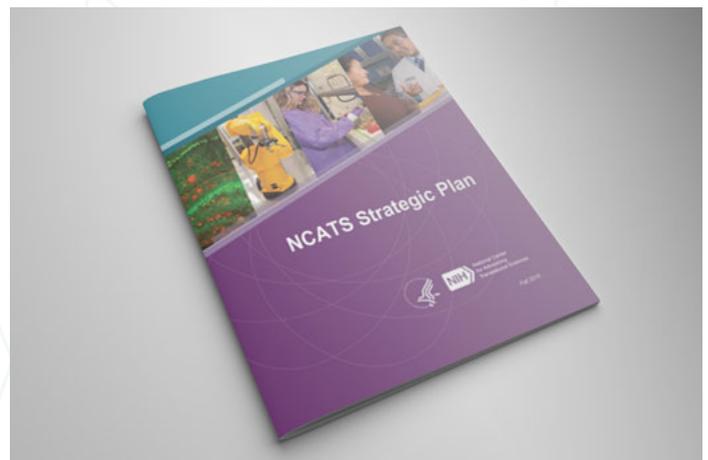
The plan also articulates NCATS' strategic principles, which represent the Center's philosophy:

Catalytic: NCATS is a catalyst that enables others to perform more efficient and effective translation.

Generalizable principles: NCATS uncovers fundamental principles shared among diseases and translational processes; widespread implementation of such generalizable principles will accelerate translation.

Innovative: NCATS programs lead to profound improvements in translational understanding and effectiveness, producing innovation that establishes fundamentally new ways of doing translation that are multiplicative in their effects.

Collaborative: Translational research endeavors require the expertise of multiple people and groups, particularly



The NCATS Strategic Plan is organized according to conceptual themes of translational science, collaborations, training and stewardship.

as the research is carried through different phases of the translational science spectrum. NCATS approaches translation as a “team sport.”

Patient focused: At all phases of translational science, NCATS is committed to patients and their communities and looks for opportunities to include the patient perspective. The ultimate goal of translation is tangible improvement in health, so the perspectives of and partnerships with patients are crucial.

Measurable: NCATS continuously improves translational effectiveness, so programs must be designed and implemented with explicit indicators of success for translational progress.



Pre-Clinical Innovation

NCATS is all about getting more treatments to more patients more quickly. This starts with improving the process of pre-clinical research, which connects the basic science of disease with human medicine. NCATS' pre-clinical programs and resources focus on key obstacles and inefficiencies in the translational process, overcoming bottlenecks that slow the development of new therapeutics. Through collaborations with industry, academia, patient advocacy and other nonprofit groups and in cooperation with other NIH Institutes and Centers (ICs) and government agencies, NCATS provides:

- Pre-clinical drug development expertise and access to resources;
- Assistance generating data needed for regulatory approval; and
- A variety of mechanisms to streamline partnerships and collaborations.

NCATS collaborates with investigators to study and develop compounds and molecules to further translational research. These resources, including the [NCATS Pharmaceutical Collection](#) and NCATS' [Compound Management](#) collection, are broadly available through NCATS' [Pre-Clinical Research Toolbox](#). Data derived from these sources can be found in the NIH's National Library of Medicine's [PubChem](#).

NCATS scientists create and test innovative methods and technologies that will enhance the development, testing and implementation of new drugs, diagnostics and other interventions. By improving the development process for these interventions, NCATS is making translational science more efficient, less expensive and less risky.

Assay Development and Screening Technology

NCATS is improving drug discovery and development efficiencies by studying general principles and processes applied in translational research and by identifying common traits across diseases. Scientists at the NCATS Chemical Genomics Center (NCGC) focus on validating new potential therapeutic approaches at the pre-clinical stage through the development of new assays, novel high-throughput screening methodologies and medicinal chemistry studies. Many of these approaches have the potential to accelerate the development of treatments for multiple diseases at once.

For example, NCATS and its collaborators at the NIH's National Human Genome Research Institute (NHGRI) found that a novel class of drugs developed for a rare genetic disease potentially could treat seemingly unrelated diseases. The discovery was the result of NHGRI initially asking NCATS for help in identifying and testing potential therapies for

High-Throughput Screening

High-throughput screening incorporates robotics, data processing and control software; liquid-handling devices; and sensitive detectors to enable scientists to conduct more than 100,000 chemical, genetic or biological tests in a single day. For these tests, the scientists access chemical libraries, made up of hundreds of thousands of chemical compounds, to assess the effects of each compound on the process of interest. The results of such experiments provide information that can be used for drug design and contribute to understanding the interaction or role of a particular biochemical process in biology.

De-Risking

Pre-clinical research, which connects basic scientific discoveries with initial testing of therapies in humans, is a failure-prone stage of translation. Innovations in translational science can substantially reduce the risks, time delays and costs of advancing basic research breakthroughs into treatments, an approach known as “de-risking.”

Gaucher disease, which belongs to a family of rare diseases called lysosomal storage disorders. Gaucher disease is an inherited disorder marked by enlargement of the liver and spleen, fatigue, anemia, nose bleeds, easy bruising and bleeding, and bone problems, with some patients also developing neurological problems. It is caused by mutations in the gene that codes for an enzyme, glucocerebrosidase (GCCase), which helps cells break down cellular waste.

In patients with Gaucher disease, defective GCCase impairs the functioning of specialized white blood cells called macrophages. Normally, macrophages travel around the body, engulfing dead cells, cell debris or pathogens such as bacteria. Once inside the macrophage, this cellular debris is shuttled to and stored in cell compartments called lysosomes. GCCase is produced in the cell and moves into the lysosome,

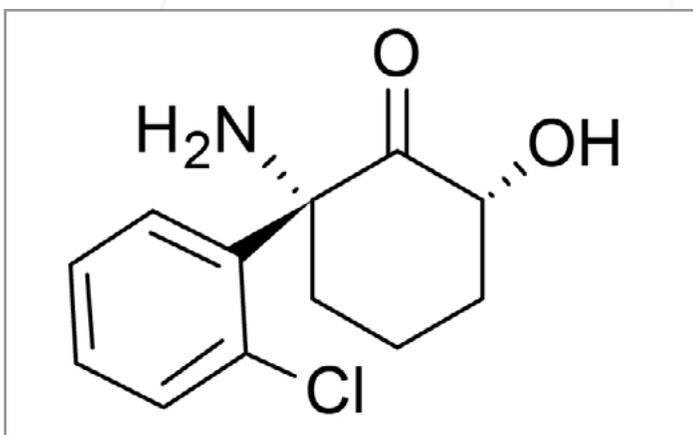
where it helps degrade debris so that the debris can be cleared from the body. In Gaucher disease, however, mutant GCCase is misshaped and disposed of before it can get to the lysosomes. As a result, undigested lipids (fatty substances) from dead cells accumulate in the lysosomes of cells in organs such as the liver, spleen, bone marrow and brain.

The NCATS and NHGRI researchers developed small-molecule chaperones that could attach to GCCase, helping to correct the misfolded mutant enzyme and facilitating its transport toward the lysosome to digest lipid waste. The team demonstrated their activity in stem cell-derived macrophages and neurons from Gaucher disease patients, reversing the disease features and returning the cells to normal.

NCATS played an important role in “de-risking” the project with the development of high-throughput assays and in working with collaborators to identify and optimize potential drug candidates. Based on this successful effort, a small biotechnology company licensed the intellectual property from NCATS and NHGRI to further develop the technology. The company selected its candidate for pre-clinical development toward human clinical trials.

The researchers thought that this class of compounds used in Gaucher disease research also might help correct underlying defects in other disorders. Clinical studies have shown that some Gaucher disease patients also develop parkinsonism, which involves symptoms and movement problems similar to those seen in Parkinson’s disease, such as trembling, stiffness of the limbs, slowness of movement and impaired balance. NCATS, in collaboration with NHGRI, published the discovery that small molecule chaperones of GCCase are also able to correct the defects of Parkinson’s disease neurons even in those cases where the patients are not affected by GCCase mutants, opening the door to the development of new treatments for Parkinson’s disease. The work was published in the [July 13](#) and [July 20, 2016](#), issues of the *Journal of Neuroscience*.

In another example of NCATS’ work to improve drug development, the Center’s [Chemistry Technology](#) scientists played a critical role in a study that found a chemical byproduct, or metabolite, created as the body breaks down



A team of NIH intramural scientists and grantees found that the antidepressant effects of ketamine are produced not by the drug itself but by one of its metabolites — a substance formed as the body breaks down ketamine. This beneficial metabolite, (2R,6R)-HNK, (above) does not cause the dissociative, euphoric effects associated with ketamine that underlie its potential abuse.

ketamine likely holds the secret to its rapid antidepressant action. NCATS' Chemistry Technology experts develop small molecules and screening approaches that other scientists can use to pursue innovations in therapeutic development.

In this case, a research team from the NIH's National Institute of Mental Health (NIMH), and National Institute on Aging (NIA), the University of Maryland School of Medicine, and the University of North Carolina recruited NCATS chemists to help isolate the specific ketamine metabolite of interest, (2R,6R)-HNK.

Clinical trials have shown that ketamine can lift depression in hours or even minutes — much faster than the most commonly used antidepressant medications now available, which often require weeks to take effect. Furthermore, the antidepressant effects of a single dose can last for a week or longer. Despite these therapeutic uses, ketamine can also have dissociative, euphoric and addictive properties, making it a potential drug of abuse and limiting its usefulness as a depression medication. In hopes of finding a more practical treatment, the research team sought to tease apart the effects of ketamine and its various metabolites.

The team found that (2R,6R)-HNK had antidepressant-like effects similar to ketamine's, lasting for at least three days in mice. Ketamine also has effects in mice that mimic its dissociative, euphoric effects in humans and underlie its abuse and addictive potential; however, the scientists did not observe these effects with (2R,6R)-HNK. A different molecular mechanism was found to be responsible for the metabolite's antidepressant effects, which may explain why (2R,6R)-HNK retains ketamine's antidepressant properties without the undesirable side effects. The team published these results in the *May 4, 2016, issue of Nature*.

In advance of an NIMH clinical trial in humans for the improved treatment of depression, the researchers are following up on their discovery with safety and toxicity studies of the metabolite.



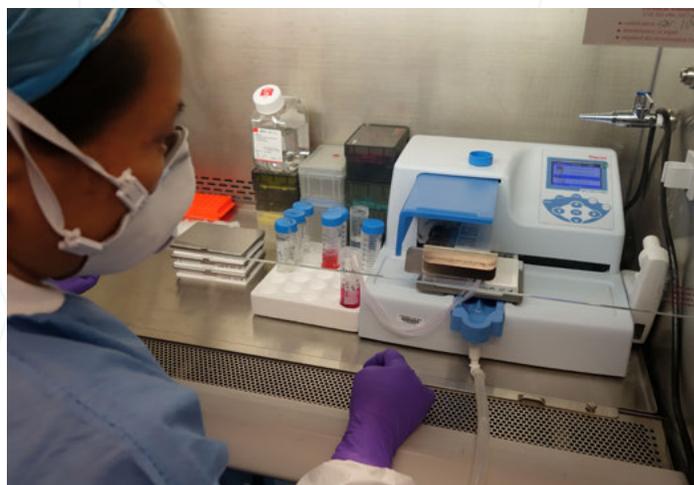
Repurposing Drugs



Discoveries about the molecular basis of disease provide unprecedented opportunities to translate research findings into new medicines. However, developing a brand-new drug takes an enormous amount of time, money and effort, mainly due to bottlenecks in the therapeutic development process. It is crucial to advance strategies that make the therapeutic development process more efficient and, therefore, more cost effective.

Drug repurposing, a process that enables researchers to find new uses for drugs (also called “agents”) that already have been approved by the Food and Drug Administration (FDA) or that have been advanced to clinical trials, is one such strategy. These agents approved for other uses already have been tested in humans, so detailed information is available on their pharmacology, formulation and potential toxicity. Because repurposing builds upon previous research and development efforts, new candidate therapies could be ready for clinical trials quickly, speeding their review by the FDA and, if approved, their integration into health care.

To enable repurposing on a broad scale, researchers can tap into the [NCATS Pharmaceutical Collection](#), a comprehensive database and screening library of investigational medicines and drugs approved for clinical use. Nearly 2,750 small molecular entities have been approved for clinical use by U.S., European Union, Japanese and Canadian authorities and also are suitable for high-throughput screening. NCATS currently has 2,500 of these small molecular entities, along



NCATS researcher Miao Xu, Ph.D., dispenses Zika virus into trays for compound screening.

with about 1,000 additional investigational compounds, as part of its screening collection.

The NCATS Pharmaceutical Collection is available in two forms: as a free electronic resource that lists each compound’s regulatory status and as a library of compounds used in high-throughput screening assays at the Center. The collection provides a valuable resource for both validating new models of disease and better understanding the molecular basis of diseases and interventions. It already has generated several useful probes for studying a diverse cross section of biology, including novel targets and pathways.

For example, using the NCATS drug repurposing platform and pharmaceutical collection for studying emerging infectious diseases can help [rapidly identify potential treatments for urgent conditions such as Zika infection](#). The Zika virus has been reported in 60 countries and territories worldwide; currently, there are no vaccines or effective drug treatments. The virus is spread primarily through bites from infected *Aedes aegypti* mosquitoes and also can be transmitted from mother to child. Infection by the Zika virus may be related to fetal microcephaly, an abnormally small head resulting from an underdeveloped and/or damaged brain. In addition, it is associated with neurological diseases such as Guillain-Barré syndrome in infected adults.

NCATS' [Therapeutics for Rare and Neglected Diseases \(TRND\)](#) program scientists, in collaboration with Zika researchers at Johns Hopkins University and Florida State University, used the Center's high-throughput screening platform to identify compounds that potentially could be used to treat Zika infection. Through its TRND program, NCATS provides expertise and resources, working with research partners to move therapeutics for rare and neglected diseases through pre-clinical testing. The goal is to "de-risk" therapeutic candidates and make them more attractive for adoption by outside business partners.

Using the pharmaceutical collection as well as additional compounds, the scientists screened 6,000 FDA-approved and investigational compounds for the ability to protect brain cells infected with Zika virus. A number of compounds were effective at either inhibiting the replication of the virus or preventing it from killing brain cells. The compounds include emricasan, an investigational drug currently being evaluated in a clinical trial to reduce liver injury and fibrosis; and niclosamide, an FDA-approved drug for use in humans to treat worm infections. The researchers also identified the anti-Zika virus activity of nine cyclin-dependent kinase (CDK) inhibitors, which are being investigated in clinical trials for various cancers, cystic fibrosis and Cushing's disease.

The research revealed that emricasan prevents cell death and that niclosamide and the CDK inhibitors stop the virus' replication. The team also found that emricasan, when combined with one of the CDK inhibitors, prevented both cell death and virus replication. In addition, the researchers noted that the niclosamide or CDK inhibitors might be useful in treating non-pregnant patients who face an increased risk

of Guillain-Barré syndrome and other conditions sparked by Zika infection. The study results were published in the [August 29, 2016, issue of *Nature Medicine*](#). These compounds now can be studied by the broader research community to help combat the Zika public health crisis.

NCATS' drug repurposing platform also proved useful for an infectious disease threat of growing concern: drug-resistant bacteria. In recent years, an alarming number of increasingly drug-resistant and sometimes life-threatening bacterial strains have begun to emerge, especially in the hospital setting.

To address this problem, NCATS' TRND scientists teamed with researchers from the National Institute of Allergy and Infectious Diseases and the NIH Clinical Center to develop an assay to rapidly screen 4,000 approved drugs and other biologically active compounds [to determine how effective they were against a variety of types of resistant bacteria](#). The compounds came from the NCATS Pharmaceutical Collection and a second, commercial library.

Twenty-five compounds suppressed the growth of two drug-resistant strains of *Klebsiella pneumoniae* that have become resistant to most major types of antibiotics. Drug-resistant *K. pneumoniae* has been a source of fatal infections in many hospitals across the country. The 25 newly identified drugs and compounds consisted of 11 FDA-approved drugs and 14 drugs still under investigation. They include antibiotics, antifungals, antiseptics and an antiviral, antimalarial and anticancer drug/compound.

In discovering that some of the 25 compounds were just slightly active, the researchers decided to examine the effectiveness of combinations of drugs. They paired newly identified drugs from the repurposing screen with a commonly prescribed antibiotic that did not work by itself due to the drug resistance. The goal was to make the drug-resistant *K. pneumoniae* sensitive again to a common antibiotic. They identified four sets of two-drug combinations that suppressed the growth of multidrug-resistant *K. pneumoniae*. Those antibiotics that previously were inactive due to resistance became active against *K. pneumoniae* in the presence of the second drug identified from the drug repurposing screen.

The researchers also examined three-drug combinations of broad-acting antibiotics that may be given immediately in the clinic to patients with severe infections, when

immediate treatment can be critical. They screened for 10 commonly seen drug-resistant bacterial strains and found three different three-drug combinations that were effective against these strains.

These results, which were published in the [Nov. 9, 2016, issue of *Emerging Microbes & Infections*](#), could lead to the development of clinically relevant drug combinations that can be used for combatting dangerous infections by drug-resistant bacteria. This approach also could be developed to help clinicians make “real-time” treatment decisions for highly resistant infections.

New Therapeutic Uses Program

To expand its drug repurposing efforts, in September 2016, NCATS [announced](#) a new Bench-to-Clinic Repurposing initiative, which is part of the Center’s [Discovering New Therapeutic Uses for Existing Molecules \(New Therapeutic Uses\)](#) program. New Therapeutic Uses provides funding for research on new indications or uses for therapeutic assets that already have been clinically tested.

A key goal of the new initiative is to identify systematic approaches for predicting which existing drug or biologic might be effective in treating a disease or condition. The Bench-to-Clinic funding opportunity supports pre-clinical (bench) repurposing studies that demonstrate utility of an approach, such as using an independent crowdsourcing effort, computational algorithm or big dataset from patient records to predict new uses for a drug or biologic. Crowdsourcing is the practice of recruiting large numbers of people to help solve a complex problem. Using existing therapeutics means positive pre-clinical findings could rapidly lead to testing in humans, and the translational approach can be adopted by the scientific community to improve other drug repurposing efforts.

NCATS plans to issue a complementary funding opportunity in 2017 to support clinical studies for projects that are further along in development.



Testing and Predictive Models



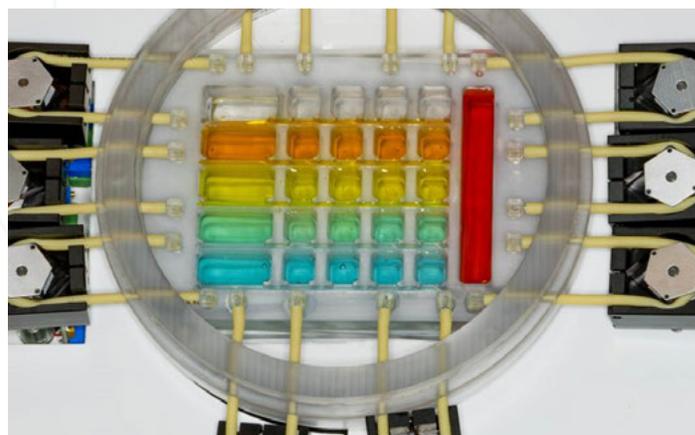
It remains difficult to predict the biological effects of drugs, chemicals and therapeutic interventions on humans based on pre-clinical testing because traditional models may not adequately represent human biology. In fact, many promising medications have failed in clinical trials because they are found to be harmful to human health or ineffective despite promising outcomes when studied in cells and animals.

Research using animal models has an important place in biomedical research because it contributes to our understanding of the intricacy of biology and disease progression. NCATS complements those efforts by supporting the development of model systems that use human-based cell and tissue models of increasing complexity. Such advances could save enormous amounts of time and expense by preventing patients from being exposed to potentially harmful or ineffective candidate drugs in clinical studies. In addition, these newer models have the potential to provide useful information about the basic biology of disease and to serve as improved testing platforms for predicting human response or toxicity to potential therapeutics and environmental chemicals.

Tissue Chips for Drug Screening

In collaboration with the Defense Advanced Research Projects Agency (DARPA) and the FDA, the Center leads efforts to develop more physiologically relevant testing systems. Through its [Tissue Chip for Drug Screening program](#)

([Tissue Chip](#)), NCATS funds research on 3-D, living human tissues and cells that are supported and survive in engineered microchip platforms. These devices — typically referred to as tissue chips or organs-on-chips — are designed as accurate models of the structure and function of human organs, such as the lungs, liver and heart.



Five separate tissue systems (heart, liver, blood vessels, skin and cancer), each within its own custom-designed chamber, are shown on a single chip (colors denote different tissue types). They can be used for modeling disease and for studying drug effectiveness and toxicity. They also may be useful in better understanding the physiological mechanisms by which drugs work. The project team is led by Gordana Vunjak-Novakovic, Ph.D., of Columbia University, in collaboration with Angela Christiano, Ph.D. (Columbia); Sangeeta Bhatia, M.D., Ph.D. (Massachusetts Institute of Technology); Christopher Chen, M.D., Ph.D. (Boston University); and Karen Hirschi, Ph.D. (Yale University). (Photo credit: Columbia University)

During the first phase of Tissue Chip, which was initially part of the NIH Common Fund's Regulatory Science program, NCATS supported the development of 3-D cellular microsystems designed to represent a number of human organ systems. The current phase of the program is focused on refining the technology using renewable cell sources and microsystems, demonstrating normal tissue and cell function, and connecting and integrating multiple organ tissue chips.

NCATS recently expanded the Tissue Chip program in the following ways:

- Awards to establish three [Tissue Chip Testing Centers \(TCTCs\)](#) are aimed at independently validating the tissue chip models so they can be reproduced by other researchers, leading to the adoption of standardized methods for pre-clinical drug testing. TCTC goals include:
 - Providing the means for scientists supported through NCATS' tissue chip program to test and validate tissue chip platforms independently;
 - Promoting adoption of this technology by the broad research community, such as pharmaceutical partners and the FDA; and
 - Ensuring wide-ranging availability of tissue chip technology.
- NCATS issued a new [Tissue Chips for Disease Modeling and Efficacy Testing](#) funding opportunity to support development of tissue chip models of human disease that mimic the pathology in major human organs and tissues. Eventually, these disease models will help scientists assess biomarkers of disease and the safety and effectiveness of candidate therapeutics prior to entry into clinical trials. The "disease-on-a-chip" models may provide critical clues to disease cause and progression, leading to better ways to prevent and treat a variety of human conditions.

Other NIH Institutes, Centers and Offices contributing expertise and resources to this initiative include the National Cancer Institute; National Institute of Arthritis and Musculoskeletal and Skin Diseases; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; National Institute of Dental and Craniofacial Research; National Institute of Diabetes and Digestive



Left: NCATS Associate Director for Special Initiatives Dan Tagle, Ph.D., and astronaut Michael Barratt, M.D., discuss the Tissue Chips in Space initiative. Right: Astronaut Commander Scott Kelly and NCATS Scientific Program Manager Lucie Low, Ph.D.

and Kidney Diseases; National Institute of Environmental Health Sciences; National Institute of Neurological Disorders and Stroke; National Institute of Biomedical Imaging and Bioengineering; National Heart, Lung, and Blood Institute; and Office of Research on Women's Health.

- NCATS and National Aeronautics and Space Administration (NASA), through the Center for the Advancement of Science in Space (CASIS), are collaborating to use tissue chip technology for translational research at the International Space Station U.S. National Laboratory (ISS-NL). The [Tissue Chips in Space](#) initiative will support scientists that leverage recent tissue-on-chip advances in order to modify and deploy these devices at the ISS-NL. The goal is to further refine tissue- and organ-on-chip platforms for in-flight experiments at the ISS-NL so that scientists can better understand the role of microgravity — diminished gravity relative to Earth, often called "zero gravity" — on human health and disease and translate those findings to affect human health on Earth.

For example, it is now widely known that symptoms of accelerated aging occur after prolonged exposure to microgravity. Health concerns that resemble aging — such as muscle deterioration, osteoporosis (bone loss), reduced cardiopulmonary function and immune deficiency — when in space have been documented, and it also has been observed that these conditions are reversible when astronauts return to Earth. Tissue chip applications at the ISS-NL will enable studies of organs at the cell and tissue levels under reduced gravity and could reveal molecular targets that can slow the aging process.

Toxicology in the 21st Century

Through a collaboration among NCATS, the National Toxicology Program at the NIH's National Institute of Environmental Health Sciences, the Environmental Protection Agency, and the FDA, the [Toxicology in the 21st Century \(Tox21\)](#) program supports innovation in testing for harmful effects of chemicals. With Tox21 support, a team composed of scientists from each of these agencies is developing better toxicity assessment methods to quickly and efficiently test whether certain chemical compounds have the potential to disrupt processes in the human body that may lead to negative health effects. This approach — developing ways to predict whether a substance will be harmful in humans — is called predictive toxicology.

Using NCATS' Tox21 high-throughput robotic screening system, the team tested a collection of 10,000 environmental chemicals and drugs for their potential to disrupt biological pathways that may result in toxicity.

Tox21 scientists have used high-throughput screening to increase the precision of toxicology testing. In fact, this approach and the promise of moving toward more informative and efficient toxicology testing was recognized by the Frank R. Lautenberg Chemical Safety for the 21st Century Act. This [law](#) mandates that regulatory and commercial decisions about chemicals be more predictive and science-driven. It also supported the advancement of science and technology for toxicology testing.



NCATS organizers and winners of the Tox21 Data Challenge Competition at the 2016 Society of Toxicology annual meeting: organizers (center, from left to right) NCATS' Menghang Xia, Ph.D., and Ruili Huang, Ph.D., and winners (from left to right) Ahmed M. Abdelaziz Sayed, Ph.D., Technical University of Munich, Germany; Günter Klambauer, Ph.D., Johannes Kepler University Linz, Austria; Gergo Barta, Ph.D. candidate, Budapest University of Technology and Economics, Hungary; and Yoshihiro Uesawa, Ph.D., Meiji Pharmaceutical University, Tokyo, Japan.

NCATS hosted a Tox21 Data Challenge in 2014, a crowdsourcing competition that attracted contestants from 18 countries to design computational models to better predict chemical toxicity. The [winners of the Tox21 Data Challenge](#) presented their models at the 2016 Society of Toxicology annual meeting and all of the contestants' papers were published in a special issue of *Frontiers in Environmental Science*.



Clinical Innovation

Once a discovery has been made in the laboratory, clinic or community, researchers must further test its safety and effectiveness in clinical studies. Clinical studies supported by NCATS can be found at [ClinicalTrials.gov](https://www.clinicaltrials.gov). Nationwide, researchers face common barriers in clinical and translational science that can delay the generation of medical evidence and the development of new interventions for patients in need. NCATS is developing solutions to address these challenges that include:

- Difficulties in recruiting, training and retaining a critical mass of qualified clinical and translational investigators;
- Increased research costs and complexity;
- Low patient recruitment and retention in clinical research studies; and
- Inflexible or inadequate study designs.

Through its [Clinical and Translational Science Awards \(CTSA\) Program](#), NCATS supports a network of medical research institutions — called [hubs](#) — that work together at the local, regional and national levels to improve the translational research process.

The CTSA Program enables research teams — including scientists, patient advocacy organizations and community



Jessica Mast, R.N., assists during an ultrasound performed by Zhaohui Gao, Ph.D., on study volunteer Josh Miller for one of many cardiac research studies. (Photo credit: Penn State College of Medicine/Darrell Peterson)

members — to tackle system-wide scientific and operational problems in clinical and translational research that no one organization can overcome. Program goals are to:

- Train and cultivate the translational science workforce;
- Engage patients and communities in every phase of the translational process;

- Promote the integration of special and underserved populations in translational research across the human lifespan;
- Innovate processes to increase the quality and efficiency of translational research, particularly of multisite trials; and
- Advance the use of cutting-edge informatics.

NCATS is leading an effort to develop common metrics to measure and improve the impact of the CTSA Program. These metrics will serve as a management tool, supporting data-driven, results-based strategic plans to improve performance in key areas such as workforce development and clinical study efficiencies. The metrics also will aid in planning for the continuing evolution of the program to best meet the needs of researchers developing interventions for patients.

NCATS also is building on the unique strengths of each CTSA Program hub by working closely with program-funded researchers on collaborative initiatives that address translational science problems that can benefit the entire CTSA program network, including:

- **CTSA Program Trial Innovation Network.** Launched in fall 2016, this network is composed of three key organizational partners: three Trial Innovation Centers, a Recruitment Innovation Center and the CTSA Program hubs. NCATS' vision for the Trial Innovation Network is to address critical roadblocks in clinical trials with operational innovation and collaboration to accelerate the translation of novel interventions into life-saving therapies. By leveraging the expertise, diversity and broad reach of the CTSA Program, the network is enhancing collaboration and operational innovation and excellence. Features include a single institutional review board (IRB) system, master contracting agreements, quality-by-design approaches, and evidence-based strategies for clinical trial recruitment and patient engagement. The goal is not only to execute trials better, faster and more cost-efficiently, but also to be a national laboratory to study, understand and innovate the processes for conducting multisite studies.
- **NCATS Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Platform.** The process of obtaining ethics approval for multisite clinical

research by multiple IRBs is a longstanding challenge that can lead to significant delays in study activation. To address this problem, NCATS supported the development of a single IRB reliance platform for multisite clinical studies, enabling study sites to rely on a single IRB of record. The platform includes resources such as umbrella agreements, guidance documents and consultation services that investigators nationwide can access to harmonize and streamline IRB review for their own multisite studies. SMART IRB is serving as a roadmap to help implement the NIH policy released in June 2016 that expects all NIH-funded multisite clinical studies to use a single IRB.

- **CTSA Program Collaborative Innovation Awards (CCIA).** In fall 2016, NCATS funded seven CCIA projects. These awards are intended to foster research collaboration by encouraging teams from three or more CTSA Program hubs to work together to develop, demonstrate and disseminate innovative, experimental approaches to overcoming translational science roadblocks. The CCIA funding promotes collaborative initiatives involving a combination of hubs and stakeholders necessary to conduct translational research. The funded projects reflect the CTSA Program goals and cover a broad spectrum of translational science, including novel approaches to diagnostics and newborn screening, acceleration of human gene therapy trials, improvement of the utility of patient-reported outcomes, and community engagement to enhance minority participation in clinical trials.

NCATS continues to support notable advances in clinical and translational science innovation. Examples include:

Building Clinical and Translational Science Capacity: The University of New Mexico Clinical and Translational Science Center (UNM CTSC) was a founding partner in the Mountain West Research Consortium (MWRC), currently a network of 11 universities spanning seven states. The MWRC's goal is to build and enhance the geographically isolated region's clinical and translational research capacity. The network provides support to arm Mountain West researchers with training, data and knowledge that helps them collaborate with basic research colleagues, successfully apply for funding and launch clinical studies. UNM CTSC representatives provide grant

writing mentoring, and the UNM CTSC also serves as a biostatistics support core for the MWRC, featuring services and training for consortium statisticians to build biostatistics capabilities locally.

In 2013, the UNM CTSC worked with other MWRC representatives to collectively and successfully apply for support through NIH's National Institute of General Medical Sciences' Institutional Development Award (IDeA) program. Through IDeA, NIH fosters health-related research and enhances the competitiveness of investigators at institutions in states with historically low success rates for NIH applications. The IDeA funding supports MWRC's clinical and translational research on diseases that affect medically underserved populations.

Revealing Genetic Components of Healthy Older

Adults: At the Scripps Translational Science Institute (STSI), researchers applied an innovative genomics approach to uncover the genetic components of healthy aging. STSI scientists led efforts to sequence and compare the genomes of 511 healthy older adults — whom they deemed the “Wellderly” — and a representative group of 686 older adults.

The study was made possible through STSI's facilities, expertise and services that are available to its investigators to accelerate clinical and translational research. The Wellderly researchers used several of these resources, including clinical trial coordinators to recruit participants and biostatisticians and computational biologists to analyze and interpret the genomic data. The team also used **REDCap**, a CTSA Program-developed software tool, to collect participant data.

Study results, published in the [May 5, 2016, issue of *Cell*](#), reveal the Wellderly had reduced genetic susceptibility to Alzheimer's disease, suggesting that protection against cognitive decline is at least one genetic feature of healthy aging. The Wellderly also had decreased genetic risk for coronary artery disease and a marginal, statistically not significant, decrease in stroke risk, which might reach statistical significance in a larger group of participants. The researchers are continuing to recruit additional Wellderly participants to validate their initial findings.

Because the findings represent only a fraction of the potential information that can be gleaned from the results,

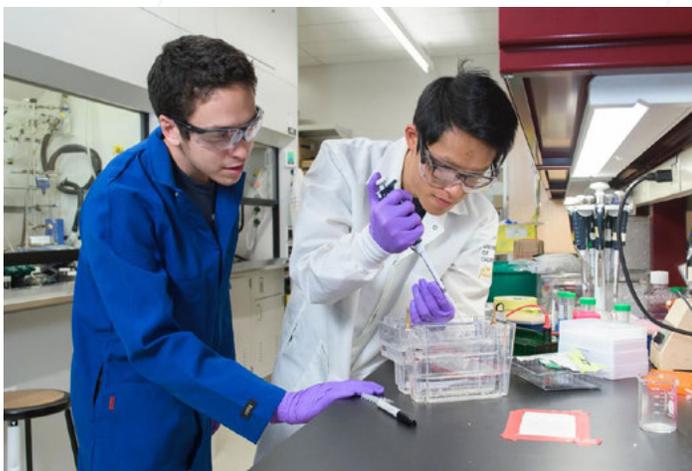


Ali Torkamani, Ph.D. (left), and Galina Erikson, authors on the Wellderly study by the Scripps Translational Science Institute. The researchers applied an innovative genomics approach to uncover the genetic components of healthy aging. (Photo credit: The Scripps Research Institute)

the investigators publicly released the study's de-identified genomic data to promote additional discoveries by other investigators. This exemplifies one of NCATS' key priorities: to foster collaboration by publicly sharing data and resources. Teasing apart the genetics of natural disease resistance could aid scientists in identifying therapeutic targets that help prevent or treat age-associated diseases.

Innovation in Early Disease Detection: Treatments have greater potential to help patients when clinicians can diagnose diseases early and accurately. Enter a research team at the Stanford Center for Clinical and Translational Research and Education (also referred to as Spectrum), a CTSA Program hub. The scientists developed a new assay for diagnosing diseases, including thyroid cancer, HIV and type 1 diabetes. The method appears to be many times more sensitive than some traditional diagnostic tests, meaning that it potentially can detect illnesses earlier, enabling clinicians to treat patients sooner and possibly slow disease progression.

The research was supported in part by a Stanford Predictives and Diagnostics Accelerator (SPADA) pilot grant, part of a funding program run by Spectrum. SPADA pilot grants support research to translate discoveries into novel predictive and diagnostic products that address unmet medical needs. The emphasis is on technologies that have the potential to advance rapidly into clinical care through commercialization or other pathways.



CTSA Program-supported researchers Jason Tsai and Peter Robinson, Ph.D., at the Stanford Center for Clinical and Translational Research and Education, two of the three co-founders of Enable Biosciences, are investigating the synthesis of reagents for their ultrasensitive antibody detection platform. Enable is developing tests for thyroid cancer, HIV and type 1 diabetes that are 1,000 times more sensitive than current methods. (Photo credit: Stanford University News/L.A. Cicero)

The new test is designed to detect antibodies, which are proteins the body produces in response to and for the purpose of counteracting a specific antigen, a toxin or other foreign substance that generates a response from the body's immune system. Clinicians commonly diagnose abnormal health conditions by testing for specific antibodies that indicate the presence of a particular disease. The new assay uses small DNA fragments to

identify and "tag" antibodies. Standard polymerase chain reaction (PCR) technology is then used to quickly amplify small segments of DNA, which enables clinicians and researchers to analyze and measure the tagged antibodies.

PCR is a decades-old, relatively inexpensive technology that can be deployed easily in most standard laboratories. Unlike many current diagnostic tests, the new assay, called antibody detection by agglutination-PCR (ADAP), does not use radioactivity. This fast and easy access to PCR technology means the test can be performed in most hospitals, enabling more clinicians to receive diagnostic results sooner.

Furthermore, ADAP can detect antibodies at much lower levels than standard techniques, meaning it could help clinicians diagnose and treat diseases at earlier stages. The researchers demonstrated that ADAP detected thyroid cancer antibodies with 1,000 times greater sensitivity than the current test approved by the FDA. They published this work in the *Feb. 16, 2016, issue of ACS Central Science*.

The team envisions expanding the technology to diagnose a wide range of other diseases. Additionally, the test could be adapted for use in basic science research, which could lead to diagnostic tests for diseases that are currently difficult to diagnose. The research group's early data led them to establish a company called Enable Biosciences and secure grants to continue to expand the test's capabilities.



Accelerating Rare Diseases Research



Several thousand rare diseases affect an estimated 25 million Americans. Only a few hundred of these diseases have any treatment. The diseases are devastating and costly for patients, families and the nation as a whole, partly due to the severity of these conditions but also because diagnosis can be difficult and is often possible only well after symptoms have appeared.

A “one disease at a time/one organ at a time” therapeutic development approach is not realistic for rare diseases. Through its work to improve health through smarter science, NCATS supports collaborative research on the commonalities and underlying molecular causes of both common and rare diseases.

The Center also disseminates its knowledge gained through collaborations in the public and private sectors, patients, patient advocates, other government agencies, and policymakers.

Rare Disease Day at NIH

As part of its role in recognizing the importance of rare diseases research, each year NCATS teams with the NIH Clinical Center to host Rare Disease Day at NIH. This event is part of the global observance of Rare Disease Day, which generally takes place worldwide in late February, to raise awareness among policymakers and the public about rare diseases and their impact on patients’ lives.

In 2016, Rare Disease Day at NIH took place on Feb. 29, and was themed “Patients and Researchers — Partners for Life.” The event brought together an unprecedented number of rare disease patients, advocates, caregivers and researchers to discuss the latest in rare diseases research advances. The day featured powerful presentations, remarks by congressional and NIH leadership, posters, exhibits and tours of the Clinical Center. All four Rare Disease Congressional



Katie and Joe Murray with their daughter Ella and son A.J. Ella is affected by a connective tissue disorder, called epidermolysis bullosa or EB, that causes the skin to be very fragile. The slightest rubbing of the skin can cause open blisters, wounds and chronic pain. (Photo credit: Katie and Joe Murray)



Megan and Shannon O'Boyle. Shannon O'Boyle has Phelan-McDermid syndrome, a rare condition that can cause autism, epilepsy and intellectual disabilities. (Photo credit: Megan O'Boyle)

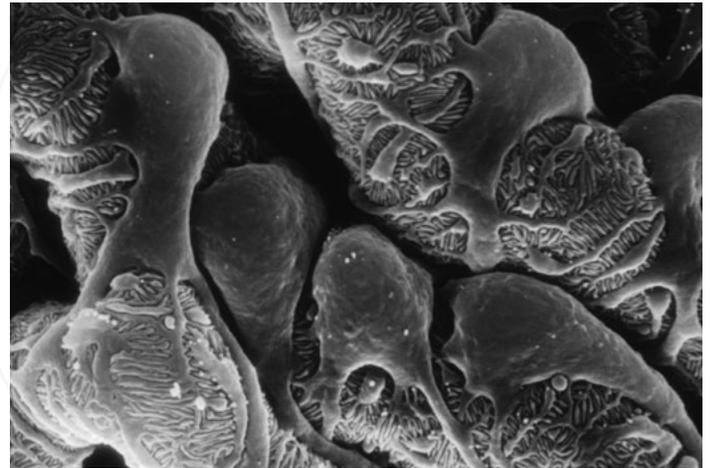
Caucus co-chairs — Senators Orrin Hatch and Amy Klobuchar and Congressmen Joseph Crowley and Leonard Lance — participated in the event.

Several rare disease patients and caregivers shared their stories of living with a rare disease, the challenges they face and how NIH- and NCATS-supported research offers hope. [Video highlights of these conversations](#) are available on the NCATS website.

Rare Diseases Clinical Research Network

NCATS' [Rare Diseases Clinical Research Network \(RDCRN\)](#) is designed to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment, data sharing and training for young investigators. The program features a national network of 22 multisite clinical research consortia overseen by NCATS in collaboration with 10 other NIH Institutes, Centers and Offices. Through the network, scientists from multiple disciplines at hundreds of clinical sites around the world collaborate with patient advocacy groups to study more than 220 rare diseases.

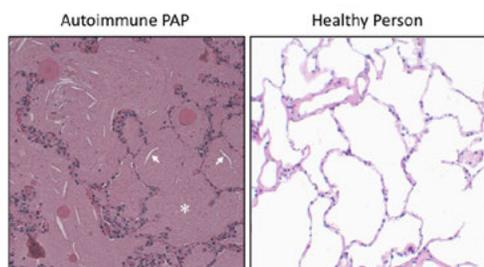
Predicting Chronic Kidney Disease: Through the RDCRN, NCATS supports the Nephrotic Syndrome Study Network (NEPTUNE) at the University of Michigan, which convenes physician scientists at 23 research consortia in the U.S. and Canada, along with the patient advocacy groups NephCure Kidney International and the Halpin Foundation. NEPTUNE's goal is to advance research on diseases that define Nephrotic Syndrome, which is a group of kidney diseases with associated, often serious complications. NEPTUNE supported research to predict which patients with chronic kidney disease (CKD) — a disorder in which damaged kidneys cannot filter blood efficiently — are at risk for worsening of their condition. The researchers found an easily detectable protein in the urine that appears to serve as a biomarker, which provides an early warning sign of CKD progression. The identification of this biomarker meets an urgent clinical need for an accessible, non-invasive way to identify patients at risk for rapid progression of kidney disease. The findings were published in [Science Translational Medicine](#) and featured in an [NIH Director's blog](#).



Scanning electron micrograph showing part of one of the kidney's glomerular filters, which are damaged in people with chronic kidney disease (CKD). The cells with the lacy cytoplasmic extensions are called podocytes. (Photo credit: Kretzler Lab, University of Michigan Health System, Ann Arbor)

Unprecedented Trans-NCATS Collaboration Enables Rapid Advancement of Rare Lung Disease Therapy to Human Trials

Through its [Therapeutics for Rare and Neglected Diseases \(TRND\)](#) program, [Clinical and Translational Science Awards \(CTSA\) Program](#), [Rare Diseases Clinical Research Network \(RDCRN\)](#) and [Office of Strategic Alliances \(OSA\)](#), NCATS has helped shepherd a potential new drug for a deadly lung disease through several steps of the drug development process and into a clinical trial.



The therapy is an inhaled medication to treat patients with autoimmune pulmonary alveolar proteinosis (aPAP), a rare, potentially deadly lung disease. It is marked by a build-up of proteins and lipids (called surfactant) in the narrow gas exchange pockets of the lung, leading to respiratory failure (see the image on the left). The body's immune system attacks a protein called granulocyte-macrophage colony-stimulating factor (GM-CSF), which is critical for proper clearance of the surfactant. Studies suggest that therapies to supplement GM-CSF could stimulate aPAP patients' own immune cells to properly clear the lungs.

The only treatment currently available for aPAP is an invasive procedure that requires patients to undergo general anesthesia. While patients are unconscious, clinicians keep one lung working via mechanical ventilation while they fill the other lung with saline, repeatedly pound on the chest to loosen the built-up surfactant and drain the contents of the lung. The process is then repeated on the other lung. Some patients must receive this procedure every six months.

A Cincinnati researcher, Bruce Trapnell, M.D., thought GM-CSF, delivered in inhaled form, could represent a less invasive treatment for aPAP patients. In the U.S., GM-CSF in drug form is approved for intravenous use in other conditions and is owned by Sanofi Genzyme, a biotechnology company based in Cambridge, Massachusetts. However, both animal and human studies outside the U.S. suggest that inhaled GM-CSF could be an effective therapy for aPAP patients. But before the drug could be studied in humans in the U.S., the FDA required pre-clinical studies in animals to demonstrate the inhaled drug's safety.

Trapnell had been studying aPAP in humans for more than a decade in his role as principal investigator of the Rare Lung Diseases Consortium (RLDC), part of the NCATS-supported RDCRN. But the RLDC was not funded to conduct animal studies, and Trapnell couldn't find financial support for the FDA-required study or attract a commercial partner with interest in further developing the inhaled drug.

To enable these studies, Trapnell applied to NCATS through its TRND program, which provides a mechanism for outside investigators to partner with NCATS researchers with the goal of moving promising therapeutics into human clinical trials. NCATS OSA staff then arranged a formal, three-way, materials-sharing agreement among the University of Cincinnati, NCATS and Sanofi Genzyme. Sanofi Genzyme provided essential, clinical-grade GM-CSF product for the animal studies, and NCATS scientists designed and completed studies that successfully demonstrated the safety of inhaled GM-CSF in animals. The NCATS-generated data led the way to the FDA giving the green light for human studies to proceed.

To fund the clinical trial, Trapnell successfully applied for a CTSA Program supplemental grant at the University of Cincinnati hub, which is a collaborative partnership among the University of Cincinnati, Cincinnati Children's Hospital, and a number of other local clinical research institutions. The preliminary clinical study of inhaled GM-CSF is taking place at two program hubs: Cincinnati Children's Hospital and the University of California, Los Angeles.

During the Phase I clinical trial, scheduled for 2017, researchers will test the safety and dosage of inhaled GM-CSF in 10 aPAP patients. The study is also serving as a pilot project of the CTSA Program's newly implemented SMART IRB Platform (see [page 16](#)). The study is expected to last about six months, after which researchers hope to move into a Phase II trial to test the drug's effectiveness in a larger group of aPAP patients. With these developments, there is optimism that a potentially life-changing treatment is one step closer to benefitting patients.



Patient and Community Engagement



Patient and community engagement is vital for every phase of translational science. Incorporating these perspectives builds trust and improves the quality of the research by enabling investigators to design studies that measure outcomes of most importance to patients and their communities.

- **Citizen Scientists as Research Partners:** In some cases, scientists can help advance translational science by engaging community members as research partners. That was the approach used by a team of bioinformatics scientists from the Scripps Translational Science Institute (STSI) at the Scripps Research Institute in La Jolla, California, an NCATS CTSA Program hub. The Scripps researchers wanted to find a better way for scientists to harness the massive amount of information contained in the biomedical literature. Currently, PubMed, the primary database for biomedical literature, housed by NIH's National Center for Biotechnology Information, contains more than 26 million articles and is expanding by more than 1 million articles per year, which is, of course, more than any human and even many computer systems can sort through and monitor.

The Scripps team invented a web-based technology platform called Mark2Cure that arranges biomedical literature into a format that is easier for computers to organize and analyze. Because of the enormity of such a task, and because computers are not good at

extracting information from free text, Mark2Cure is designed to use crowdsourcing to sort and organize thousands of biomedical papers. The aim is to make the biomedical literature more manageable and useful by enabling scientists to rediscover buried knowledge that can spur new research hypotheses. Volunteers from the general public — called “citizen scientists” — log onto the web-based platform and undergo a brief



Citizen scientists Judy and A.J. Eckhart share their motivations for contributing to the CTSA Program-supported Mark2Cure project. Citizen scientists contribute data, as well as insight, suggestions and feedback on how to improve a project. The Eckharts and many other participants provided feedback on how to improve Mark2Cure's tutorials and interface. (Photo credit: Su Lab, The Scripps Research Institute)

training to become comfortable with scientific language and concept identification. Next, they complete a two-step process: First, they identify relevant concepts in text, such as genes, proteins, drugs or diseases; and second, they define the relationships between concepts. A relationship may be expressed by stating that a particular drug treats a certain disease; for example, insulin (drug) treats diabetes (disease). Carrying out those two steps for hundreds or even thousands of articles could generate a powerful knowledge base that computers can mine more effectively.

In an initial experiment, the Scripps team tested the effectiveness of the Mark2Cure approach by comparing the citizen scientists' efforts with those of experts performing the same task. The Scripps researchers found that in aggregate, the citizen scientists performed the task (highlighting disease mentions within biomedical text) with very high accuracy, comparably to the experts. They also found, through survey responses, that the citizen scientists had high levels of desire and motivation to volunteer for Mark2Cure; most cited advancing science or learning as their motivations for participating. The Scripps scientists published these findings in *Citizen Science: Theory and Practice*.

The Scripps team now has turned to testing Mark2Cure in the context of an actual disease. To start, they are focusing on N-glycanase 1 (NGLY1) deficiency, an extremely rare inherited disorder that affects multiple organs, causing developmental delays, movement problems and seizures, among other symptoms. The researchers are starting with rare diseases because the literature base is relatively small and members of patient groups are often well-informed and highly motivated to help with research. Mark2Cure is designed to help explore virtually any disease, rare or common, and the Scripps team plans to expand beyond NGLY1 deficiency in future projects. The hope is that Mark2Cure will enable researchers to make unexpected connections between various diseases, their underlying mechanisms and potential treatments.

- **Building Scientific and Community Health**

Collaborations: Engaging patients and communities in the translational process has the potential to strengthen the impact of studies and increase the likelihood that

results are disseminated and implemented. Scientists at the Rockefeller University Center for Clinical and Translational Science (RU-CCTS), a CTSA Program hub, developed a process to facilitate translational research collaborations between basic science researchers and community stakeholders. The goal of the initiative, called Community-Engaged Research Navigation (CEnR-Nav), is to develop research projects that address both scientific and community health aims. RU-CCTS leadership provides a framework and resources for the process, whereby basic scientists and their community partners work together at every stage of a project, from conceptualizing, designing, planning and implementing a study to collecting, analyzing and publishing results. Topics explored included community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), obesity and diabetes, Down syndrome, psoriasis and methods for engaging patients to use data registries. The Rockefeller team concluded that the CEnR-Nav initiative could serve as a model for more comprehensive translational research approaches, and the team reported on the outcomes in the [April 26, 2016, issue of *Academic Medicine*](#).

Genetic and Rare Diseases Information Center

An important part of NCATS' patient and community engagement is to make easily accessible, up-to-date research information available to the public. NCATS collaborates with the National Human Genome Research Institute (NHGRI) to support the Genetic and Rare Diseases Information Center (GARD), which is designed to provide comprehensive information about rare and genetic diseases to patients, their families, health care providers, researchers and the public. The [online GARD database](#) provides reliable, up-to-date and easy-to-understand information about ongoing research, symptoms, treatment options and other details.

GARD information specialists are available to discuss questions by phone in English and Spanish. Volunteer contacts also can provide translations of requests and responses into other languages, including French, Portuguese, Russian and German.

NCATS updated the GARD website in 2016 with a more user-friendly design, including a Spanish-language section. An enhanced search feature enables users to filter their

findings into the main content areas. Users can sort disease information by language (English or Spanish) and by categories (e.g., eye diseases, skin diseases, rare cancers). The GARD site also has an interactive navigation tool that can help people more easily locate or learn more about relevant resources. In 2016, more than 3 million people visited the site, and visits have steadily increased to more than 500,000 each month.

The site's En Español section includes navigation instructions as well as comprehensive information and resources for more than 205 rare diseases. The Spanish section also features

six guides that answer frequently asked questions about challenges facing individuals living with a rare or undiagnosed disease. NCATS also launched a GARD Facebook page in Spanish as an additional communication tool.

NCATS continues to develop user-friendly guides to address frequently asked questions. These guides are featured prominently on the website and organized by user category. In 2016, several new guides were developed, including [Support for Patients and Families](#), [How to Get Involved in Research](#) and [Finding Funding Opportunities](#).



Partnerships and Collaborations



Moving a basic discovery to a demonstrated improvement in public health requires a translational research team of scientists, clinicians, research participants and other stakeholders having a wide range of expertise and perspectives of the scientific and operational roadblocks. Progressing through the phases of the translational science spectrum requires the creation of productive and mutually beneficial collaborations that depend not only on individual excellence but on teamwork, coordination, cooperation and communication.

Partnerships and collaborations among individuals and organizations are essential, because the capabilities and viewpoints required for successful translation tend to reside in different groups with distinct missions. For example, developing a potential therapy to the point of regulatory approval can require expertise in molecular biology, medicinal chemistry, compound synthesis and formulation, pharmacology and toxicology, technology transfer, clinical science, regulatory science, and entrepreneurship, as well as integration of patient perspectives. However, academic advancement and tenure structures and professional and cultural barriers can make teamwork difficult to navigate. For this reason, NCATS places high value on innovation in team science and partnership development, and it designs and tests novel partnership structures that cut across traditionally siloed scientific disciplines, organizations and sectors. Successful approaches are shared for all in the biomedical research community to use to improve their own translational efforts.

Building Alliances

The business aspects of conducting collaborative, translational science — such as negotiation of standard forms and model agreements between NCATS and outside parties — are critical but often overlooked facets for de-risking a project to enable its continued success. Enter NCATS' [Office of Strategic Alliances \(OSA\)](#) staff, who provide key expertise and services in formalizing the Center's partnerships and collaborations through legal agreements, licensing, technology transfer and patents. For example, in 2016, OSA staff were instrumental in the following activities:

- Establishing a three-way cooperative research and development agreement among NCATS, Sanofi Genzyme and University of Cincinnati researchers, enabling FDA-required pre-clinical studies of a potential treatment for a rare lung disease. Sanofi Genzyme provided the study drug to NCATS' TRND program scientists, and now it is being tested in a human clinical trial (see [Rare Disease](#) story on [page 21](#)).
- Developing a memorandum of understanding between NCATS and CASIS to enable a collaboration to send tissue chip experiments to the ISS-NL. OSA also helped refine a user agreement for NCATS grantees to execute with CASIS and the NASA (see [Tissue Chips in Space](#) on [page 13](#)).

- Developing a memorandum of understanding that will enable technology transfer office partners at NCATS, NIA and NIMH to collectively manage and coordinate patent and licensing activities related to the development of a ketamine metabolite to treat depression (see Ketamine on [page 7](#)).

Translational Science Collaboration on a Global Scale

NCATS recognizes that translation is a global effort and therefore engages in partnerships and collaborations with international entities in multiple sectors. The Center's goal of getting more treatments to more patients more quickly will be realized most effectively through teamwork with fellow researchers worldwide. Launched in 2011, the International Rare Diseases Research Consortium (IRDiRC) brings together the many stakeholders invested in rare diseases research globally to foster better coordination and thus maximize productivity. In March 2016, NCATS Director Christopher P. Austin, M.D., became chair of the IRDiRC Consortium Assembly.

In April 2016, NCATS' Senior Advisor Stephen Groft, Pharm.D., moderated a panel on gene and stem cell therapies to treat rare diseases at the Third International Conference on Regenerative Medicine in Vatican City. At the conference, which was attended by Pope Francis, Groft emphasized the role of patients and families in finding new treatments and the need for research on both adult and pediatric rare diseases.



NCATS' Stephen Groft, Pharm.D., meets Pope Francis at the Third International Conference on Regenerative Medicine in Vatican City.

NCATS's global partnerships extend beyond rare diseases research: In the [April 1, 2016, issue of *Nature Reviews Drug Discovery*](#), the Center introduced a new international collaboration of dedicated translational science organizations led by governments, non-profit organizations and researchers in multiple countries. Its members include:

- NCATS;
- Medical Research Council Technology in the United Kingdom;
- The European Infrastructure for Translational Medicine in the European Union;
- The Centre for Drug Research and Development in Canada; and
- Therapeutic Innovation Australia.

The collaboration was established to leverage the experience, expertise and credibility of each member organization and to promote translational science with a unified voice. These organizations recognize the common need to raise the level of awareness and understanding of translation and translational science among basic scientists, funders, policymakers, and patients and their associated communities.

Resources for Small Businesses

Often, small startup companies lack the early-stage funding to carry an idea through further development and into commercial markets. This represents a translational science roadblock that can prevent interventions from being developed for dissemination to patients. [NCATS' Small Business Innovation Research \(SBIR\) and Small Business Technology Transfer \(STTR\) programs](#) help bridge this research-to-commercialization translational gap. Following are just a few examples:

- **Patient Medication Adherence:** Researchers often encounter a major problem during clinical trials and outpatient care settings; too many individuals take their medications incorrectly or do not take them at all. This can reduce the accuracy of clinical studies, make drug development less efficient and more costly, and be detrimental to patient health. AiCure, a small, Manhattan-based company, was established to find ways to improve patient adherence to medication regimens.

AiCure researchers developed an artificial intelligence smartphone application that would visually confirm medication ingestion. In other words, it would help ensure that the right patient takes the right medication at the right time.

The technology platform uses a mobile device's camera and software algorithms to confirm the identities of the patient and the medication and to verify intake. The application sends this information to a cloud-based information dashboard that researchers or health care providers can use to monitor adherence and identify issues in real time. Providers can communicate with patients through the dashboard to offer immediate assistance. The application also gives interactive instructions, reminders and suggestions to patients to further increase medication adherence. For now, the technology only monitors pill intake, but it will be adapted to recognize any form of administration, such as injections or oral liquids.

An initial (Phase I) SBIR grant enabled the AiCure team to successfully demonstrate that the platform was technically feasible and able to confirm that patients had taken medication. Based on this success, NCATS awarded AiCure a second (Phase II) SBIR award that enabled validation of the technology against blood levels of medications and showed that the application improves adherence rates in schizophrenia and stroke patient populations.

The initial two SBIR awards led to the team's receipt of additional NIH grants. Collectively, the NIH support enabled AiCure to attract and leverage additional financing from venture capital investors. AiCure also has entered into contracts with five of the top 12 global pharmaceutical companies to provide the adherence monitoring application for clinical trials of experimental drugs. One of these companies, Takeda Pharmaceuticals U.S.A., Inc., is testing the technology in a clinical trial for patients with psychiatric illnesses.

In addition to their work with the drug development industry, the AiCure team is continuing to test the platform in NIH studies of substance abuse. The team also is partnering with government organizations and insurance companies on population health contracts in



A patient takes medication while using the NCATS-supported AiCure application on her smartphone. (Photo credit: AiCure)

infectious and cardiovascular disease. Ultimately, AiCure envisions deploying the technology globally to assist in care for high-risk patients for whom missed doses could lead to serious outcomes such as hospitalization or death.

- **Supporting Entrepreneurs in Drug Discovery:**

Academic scientists can benefit from SBIR/STTR support. Often, these researchers make important discoveries in the laboratory but lack the resources and know-how to carry those ideas further along in the translational science process.

This was the case for Christopher Gibson, an M.D./Ph.D. student at the University of Utah, who developed a high-throughput screening approach, coupled with automated computer analysis, that could enable researchers to quickly and efficiently discover potential disease treatments. Initially, he used the platform to screen thousands of drugs for their ability to correct cell defects related to cerebral cavernous malformation (CCM), a rare disorder in which misshapen, weakened vessels leak blood into the brain and cause strokes. An entrepreneurship course helped him realize that he could expand his platform beyond CCM by using automation and robotics to carry out high-throughput drug repurposing screens for many rare diseases in parallel.

With that vision, Gibson founded Recursion Pharmaceuticals and was awarded an NCATS SBIR Direct to Phase II grant, which is a \$1 million award given to applicants who have already established the technical



Recursion Pharmaceuticals co-founder and CEO Chris Gibson, Ph.D. (back row, second from right), and his team developed more than 200 rare disease models on which to test potential drug therapies. (Photo credit: Recursion Pharmaceuticals)

merit and feasibility of a project. The SBIR award helped Recursion attract additional private investments as its technology was validated by the NIH peer review system. The SBIR Phase II award qualified Recursion to apply to and was accepted into the 2016-2017 cohort of the NIH Commercialization Accelerator Program (CAP) which provided Recursion with expert technical assistance to enhance the commercialization efforts of their technology. Further, NIH co-sponsored the BIO Innovation Zone at the annual 2016 Biotechnology Industry Organization (BIO) International Convention to provide NIH SBIR/STTR awardees with this commercial opportunity. NCATS nominated Recursion to participate in the BIO Innovation Zone where the company was able to meet and market their technologies to companies and other attendees. The award, along with these associated NIH opportunities, also helped Recursion garner attention from major pharmaceutical companies, and negotiations are underway with several large firms.

The SBIR award combined with private investments quickly enabled Recursion to establish a core group of employees and a few initial rare disease models. The company has continued to grow rapidly; at the end of 2016, it had 10 full-time employees and was actively recruiting for at least six more full-time positions. In

addition, the team has developed more than 200 rare disease models on which to test potential therapies and is working to validate 12 promising repurposed drug candidates for several rare diseases.

Although the team began with rare diseases, the platform can be adapted to study any number of common diseases and conditions as well. Already, the Recursion scientists have begun pilot studies to use their system to screen for potential therapies for viral infections, aging, inflammation and cancer.

- **Improving Operational Inefficiencies in Translational Research:** NCATS' SBIR/STTR efforts also extend to methods for improving operational inefficiencies in translational research. For example, NCATS' Research Support Services' [automation](#) and [compound management](#) staff developed and demonstrated the value of cleaning and reusing high-throughput screening plates, saving NCATS almost one-half million dollars and keeping nearly 50,000 plastic plates out of landfills. The team was recognized with a U.S. Department of Health and Human Services Green Champions Award for the innovation.

This process improvement was expanded for dissemination to the research community through an SBIR contract award to IonField Systems in Moorestown, New Jersey. Ten pharmaceutical companies, biotechnology organizations, research universities and other institutes — as well as NCATS — have validated the company's effective process through multiple rounds of testing, and IonField Systems reported having doubled its business within a year after receiving the NCATS SBIR contract.

IonField Systems expanded from two employees in 2012 to five full-time staff and more than 20 subcontractors in 2016. NCATS also nominated IonField Systems to participate in the BIO Innovation Zone where the company was able to meet and market their technologies to companies and other attendees at the annual 2016 BIO International Convention. IonField recently put its first PlasmaKnife™ plate cleaner into operation with a major pharmaceutical company, making the SBIR program goal of commercializing innovative new technologies a reality.

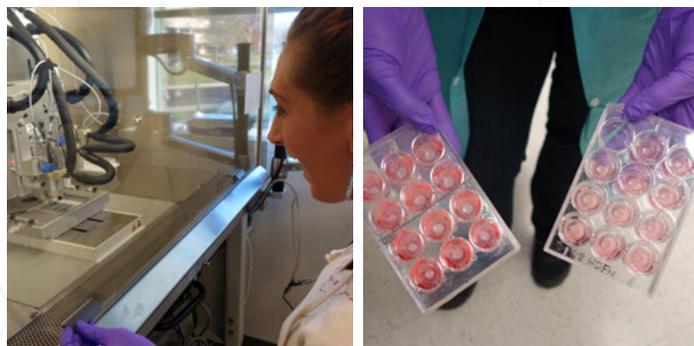


Tools for Accelerating Translational Science

To address the many scientific and operational opportunities for translational science, NCATS develops, demonstrates and disseminates tools and resources — and provides relevant staff expertise — to the broader scientific community. One approach is through the continuous expansion of the Center’s Research Support Services that features [automation](#) and [compound management](#) to enable efficiencies in all its translational research activities, which include collaborations with others at the NIH and beyond. NCATS’ automation engineers are responsible for the maintenance, operation and continuous improvement of the Center’s laboratory instrumentation and processes for high-throughput screening, assay development and optimization. These staff members evaluate and implement novel technologies and methods and also develop custom software and web development solutions. For example:

- **Automated Tissue Culture Systems and Imagers:**

In 2016, the team provided equipment to improve translational efficiencies — including automated tissue culture systems and imagers called Compact SelectT — to support the recently established [NCATS Stem Cell Translation Laboratory](#), which is part of the NIH Common Fund’s Regenerative Medicine Program. Compact SelectT can run approximately 30 cell lines simultaneously and is serving the needs of NCATS’ entire in-house pre-clinical research program. The system frees biologists from some of the tedium and time requirements typically placed on them when



Left: NCATS scientist Kristy Derr, works on the Center’s 3-D bioprinter. Right: Samples of skin tissues Derr has printed.

preparing and harvesting cells for use in experiments, allowing them to focus on higher-level tasks.

- **3-D Bioprinting:** Automation and compound management staff also have played a crucial role in the newly formed NCATS tissue printing program. Tissue printing — or, more specifically, 3-D bioprinting — entails creating artificial human tissue that structurally resembles actual human tissue and can be used for drug screening. NCATS researchers are working to create a skin tissue model and, through collaboration with the NIH’s National Eye Institute, are developing a retina tissue model.
- **Expansion of Compound Libraries:** In 2016, NCATS experts used a smarter, more focused approach to develop two innovative chemical compound libraries,

which are available to outside researchers through collaborations with NCATS scientists. One library, NPACT, is designed to enable broad chemical biology research and drug repurposing opportunities and includes biologically active compounds that play roles in biochemical mechanisms, cellular processes or biological makeup. A second library, Genesis, contains modern synthetic chemistry-derived compounds that may serve as drug precursors. NCATS researchers recently used the Genesis library in a repurposing screen for compounds against the Zika virus (see story on [page 10](#)). Both compound libraries promise to greatly widen NCATS' important role in facilitating translational science and the process of therapeutics development.

NCATS Biomedical Data Translator

As a result of recent scientific advances, a tremendous amount of biomedical research data and patient health information could be useful for understanding wellness and disease. Currently, these very rich yet different data sources are housed in various locations, often in formats that are not compatible. Ideally, scientists could mine these data to gain insights into the relationships between molecular and cellular processes — the targets of potential therapies — and the signs and symptoms of diseases.

To address these problems, in spring 2016, NCATS launched its [Biomedical Data Translator \(Translator\) program](#). The goal

of this multi-year initiative is to assess the feasibility and architecture requirements for developing a groundbreaking, comprehensive, relational and publicly available resource that brings together multiple types of existing data sources using an informatics platform. The potential is that Translator would provide scientists with a powerful system that enables discovery of complex relationships among these data and evaluating new ways for classifying and developing treatments for disease.

NCATS is funding Translator through its Cures Acceleration Network, which includes Other Transaction authority (OTA). OTA is a support mechanism that enables more flexibility than NIH's more traditional business transactions associated with grants, contracts or cooperative agreements. With OTA, NCATS can support high-risk, high-reward research; attract non-traditional government partners; and, if needed, modify or discontinue activities to meet programmatic needs.

In fall 2016, NCATS [issued awards](#) to form a project team of experts from 15 leading universities and other research institutions. Through a series of feasibility assessments, this team is examining components and testing solutions for specific aspects of Translator. The team will define the infrastructure requirements needed to support diverse data types and will demonstrate the potential impact of new analytical tools to promote faster scientific discoveries.



Training and Workforce Development



Training and workforce development are crucial to ensuring that our nation will continue to have trained investigators who can move basic research findings into applications for improving health. NCATS supports career development for both new and established scientists both within and beyond the NIH, from the earliest phases of training through the span of their careers. For example:

Translational Science Training Program: NCATS and the NIH Office of Intramural Training and Education have sponsored multiple Translational Science Training Program workshops to educate graduate students and postdoctoral research fellows working at the agency. The course follows a two-day “boot camp” format and intertwines interdisciplinary scientific content such as understanding the drug development process, professional skills development, clinical trial terminology and career exploration. Participants who complete the “boot camp” are eligible to apply for an intensive one-day workshop at NCATS focused on the pre-clinical development phase of translation. They also tour NCATS’ laboratories to view the cutting-edge equipment and tools used to discover and develop new therapies and technologies. NCATS staff published a detailed description of the curriculum in [May 2016 in *Biochemistry and Molecular Biology Education*](#). The paper is designed to help academic and research institutions, as well as the biopharmaceutical industry, expand their educational offerings in translational science.

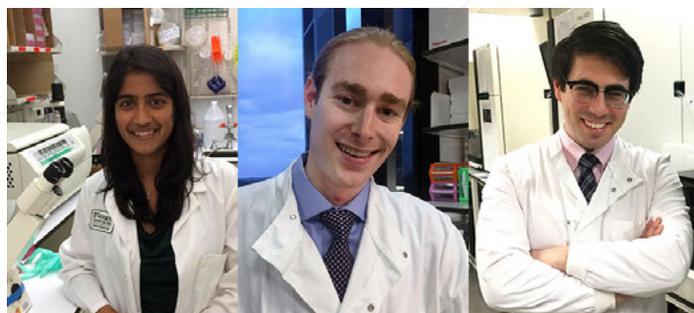


Participants of the 2016 Translational Science Training Program receive a tour of the NCATS high-throughput screening facility from Charles Bonney, an engineer with the automation group.

NIH Oxford-Cambridge Scholars Program (OxCam): OxCam enables scholars to begin thesis research immediately upon starting the program, and trainees split their research time over four years with scientific mentors at NIH and at the University of Oxford or the University of Cambridge in England. This accelerated, individualized doctoral training program for outstanding students committed to biomedical research careers enabled three M.D./Ph.D. students to harness NCATS’ assay development and high-throughput

screening capabilities to [identify several potential new therapeutics](#). All three students finished their Ph.D. work and began medical school in fall 2016 to complete the second portion of their doctoral programs. Each student anticipates establishing a clinically focused research career, through which they can continue the drug discovery efforts they began in the OxCam program. Meanwhile, their former Ph.D. labs will continue to pursue the therapeutic leads these students uncovered. Following are more details about their work at NCATS:

- Monica Kasbekar, Ph.D., accessed NCATS' robotic technology to perform high-throughput screens of a library containing more than 400,000 small molecules to find an inhibitor to block fumarate hydratase, an enzyme critical to the functioning of the bacteria that causes tuberculosis. Using an assay she developed in her lab at Cambridge, Kasbekar found an inhibitor that was selective for the bacterial version of the enzyme but not the human version. The compound's selective nature makes it an ideal tuberculosis drug candidate, because it would be unlikely to cause toxic side effects in patients. She published the results of this work in the [July 5, 2016, issue of the *Proceedings of the National Academy of Sciences*](#).
- Ian Goldlust, Ph.D., performed high-throughput screens for potential ovarian cancer drugs, using the NCATS Pharmaceutical Collection and one of the Center's libraries of approved and investigational drugs. Goldlust was searching for agents that could kill ovarian tumor spheroids, tiny clusters of cancer cells that often remain and spread (metastasize) throughout the body after surgical removal of an ovarian tumor. The screens identified a possible match called elesclomol, a drug originally developed to treat metastatic skin cancer. Goldlust continued to study the compound at his Cambridge lab to determine the mechanisms by which elesclomol kills ovarian cancer spheroids.
- Michael Gormally, Ph.D., used the OxCam learning environment to explore an even broader research objective: He wanted to find a drug to block FOXM1, a protein that is overactive in many types of cancer. At Cambridge, he developed an assay for FOXM1 activity and brought it to NCATS to run a high-throughput screen of an NCATS library, this one containing more than 54,000



NCATS' 2016 NIH Oxford-Cambridge Scholars (from left to right): Monica Kasbekar, Ph.D., Ian Goldlust, Ph.D., and Michael Gormally, Ph.D.

drug-like small molecules. The experiment yielded several promising inhibitors of FOXM1. Gormally published his results and returned to Cambridge to continue to study and characterize the compounds, ultimately generating new insights into how FOXM1 and similar proteins work in cancer cells.

CTSA Program-Supported Training: Training and cultivating the translational science workforce is a key CTSA Program goal. Through the program, NCATS fosters innovation in training using methods that are uniquely tailored to the needs of translational science. For example, Shawn Hingtgen, Ph.D., an assistant professor at the University of North Carolina (UNC) Eshelman School of Pharmacy, received support to conduct research through the UNC CTSA (NC TraCS) mentored career development program. Hingtgen, with his mentoring team members Matthew Ewend, M.D., chair of neurosurgery; and Kam Leong, Ph.D., world-renowned expert in drug delivery systems for the brain, were able to convert a patient's skin cells into personalized, tumor-targeting drug carriers as a potential treatment for glioblastoma multiforme, which is an aggressive brain cancer. In the clinical setting, the final product would be the first of its kind that enables efficient delivery of an anti-cancer agent into the tumor cavity of brain cancer patients. At the delivery site, the therapeutic stem cells would seek out residual tumor cells that cannot be treated through standard surgery and chemotherapy.

NC TraCS enabled Hingtgen's access to its 4D (Drugs, Devices and Diagnostics Development) program for (1) consultation with experts in pharmaceutical product development, (2) the joint NC TraCS-Research Triangle International Regulatory Service to obtain advice on preclinical regulatory requirements, (3) IRB guidance to gain approval for collection of human cancer tissue and (4) the pilot award



CTSA Program-supported researcher Shawn Hingtgen, Ph.D., an assistant professor at the University of North Carolina (UNC) Eshelman School of Pharmacy. (Photo credit: UNC School of Medicine)

program to provide foundational data that was vital for both further research funding and defining a path toward clinical implementation.

Hingtgen has engaged with patient and clinical stakeholders and business experts, resulting in an award from the Eshelman Institute for Innovation, a grant from the state of North Carolina and a newly funded investigator-initiated research project grant from NIH. In addition, his work led to filing two provisional patent applications and the launch of a new startup company.

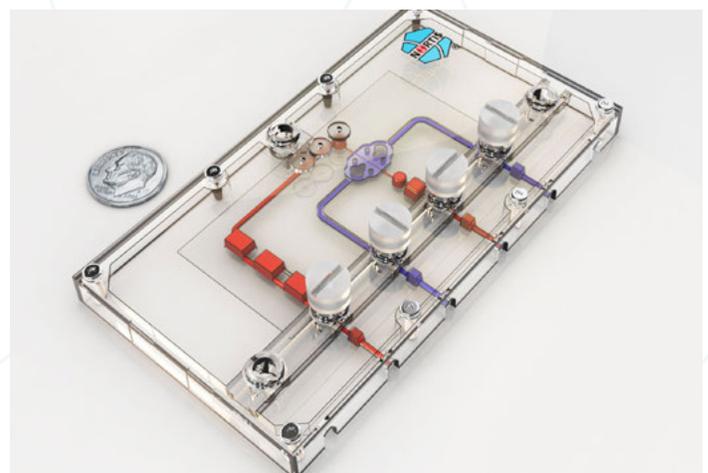
NCATS SBIR and Innovation Corps (I-Corps™) at NIH:

NCATS supports career training even for well-established investigators who already have entered the commercialization realm. Two biotechnology companies supported through the NCATS' SBIR program received supplements to participate in an NIH I-Corps™ training program to help company leaders navigate the challenges of product development. I-Corps™ at NIH is an innovative program to develop and nurture a national innovation ecosystem that builds upon biomedical research to develop technologies, products and services that benefit patients.

Two of the scientists who attended the training were from the Seattle-based biotechnology company Nortis, Inc., which focuses on tissue engineering; and CrossLife Technologies, Inc., in Carlsbad, California, a six-year-old company at which scientists develop diagnostic devices.

Companies commit to eight weeks of I-Corps™ training, assembling a three-person team, including a principal investigator, a company officer and a key opinion leader who knows the company and the field. Every team member must commit to 20 hours a week on the program. During the training, participants are asked to interview a minimum of 100 potential customers for their product, and they have the opportunity to speak with regulatory agencies, insurance companies, potential customers and others. Experienced trainers, who often are entrepreneurs themselves, provide advice and guidance on what the participants can learn from customer interviews.

CrossLife's scientists were developing a quick and easy bedside test to determine whether a person has dengue fever, a potentially life-threatening, mosquito-borne illness caused by a virus. The CrossLife team originally thought their customers would be the companies developing dengue fever vaccines. But after interviewing more than 110 potential customers, including village hospital doctors in Southeast Asia, Central America and South America (where dengue is most prevalent), as well as vaccine developers, distributors and others, the team realized they had made a mistake. Vaccine companies were not interested, but nongovernmental organizations and physicians in those regions wanted a test to diagnose and treat patients as quickly as possible. The CrossLife group adjusted its plan and is working on the development and evaluation of the test with the new customer base in mind.



Supported in part by NCATS, researchers at Nortis, Inc., are developing a tissue chip to grow stem cell-derived kidney cells to study kidney function. (Photo credit: Nortis, Inc.)

Nortis researchers develop microchips with three-dimensional chambers to grow miniature human tissues, organs and systems. The Nortis scientists planned to use tissue chip technology to create a human tissue environment that allowed them to study stem cell quality. The current stem cell quality test can be expensive, requires a large number of animals and may not always be accurate.

When Nortis researchers interviewed more than 100 potential customers, including academic researchers and industry experts, they were disappointed to learn that few people were interested in a new stem cell quality test. But in further conversations, the Nortis team discovered there was a need for a tissue chip with a stem cell-based model to study kidney function. Historically, Nortis' chips used kidney cells harvested from humans. In contrast, stem cell-derived kidney cells offered a standardized and renewable supply for tissue chips and a more accessible and convenient option for scientists using the chips.

When the Nortis team again polled potential customers for interest in the tissue chip to study kidney function, the team found a very different response in that 99 percent of those interviewed said they would use such a device. The new product is intended to provide a steady source of stem cell-derived kidney cells, allowing researchers to test the effects of various concentrations of drugs on the kidneys.

Knowledge Management and Dissemination: NCATS manages the content of the [Assay Guidance Manual \(AGM\)](#), a free, best-practices online resource devoted to the successful development of robust, early-stage drug discovery assays. The manual was originally developed by Eli Lilly and Company



NCATS' Assay Guidance Manual is a guide designed to provide researchers with step-by-step guidance through the complex process of turning a basic research finding into an assay that will start the process of discovering pharmacological tools and drugs.

as an internal document to provide step-by-step guidance based on knowledge from drug developers for planning and creating projects for high-throughput screening, lead optimization and early phases of regulated drug development. NCATS collaborated with Eli Lilly to make this resource publicly available, and today, with contributions from more than 100 scientists worldwide, the AGM is hosted online by NIH's National Library of Medicine. In 2016, AGM content was accessed more than 375,000 times.

NCATS also offers AGM training workshops for researchers involved in the drug discovery process, organizing three workshops in 2016. Topics included best practice guidelines to support early-stage assay development and target validation in drug discovery, including high-throughput screening.



Appendix: Therapeutics for Rare and Neglected Diseases (TRND) Program

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Brief Overview

Through 2016, TRND maintained a portfolio of projects addressing a range of conditions. These conditions included rare muscular, neurologic, metabolic and hormone defects; diseases of the blood, bone, lungs and eyes; and neglected infectious diseases affecting millions around the world. TRND supported both preclinical and clinical activities, including trials of novel therapeutic candidates as well as natural history studies of disease progression to help inform these trials. The comprehensive operational teams executing each project have successfully achieved interim milestones and are progressing according to schedules.

Notable regulatory, clinical, and partnering milestones were once again achieved in 2016. Two projects that TRND successfully de-risked (GNE myopathy and Niemann-Pick type C1 disease, or NPC1) were transitioned to external partners to continue their clinical development. Led by partner Vtesse, Inc., the NPC1 project expanded its pivotal multinational Phase IIB/III trial to additional clinical sites and received the Food and Drug Administration (FDA) “Breakthrough Therapy” designation. A Phase II trial was completed in GNE myopathy patients at the NIH Clinical Center, and the project has been successfully transitioned to Escala Therapeutics, Inc., for continued commercialization. Lumos Pharma, Inc., received clearance from the FDA to begin clinical studies for creatine transporter deficiency (CTD), while TRND’s partners at Cincinnati Children’s Hospital received similar clearance to initiate trials for pulmonary alveolar proteinosis (PAP) patients that will leverage existing resources from within the NCATS Clinical and Translational Science Awards (CTSA) Program. TRND milestone achievements also enabled the collaborators at Brigham and Women’s Hospital to raise venture capital funding and establish a biotechnology startup company to speed the team’s ongoing efforts of developing a treatment for fibrodysplasia ossificans progressiva (FOP).

In 2016, new collaborations were initiated at TRND, signaling a strategic commitment to develop biologic products to treat rare and neglected diseases. Most significantly, a concerted effort established a gene therapy development platform at TRND. Gene therapy is particularly relevant to rare disease patients, as more than 70 percent of rare diseases have known monogenic molecular pathology. These new collaborations with biotechnology and academic groups were strategically selected to serve as inaugural pilot

projects, enabling TRND to build a gene therapy translation toolbox. As a new modality of treatment, gene therapy presents unique technical and regulatory challenges. To help accelerate the field of gene therapy, each of these projects at TRND is designed to address specific translational pain points for gene therapy development. New technologies to scale up gene vector manufacturing and to deliver the transgene to the right tissue at the right time and dosage are among those being developed at TRND. These technologies and best practices to achieve regulatory approval of gene therapy will help improve the speed and reduce costs for gene therapy in general.

Detailed Accomplishments

See [Table 1](#) for detailed listing of scientific resources provided.

Therapeutic Development Portfolio: Projects listed in order of initiation

Project: Cyclodextrin for Niemann-Pick Type C1 Disease

Lead Collaborator: Daniel Ory, Washington University in St. Louis, MO

Collaborating NIH Institutes/Centers: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); National Institute of Neurological Disorders and Stroke (NINDS); National Human Genome Research Institute (NHGRI)

Initiated: September 2009

Description: Niemann Pick type C1 disease (NPC1) is a fatal genetic disease characterized by a failure to metabolize and dispose of cholesterol and lipids, causing progressively impaired movement and intellectual function. It strikes in early childhood and is lethal within a decade of diagnosis. There are no FDA-approved therapies for NPC1. HPBCD (2-hydroxypropyl-beta-cyclodextrin) appears to reduce the cholesterol and lipid accumulation and prolongs survival in NPC1 disease animal models. The goal of this project is to generate the extensive data needed to establish safe, effective dosing for the delivery of HPBCD directly into the central nervous system of NPC1 patients and to test the drug for safety, efficacy and biomarker reliability in NPC1 patients.

Outcomes: TRND established an interdisciplinary project team of academic and industrial scientists from nine different organizations and received ongoing input from patient advocacy groups in order to accomplish the clinical evaluation of HPBCD most efficiently. TRND scientists conducted the animal toxicology studies necessary to file an Investigational New Drug (IND) application with the FDA and helped support biomarker studies. Through TRND, NCATS provided support for the IND application and, in November 2012, received FDA notification that the clinical trials could proceed. The first-in-human clinical trials began in January 2013 at the NIH Clinical Center.

In January 2015, the collaborative team entered into an agreement with the biotechnology company Vtesse, Inc., to continue development of HPBCD and investigate additional therapies for other lysosomal storage disorders. The Phase I trial was concluded successfully, enabling Vtesse to initiate a pivotal multicenter, multinational Phase IIB/III clinical efficacy trial. Due to the strong preclinical and early clinical data, Vtesse received the FDA's "Breakthrough Therapy" designation in early 2016. This designation could accelerate approval to provide the first effective treatment for slowing the progress or stabilizing the devastating impacts of NPC in children and adolescents. This TRND project is now concluded.

Project: DEX-M74 for GNE Myopathy (Hereditary Inclusion Body Myopathy)

Lead Collaborator: William Gahl, National Human Genome Research Institute (NHGRI) Intramural Research Program and NIH Clinical Center, Bethesda, MD

Collaborating NIH Institutes/Centers: NHGRI; NIH Clinical Center

Initiated: September 2009

Description: GNE myopathy (formerly known as hereditary inclusion body myopathy or HIBM) is a rare genetic disorder characterized by progressive muscle weakness resulting in severe incapacitation. This condition has been traced to specific mutations in the GNE gene and the biochemical pathways (sialic acid synthesis) this gene affects within muscle cells. There are no approved therapies for GNE myopathy, and treatment is limited to palliative care. This project aims to develop

a small molecule (DEX-M74) specifically targeted to address the biochemical pathway deficits caused by the GNE mutations that lead to muscle wasting.

Outcomes: TRND supported the completion of animal toxicology studies and generated required data on the manufacturing processes to produce the final drug product. This work allowed TRND to submit information to the FDA that provided a basis for the agency lifting the clinical hold that was preventing initiation of human trials. To gather the information on the disease required for a clinical trial, TRND scientists began a natural history study of GNE myopathy disease progression in 2011.

After the FDA lifted the clinical hold, TRND scientists concluded Phase I and Phase II clinical studies in GNE myopathy patients at the NIH Clinical Center. In 2015, Altamira Bio, Inc. (now Escala Therapeutics, Inc.) acquired a license and entered into a Cooperative Research and Development Agreement (CRADA) with NIH to continue the development of DEX-M74 for GNE myopathy, as well as other disorders related to the sialic acid biochemical pathway. This TRND project is now concluded.

Project: A Novel Compound for Targeted Treatment of CBF Leukemia

Lead Collaborator: Paul Liu, NHGRI Intramural Research Program, NIH, Bethesda, MD

Collaborating NIH Institutes/Centers: NHGRI

Initiated: June 2011

Description: Core-binding factor (CBF) leukemia is a rare cancer with a survival rate of less than 50 percent. Standard treatments consist of non-specific chemotherapy and/or bone marrow transplantation, which are frequently associated with significant side effects, including life-threatening infections, bleeding, kidney dysfunction and even death. This project seeks to develop a drug targeted to the specific causal genetic abnormality responsible for CBF leukemia, with the aim of significant improvement in survival and reduced complications compared with current treatments.

Outcomes: TRND researchers have successfully optimized and demonstrated the utility of the animal disease model. TRND scientists are performing medicinal chemistry

optimization to identify a compound suitable for formal preclinical development. Once such a compound is identified, TRND will conduct the necessary studies to support filing an IND with the FDA.

Project: Inhaled GM-CSF Therapy of Autoimmune Pulmonary Alveolar Proteinosis

Lead Collaborator: Bruce Trapnell, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Collaborating NIH Institutes/Centers: Not applicable

Initiated: September 2011

Description: Autoimmune pulmonary alveolar proteinosis (PAP) is a rare disease marked by accumulation of surfactant (proteins and lipids) in the narrow gas exchange pockets of the lung, leading to respiratory failure. Patients generate antibodies against a normal protein (GM-CSF) that is critical for proper clearance of these accumulated proteins and lipids. Current therapy requires lifelong, periodic washing of the lungs (whole-lung lavage, or WLL) under general anesthesia, a risky and invasive procedure that is particularly problematic in children. The purpose of this project is to develop an inhaler-based formulation of the GM-CSF protein to stimulate PAP patients' own immune cells to properly clear the lungs and thus avoid WLL.

Outcomes: A comprehensive project plan was developed by TRND and the lead collaborators at Cincinnati Children's Hospital. The team subsequently entered into collaboration with Genzyme Corporation, which provided essential research materials to the partnership. TRND scientists supported extensive preliminary toxicology and dosing studies in primates, which were necessary to demonstrate the safety of using inhaled GM-CSF. TRND supported formal toxicology studies that enabled the lead collaborator to successfully open an IND with the FDA. The lead collaborator subsequently secured additional resources through the NCATS Division of Clinical Innovation's Clinical and Translational Science Awards (CTSA) Program to support a Phase I clinical evaluation of inhaled GM-CSF in autoimmune PAP patients, utilizing existing infrastructure provided by the Rare Lung Diseases Consortium.

Project: BMP Inhibitors to Treat Fibrodysplasia Ossificans Progressiva

Lead Collaborator: Paul Yu, Brigham and Women's Hospital, Boston, MA

Collaborating NIH Institutes/Centers: Not applicable

Initiated: September 2011

Description: Fibrodysplasia ossificans progressiva (FOP) is a rare, fatal disease marked by inappropriate growth of bone fragments within the muscles, ligaments and other connective tissues, causing pain and progressive immobility. There are no FDA-approved disease-modifying therapies. This bone formation is initiated by inappropriate activation of the bone morphogenetic protein (BMP) pathway. The lead collaborator has identified a compound that inhibits this spurious activation of the BMP pathway. The goal of this project is to develop this early-stage inhibitor compound into a drug that may be taken orally and to perform the studies needed for testing in FOP patients.

Outcomes: TRND researchers determined that the initial lead molecule was unsuitable for further preclinical development. As such, TRND scientists are performing medicinal chemistry optimization to identify a compound suitable for formal preclinical development. The TRND achievements to date have enabled the lead collaborator to raise additional funding and establish a startup company to speed the team's ongoing development efforts.

Project: LUM-001 as a Treatment for Creatine Transporter Deficiency (CTD)

Lead Collaborator: Robert Davis, Lumos Pharma, Inc., Austin, TX

Collaborating NIH Institutes/Centers: NICHD

Initiated: September 2011

Description: Creatine serves as a crucial energy source in the brain, and it is delivered to brain tissue by a specialized transport protein. Approximately 42,000 males in the United States are affected by CTD, in which creatine cannot enter the brain, resulting in profound learning disabilities, autistic behavior, recurring epileptic seizures and lifelong care needs. There are no FDA-approved therapies for these patients. The

lead collaborator has identified a creatine analog (LUM-001) that is able to penetrate the brain and serve the same role as creatine, even when creatine transporters are defective. The goal of this project is to develop LUM-001 into an oral therapeutic to treat CTD.

Outcomes: After TRND's acceptance of the project, Lumos was able to secure additional funding from the Wellcome Trust to speed the team's collaborative work. TRND scientists performed pharmacokinetic studies in animal models of the disease to better understand brain uptake of LUM-001. Key toxicology, formulation development, and chemistry and manufacturing activities have been completed, enabling Lumos to successfully file an IND application with the FDA. To support future clinical trials of LUM-001, TRND is collaborating with Lumos on a prospective natural history study of the disease course in patients, which will occur at multiple sites, including the NIH Clinical Center.

Project: Long-Acting Parathyroid Hormone Analog for the Treatment of Hypoparathyroidism

Lead Collaborator: Henry Bryant, Eli Lilly and Company, Indianapolis, IN

Collaborating NIH Institutes/Centers: NICHD

Initiated: September 2013

Description: Hypoparathyroidism is a rare hormone-deficiency syndrome in which the body lacks parathyroid hormone (PTH). Due to PTH's central role in maintaining the balance of calcium and phosphate in the blood, symptoms of hypoparathyroidism include muscle cramping, convulsions, intellectual disabilities, cataracts and abnormal heart rhythm. Due to a persistent lack of calcium, patients must receive high-dose calcium supplements, which can have negative effects on the kidneys. The goal of this project is to develop a PTH replacement that will demonstrate a more normal, stable level of PTH activity and lessen the need for chronic high-dose calcium supplements.

Outcomes: TRND scientists, in collaboration with researchers from Eli Lilly and Company, have validated and further developed the animal model of hypoparathyroidism

to generate robust efficacy data. TRND will support the preparation and filing of the IND application with the FDA to enable the subsequent proof-of-concept clinical study in hypoparathyroidism patients.

Project: Use of Rapamycin for the Treatment of Hypertrophic Cardiomyopathy in Patients With LEOPARD Syndrome

Lead Collaborator: Maria Kontaridis, Beth Israel Deaconess Medical Center, Boston, MA

Collaborating NIH Institutes/Centers: Not applicable

Initiated: September 2013

Description: LEOPARD syndrome (LS) is a rare genetic disease affecting only about 200 patients worldwide. Nearly all cases of LS result from mutations in a single gene, PTPN11. In the heart, the most common manifestation of LS is hypertrophic cardiomyopathy (HCM), a thickening of the walls of the heart. There is no existing treatment for LS patients who have HCM, and end-stage heart failure can lead to early death. The lead collaborator has shown that rapamycin can prevent and reverse HCM in animal models of LS. The purpose of this project is to develop rapamycin or similar compounds as effective HCM therapies for LS patients.

Outcomes: TRND researchers are conducting additional animal efficacy studies with the lead molecule. The results of these studies, in addition to known toxicology and other supporting information, will determine what further studies will be needed to support development of a clinical plan and will enable filing an IND application with the FDA to enter human trials.

Project: Repurposing an EU Therapeutic for Hemoglobinopathies

Lead Collaborator: Susan Perrine, Phoenicia BioSciences, Inc., Weston, MA

Collaborating NIH Institutes/Centers: Not applicable

Initiated: September 2014

Description: The most common global genetic diseases — beta-thalassemia and sickle cell disease (SCD) — are caused by defects in one part (beta-globin) of hemoglobin, the protein in red blood cells that carries oxygen throughout the body. These hemoglobin disorders, called hemoglobinopathies, can result in moderate to severe anemia, with symptoms ranging from weakness and fatigue to damage to the heart, brain, lungs and other organs. These symptoms can cause chronic disabilities and early death. No drugs are approved to treat the underlying causes of these disorders. The lead collaborator has identified a drug that is currently approved in the European Union to treat another condition, which has the potential to treat beta-thalassemia and SCD. The goal of this project is to develop this existing drug as an effective therapy targeted at the underlying cause of both beta-thalassemia and SCD.

Outcomes: The TRND team formalized and initiated a comprehensive preclinical project plan with a primary focus on beta-thalassemia as the first indication. Cell-based and animal pharmacology and efficacy studies are in progress to recapitulate key data generated by the collaborator, with further studies planned to support IND filing with the FDA.

Project: Development of Malaria Transmission-Blocking Drugs

Lead Collaborator: Kim Williamson, Uniformed Services University of the Health Sciences, Bethesda, MD

Collaborating NIH Institutes/Centers: Not applicable

Initiated: September 2014

Description: Malaria is a parasitic disease that spreads through the bite of an infected mosquito. Malaria affects an estimated 250 million people worldwide, particularly in the tropical regions of sub-Saharan Africa. The disease affects multiple organs in the body, and symptoms include cycles of chills, fever and sweating, along with headaches, tiredness, muscle pain, vomiting and diarrhea. Current therapies generally lead to complete recovery, but approximately 650,000 patients die each year. Even while on current therapies, patients remain infectious for a period of time, allowing further mosquito-borne transmission to others. The purpose of this project is to develop a novel class of drugs that will not only prevent infection and relieve symptoms but also block mosquito-borne transmission from person to person.

Outcomes: Pilot studies between the lead collaborator and NCATS scientists resulted in identification of a series of compounds suitable for lead optimization. The TRND team is performing medicinal chemistry optimization to identify a lead candidate for further development. Initial pharmacology and absorption, distribution, metabolism and excretion (ADME) studies are being performed, with further studies planned to support IND filing with the FDA.

Project: Treatment of Acid Ceramidase Deficiency

Lead Collaborator: Ivan Galanin, Plexcera Therapeutics LLC, Vero Beach, FL

Collaborating NIH Institutes/Centers: Not applicable

Initiated: May 2015

Description: Ceramides are a group of naturally occurring molecules present in the cell membrane. However, excess ceramide is toxic to the cell. The acid ceramidase (AC) enzyme is responsible for breaking down excess ceramide to maintain an appropriate balance. Genetic mutations that disrupt normal AC function (AC deficiency) lead to rare metabolic conditions, such as Farber's disease. These diseases strike infants, causing crippling arthritis, lung inflammation, nervous system degeneration and liver disease, and result in premature death. The only available therapy for AC deficiency is a bone marrow transplant, an invasive procedure with significant risks. The scientists at Plexcera Therapeutics developed an approach to deliver functional AC protein without resorting to bone marrow transplantation. The purpose of this project is to support the pre-clinical development of this novel enzyme replacement therapy.

Outcomes: TRND scientists completed a rigorous gap analysis and created a pre-clinical development plan that identified a set of critical experiments and milestones for the project. During the planning phase, the lead collaborators established a new business alliance, enabling them to use internal corporate resources to continue preclinical development. This TRND project is concluded.

Project: A Protein Replacement Drug for Friedreich's Ataxia

Lead Collaborator: R. Mark Payne, Chondrial Therapeutics LLC, Indianapolis, IN

Collaborating NIH Institutes/Centers: Not applicable

Initiated: May 2015

Description: Friedreich's ataxia (FA) is a rare, progressive condition affecting multiple systems in the body. The disease typically begins in mid-childhood, leading to an inability to stand or walk within 15 years of onset. Patients experience progressive loss of voluntary muscle control and coordination, debilitating scoliosis (abnormal curvature of the spine) and heart failure leading to premature death by age 50. Some patients also develop diabetes and suffer loss of hearing and vision. There are no approved treatments for FA other than supportive care. The lead collaborator has developed a technology to deliver functional frataxin protein to patients. The purpose of this project is to support the development of this protein replacement therapy.

Outcomes: TRND scientists are developing and manufacturing a suitable formulation of therapeutic frataxin protein, conducting additional efficacy and toxicology studies and developing and validating the biochemical assays necessary to evaluate the drug product. Successful completion of these studies will enable the collaborator to submit an IND application to the FDA.

Project: Therapy for Fuchs Endothelial Corneal Dystrophy

Lead Collaborator: David Eveleth, Trefoil Therapeutics, Inc., San Diego, CA

Collaborating NIH Institutes/Centers: Not applicable

Initiated: May 2016

Description: Fuchs endothelial corneal dystrophy (FECD) is a degenerative disease of the eye. The front surface of the eye, called the cornea, helps regulate vision by focusing light onto the lens. FECD affects the thin layer of cells at the back of the cornea, which progressively become damaged and die. As these cells are lost, the cornea retains excess fluid, resulting in loss of optical quality and decreased vision.

Most patients are diagnosed with FECD only after significant numbers of corneal cells have been lost, and the only treatment for advanced disease is corneal transplantation. The lead collaborators have developed a growth factor therapy that aims to halt — and potentially reverse — the degeneration of endothelial cells. The purpose of this project is to support further preclinical development and enable clinical trials.

Outcomes: The TRND project team has conducted a rigorous gap analysis to determine the project plan. TRND scientists are developing a formulation and production process, conducting preclinical safety studies and manufacturing clinical-grade material. Completion of these studies will enable the lead collaborator to submit an IND application to the FDA.

Project: Gene Therapy for the Treatment of AADC Deficiency

Lead Collaborator: Jodi Cook, Agilis Biotherapeutics, Inc., Boston, MA

Collaborating NIH Institutes/Centers: Not applicable

Initiated: May 2016

Description: Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare, inherited disorder that typically appears within the first year of life. The AADC enzyme is necessary for the production of important chemical messengers in the brain and nervous system. Children with the condition experience a number of symptoms, including severe developmental delays, weak muscle tone, involuntary movements of the arms and legs, and painful seizures. Patients require lifelong care, and particularly severe cases can lead to death within the first decade of life. There are no approved treatments for AADC deficiency. The lead collaborators are developing a gene therapy technology (AGIL-AADC) to restore AADC enzyme production in the brain. The purpose of this project is to support further preclinical development work to accelerate the approval of this life-saving therapy for patients.

Outcomes: The TRND project team has conducted a rigorous gap analysis to determine the project plan. TRND scientists have initiated a number of activities including product development and manufacture of clinical-grade AGIL-AADC, epidemiological studies, non-clinical safety studies and regulatory filing with worldwide regulatory agencies. In 2016, AGIL-AADC received both "Orphan Drug" and "Rare Pediatric

Disease” designations from the FDA, as well as an “Orphan Medicinal Product” designation from the European Medicines Agency. These regulatory designations provide important incentives to further the development and commercialization of AGIL-AADC.

Project: Gene Therapy for the Treatment of Pompe Disease

Lead Collaborator: Dwight Koeberl, Duke University, Durham, NC

Collaborating NIH Institutes/Centers: Not applicable

Initiated: May 2016

Description: Pompe disease is a rare, inherited metabolic disorder. Mutations in the acid alpha-glucosidase enzyme cause toxic buildup of cellular byproducts, leading to damage to multiple organs and tissues, particularly the muscles.

Symptoms can appear within a few months of birth or may arise later in life. Affected babies commonly experience muscle weakness, poor muscle tone, and liver and heart defects that can lead to premature death in the first year of life. Later-onset forms of the disease can result in delayed motor skills and progressive muscle weakness, leading to breathing problems and respiratory failure. Enzyme replacement therapy is available, but outcomes are variable. The lead collaborators have developed a gene therapy approach that aims to overcome the variability of current enzyme treatment. The purpose of this project is to support further preclinical development and enable clinical trials.

Outcomes: The lead collaborator has obtained IND clearance from the FDA to initiate clinical trials. TRND scientists are supporting the manufacture of clinical-grade therapeutic vector. Completion of these activities will enable the lead collaborator to conduct the planned clinical studies.

Table 1. TRND Projects and Scientific Resources

See text for outcomes.

Project	Collaborating Institutions	Scientific Resources
Cyclodextrin for Niemann-Pick Type C1 Disease	Ara Parseghian Medical Research Foundation; Support of Accelerated Research for NPC Disease (SOAR-NPC); Washington University; Albert Einstein College of Medicine; University of Pennsylvania; Johnson & Johnson; Vtesse, Inc.; NICHD; NINDS; NHGRI	Project Management, Pharmacology, ADME/PK, Toxicology, Formulation, Regulatory, Clinical
DEX-M74 for GNE Myopathy	NHGRI; New Zealand Pharmaceuticals Limited; NIH Clinical Center	Project Management, ADME/PK, Toxicology, Formulation, Process Chemistry, Regulatory, Clinical
A Novel Compound for Targeted Treatment of CBF Leukemia	NHGRI	Project Management, Medicinal Chemistry, Pharmacology, ADME/PK, Toxicology
Inhaled GM-CSF Therapy of Autoimmune Pulmonary Alveolar Proteinosis	Cincinnati Children's Hospital; Genzyme Corporation	Project Management, Pharmacology, Toxicology, Formulation
BMP Inhibitors to Treat Fibrodysplasia Ossificans Progressiva	Brigham and Women's Hospital	Project Management, Medicinal Chemistry, Informatics, Pharmacology, ADME/PK, Toxicology
LUM-001 as a Treatment for Creatine Transporter Deficiency	Lumos Pharma, Inc.; Cincinnati Children's Hospital; NICHD	Project Management, ADME/PK, Toxicology, Formulation, Process Chemistry, Regulatory, Clinical
Long-Acting Parathyroid Hormone Analog for the Treatment of Hypoparathyroidism	Eli Lilly and Company; NICHD	Project Management, Pharmacology, ADME/PK, Toxicology, Formulation, Process Chemistry
Use of Rapamycin for the Treatment of Hypertrophic Cardiomyopathy in Patients with LEOPARD Syndrome	Beth Israel Deaconess Medical Center	Project Management, Pharmacology
Repurposing an EU Therapeutic for Hemoglobinopathies	Phoenicia BioSciences, Inc.	Project Management, Pharmacology
Development of Malaria Transmission-Blocking Drugs	Uniformed Services University of the Health Sciences	Project Management, Medicinal Chemistry, Pharmacology, ADME/PK
Treatment of Acid Ceramidase Deficiency	Plexcera Therapeutics LLC	Project Management
A Protein Replacement Drug for Friedreich's Ataxia	Chondrial Therapeutics LLC	Project Management, Pharmacology, ADME/PK, Toxicology, Formulation, Process Chemistry
Therapy for Fuchs Endothelial Corneal Dystrophy	Trefoil Therapeutics, Inc.	Project Management, Formulation, ADME/PK, Toxicology, Process Chemistry
Gene Therapy for the Treatment of AADC Deficiency	Agilis Biotherapeutics, Inc.	Project Management, Toxicology, Process Chemistry, Clinical
Gene Therapy for the Treatment of Pompe Disease	Duke University	Project Management, Process Chemistry

Glossary of Terms

ADME/PK – Absorption, distribution, metabolism and elimination (ADME) and pharmacokinetics (PK). PK studies determine how a drug molecule moves within the body after administration. ADME studies examine how the drug is absorbed by tissues and organs after a dose is given, how the drug is distributed throughout the various organs and tissues of the body, how the drug is metabolized and broken down in the body and how the drug is eliminated from the body.

Clinical Support – Includes human trials of therapeutic candidates up to Phase II to assess the candidates' safety and effectiveness in treating the intended disease, as well as non-drug studies of patients with a particular disease (e.g., natural history studies).

Dosing – Determining the appropriate amount of a drug needed to achieve the intended beneficial effect on the disease.

Formulation – Determining the most appropriate form of the molecule for administration as a drug (e.g., solid pill, drinkable solution, injection). Development of a specific formulation takes into account not only the chemical reactions required to create the drug molecule but also the manufacturing processes involved in creating pure, safe, sufficient amounts of the drug to be dispensed.

Informatics – Using computational techniques to analyze relationships between chemical structure and biological properties. These information-based approaches can help guide the selection of drug candidates and inform medicinal chemistry efforts.

Investigational New Drug (IND) Application – The complete pre-clinical data package required by the FDA prior to the clinical testing of a new therapeutic in humans. The IND package is meant to demonstrate to the FDA that it is reasonably safe to conduct human clinical trials with the intended therapeutic.

Medicinal Chemistry – Refining the chemical structure of a candidate drug molecule in order to improve its efficacy and safety in treating a disease.

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

Pharmacology – Considering the effects a drug has on the body and its organs. Pharmacology studies examine the specific biological pathways involved in how the drug exerts its intended therapeutic effect. Also known as pharmacodynamics (PD).

Process Chemistry – Developing and refining the procedures and processes for efficiently manufacturing a drug in sufficient quantities to treat the patient population.

Project Management – Providing project oversight and leadership throughout all phases of TRND projects, including planning, execution and completion. This process drives team decisions and communicates with all project stakeholders to ensure high-quality outcomes in the most cost-efficient and timeline-effective manner.

Regulatory Support – Support offered to collaborators in submission of IND applications. TRND supports its collaborators by participating in early-stage advisory meetings with the FDA, preparing the full data package reflecting all results from pre-clinical studies and responding to any concerns raised by the FDA.

Toxicology – Defining the adverse (toxic) side effects that a drug may have.

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