National Center for Advancing Translational Sciences

2015 REPORT

National Center for Advancing Translational Sciences

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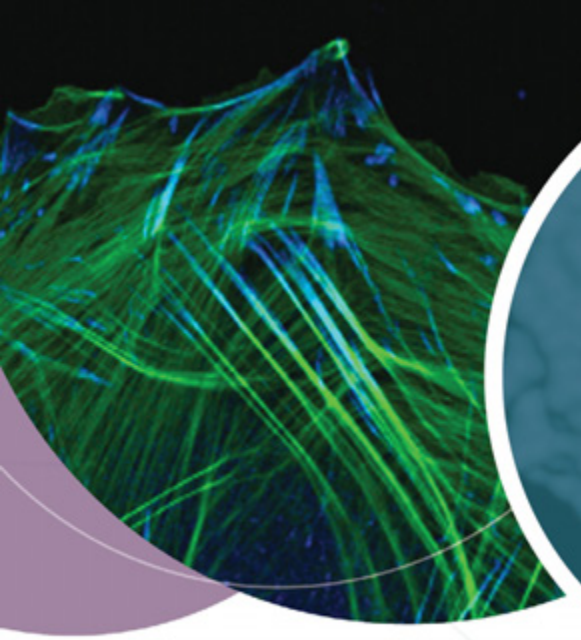
Front cover, Translational Science Spectrum: In 2015, NCATS developed the translational science spectrum to help researchers, patients and the public understand the translational science process. See page 4 for more information.



Introduction and Director's Message

Christopher P. Austin, M.D.

I am delighted to share the 2015 annual report of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH). This report features recent highlights of NCATS' work to get more treatments to more patients more quickly by developing new technologies and operational models to accelerate translation; demonstrating their usefulness in specific applications; and disseminating the approaches, data and methodologies to the scientific community.

Our cover illustrates how NCATS conceptualizes the translational science spectrum (see page 4) as a continuum from discoveries about the biological basis of health and disease to interventions that have been shown to improve the health of individuals and the public. The spectrum is nonlinear and multidirectional, meaning that each stage builds upon and informs the others — with patients being central to all stages — and progress often occurring in multiple directions at once. Translational science is a new discipline, so educational efforts like this one help NCATS' many stakeholders and partners accurately conceptualize the translational process, the current roadblocks to its efficient operation, and the opportunities for progress. In an advance from 2015 that illustrates the multidirectional nature of the spectrum, NCATS scientists and collaborators tested thousands of combinations of known and investigational drugs and not only identified potential new drug combinations as treatments for malaria, but also provided fundamental insights into the biology of this highly prevalent and lethal disease. Read more on page 7.

A new drug currently takes about 14 years and more than $1 billion to develop, with a failure rate exceeding 95 percent. NCATS is working on many approaches to decrease the time and failure rate of new drug development, and also is working to bypass these problems through drug repurposing, a process that enables researchers to find new uses for drugs that already have been approved by the Food and Drug Administration (FDA) or that have cleared several key steps along the development pathway. NCATS' repurposing efforts resulted in crucial advances in 2015, including the identification of drugs that may treat multiple sclerosis, hepatitis C and Ebola virus infection. In addition, through NCATS' Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) program, investigational compounds from pharmaceutical companies are being rapidly developed for new disease indications, including a potential treatment for Alzheimer's disease. Read more on page 11.

A major current roadblock in the path to developing new therapeutics is the difficulty of accurately predicting whether a potential drug will be safe or effective in humans. Through its Tissue Chip for Drug Screening program, NCATS is tackling

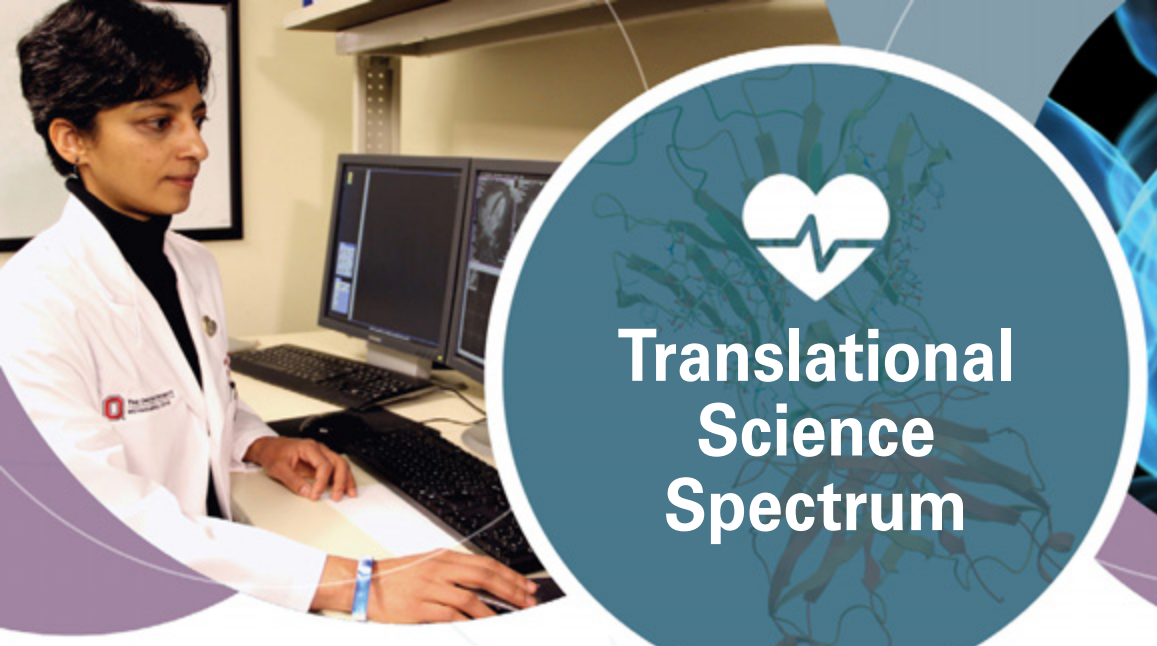
this problem by supporting the development of 3-D human "tissue chips" that mimic the structure and function of human organs. In 2015, scientists funded through this program began integrating individual organ chips into multi-organ microfluidic platforms that accurately model the complex functions of the human body. Once fully developed and validated, these systems promise to predict the beneficial and adverse effects of a candidate drug, vaccine or biologic agent more quickly and accurately than the current animal or cell culture models. As just one example, an NCATS-supported team of scientists at Northwestern University created a chip containing female reproductive tissues that interact with each other over phases of a month or more, much like they do in the human body. The device, called EVATAR™, will be used in drug development research and to study basic female reproductive biology. Learn more on page 15.

NCATS' Clinical and Translational Science Awards (CTSA) Program supports an innovative national network of medical research centers collaborating to improve the clinical and translational research process. CTSA Program investigators and NCATS staff worked together in 2015 to pilot several new initiatives. These were aimed at the largest problems limiting translational effectiveness, including improving clinical trial recruitment, streamlining the review process for safe conduct of multisite clinical trials, and training and cultivating biomedical researchers skilled in the new field of translational science. Read more on page 18. These advances in the way clinical studies are conducted will be particularly important to efforts in precision medicine, which will require the ability to efficiently identify, involve and study individuals with specific genetic or other characteristics.

Rare diseases research remains a special priority for NCATS. Innovative discoveries about the molecular basis of rare diseases offer unprecedented opportunities to improve the diagnosis and treatment of thousands of such diseases, most of which have no treatment. New scientific insights from genomics and experimental therapeutics increasingly show that rare and common diseases often share biochemical pathways and mechanisms, enabling rapid application of the insights gained from the study of one disease to the treatment of others. To this end, NCATS' Rare Diseases Clinical Research Network (RDCRN) brings researchers and patient advocates together to collaborate on studies to understand and treat groups of rare diseases and to share data. Just one of the many results of the novel team-based work of the RDCRN in 2015 was the approval by FDA of sirolimus, which became the first approved treatment for lymphangioleiomyomatosis, a debilitating and progressive lung disease that strikes women of childbearing age. See more about the RDCRN program on page 21.

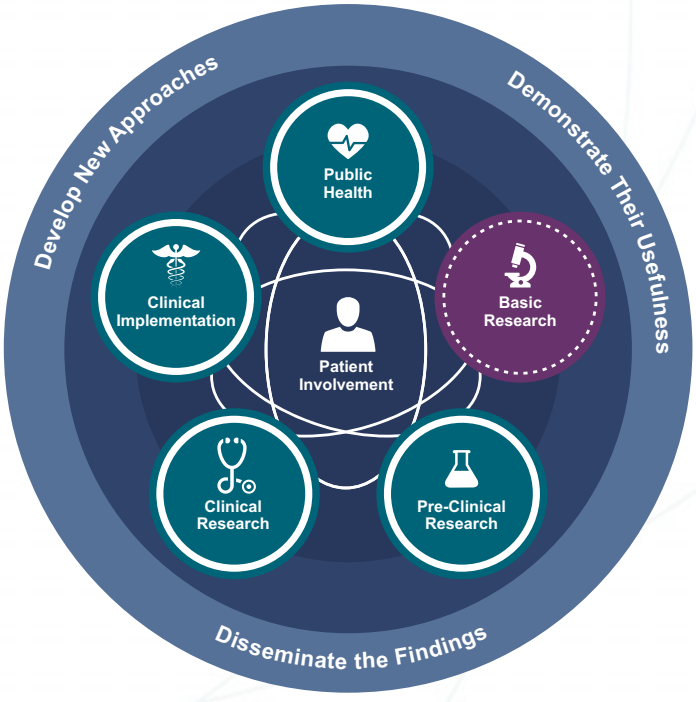
These and many other highlights of NCATS' 2015 achievements are described in the following pages. I hope you enjoy reading about the remarkable work of our committed and creative NCATS-supported researchers and are encouraged by the progress we are achieving in accelerating translation for the benefit of patients in need.

Christopher P. Austin, M.D.
Director
National Center for Advancing Translational Sciences



Translational Science Spectrum

In 2015, NCATS articulated a holistic view of the translational science process. As illustrated in the diagram on the cover of this report and below, the Center envisions a spectrum encompassing each stage of research along the path from the biological basis of health and disease to interventions that improve health. The five stages delineated are Basic Research, Pre-Clinical Research, Clinical Research, Clinical Implementation and Public Health. Note that the spectrum is multidirectional and nonlinear: 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.



NCATS' translational science spectrum. Following are descriptions of the five stages.

Basic Research

Basic research involves scientific exploration that can reveal fundamental mechanisms of biology, disease or behavior. Every stage of the translational research spectrum builds upon and/or informs basic research. NCATS scientists typically do not conduct basic research; however, insights gained from the Center's studies along the translational spectrum can inform basic research.

Pre-Clinical Research

Pre-clinical research connects the basic science of disease with human medicine. During this stage, scientists develop model interventions to further understand the basis of a disease and find ways to treat it. Testing is carried out using cell or animal models of disease; samples of human or animal tissues; or computer-assisted simulations of drug, device or diagnostic interactions within living systems.

Clinical Research

Clinical research includes studies to better understand a disease in humans and relate this knowledge to findings

in cell or animal models; testing and refinement of new technologies in people; testing of interventions for safety and effectiveness in those with or without a disease; behavioral and observational studies; and outcomes and health services research. The goal of many clinical trials is to obtain data to support regulatory approval for an intervention.

Clinical Implementation

The clinical implementation stage of translation involves the adoption of interventions that have been demonstrated to be useful in a research environment into routine clinical care for the general population. This stage also includes implementation research to evaluate the results of clinical trials and to identify new clinical questions and gaps in care.

Public Health

In this stage of translation, researchers study health outcomes at the population level to determine the effects of diseases and efforts to prevent, diagnose and treat them. Findings help guide scientists working to assess the effects of current interventions and to develop new ones.

Pre-Clinical Innovation

Pre-clinical research connects basic scientific discoveries with initial testing of therapies in humans. NCATS' pre-clinical programs support the development of new technologies to make this stage of the translational science spectrum more predictive and efficient and to "de-risk" targets and disease projects so they will be more attractive to potential partners. 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:

- New scientific understanding, technologies and approaches that directly address bottlenecks that limit the efficiency of the therapeutic or diagnostic development process;
- Collaborative pre-clinical drug development expertise and resources, including the generation of data needed for regulatory approval; and
- A variety of mechanisms to streamline partnerships and collaborations.

Improving the Drug Development Process

Assay Development and Screening Technology

One of the first steps in the drug development process is creating tests (assays) through which scientists can assess the effects of chemical compounds on cellular, molecular or biochemical processes of interest. Investigators from the biomedical research community submit ideas for assays

High-throughput screening

uses 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. In 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.

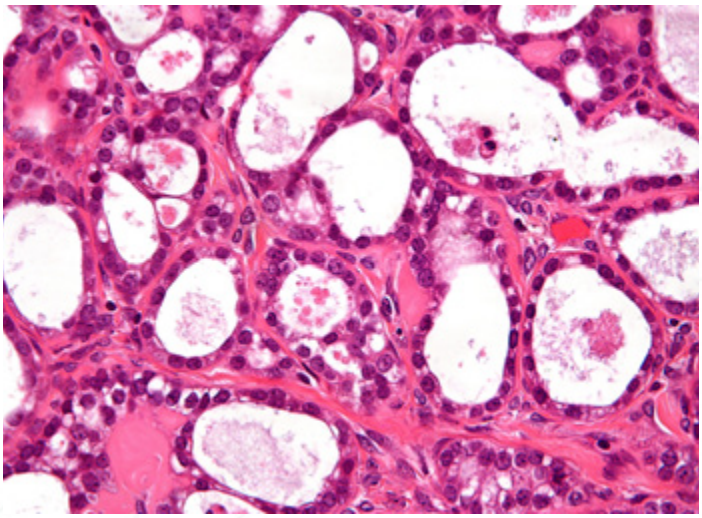
to NCATS scientists, who help to optimize them for high-throughput screening (see box on page 6 for definition). The results of these screens, called probes, can be used to further explore protein and cellular functions and biological processes relevant to human health and disease. In addition, these probes can be developed to become potential therapeutic candidates for further drug development.

Historically, scientists have developed disease models by growing cells in a single layer in a laboratory. It is a relatively straightforward process to grow and maintain these cellular monolayers, but they do not represent the complexities of tissues and organs in the human body. As a result, many compounds that seem effective in a monolayer culture in plastic dishes in a laboratory are not found to be safe or effective in animal and human studies.

To develop a better model, NCATS researchers worked with University of Chicago scientists to optimize a 3-D model of ovarian cancer metastasis (the process by which cancer spreads beyond the original tumor to other parts of the body) that could be utilized for high-throughput screening. The collaborative team used cells from ovarian cancer patients to construct a 3-D system that included connective tissue cells and the extracellular matrix (a collection of supportive molecules outside cells), creating a more lifelike simulation of the human body environment. NCATS scientists helped the researchers adapt the assay for testing at the Center's high-throughput screening facility, which enabled them to systematically test the 3-D ovarian cancer cell model against 2,420 different compounds at varied concentrations.

Only a few of the compounds screened, including one called beta-escin, demonstrated an ability to prevent all three metastatic stages both *in vitro* (in an artificial environment) and *in vivo* (in whole, living organisms, in this case, using a mouse model). Beta-escin, a naturally occurring substance derived from the seed of the horse chestnut tree, is commonly used to improve chronic venous insufficiency, a condition in which veins cannot pump enough blood back to the heart.

The compound's role in metastasis, which came as a surprise to the team, represents a promising lead for further explorations of its therapeutic potential. In the next phase of the project, the researchers will use the same 3-D model to screen 400,000 additional compounds. The system could be modified to model the metastasis of other cancers.



High-magnification image of an ovarian clear cell carcinoma. NCATS and University of Chicago scientists collaborated to test a 3-D ovarian cancer cell model to identify compounds with the potential to prevent the spread of ovarian cancer. (Photo credit: Copyright 2011 Michael Bonert http://www.gnu.org/copyleft/fdl.html)

Additionally, scientists could use it to study the basic biology of cancer metastasis. The results were published in the Feb. 5, 2015, issue of *Nature Communications*.

Another high-throughput screening project that illustrates the multidirectional nature of the translational science spectrum involves a recent screen of malaria drug combinations. Artemisinin-based combination therapies (ACTs) are recommended by the World Health Organization for first-line treatment of uncomplicated malaria caused by Plasmodium falciparum, a common and deadly parasite. These malaria medications have proven remarkably effective, but drug resistance to the treatments is on the rise, creating an urgent need for better treatments.

To help address the challenges, NCATS researchers and collaborators from the NIH's National Institute of Allergy and Infectious Diseases, Georgetown University, and the University of California, San Francisco, released a large dataset of potential drug combinations for malaria. Using NCATS' state-of-the-art high-throughput combination drug-screening platform, the Center's researchers tested 13,910 combinations of known and newly identified antimalarial drugs in three malaria parasite lines. The results were published in the September 25 issue of *Scientific Reports*.

The screening analyses done by the research team not only led to the identification of new ACTs but also provided insights into the basic biology of malaria that the research community can use further.

NCATS Chemical Genomics Center (NCGC)

Small-molecule chemical compounds, which can be used to test or "probe" the effects of increasing or decreasing the activity of a biological target in cells or animals, are some of the most powerful tools for target validation (the process of demonstrating that engaging a target provides meaningful therapeutic benefit). Generating these chemical probes requires specialized expertise and facilities, and NCATS has built cutting-edge collaborative services to meet these needs. Through the NCGC, formerly known as the NIH Chemical Genomics Center, NCATS scientists collaborate with more than 200 NIH-supported investigators in NIH laboratories, academia, industry and non-profit organizations to generate probes for studying a diverse cross-section of human biology, focusing specifically on novel targets and untreatable diseases. Probes enable researchers to investigate protein and cell functions and biological processes and, if appropriate, can be optimized to become potential drug candidates. NCATS' probe development activities also focus on finding more efficient ways to make probes, use probes to understand diseases, and validate targets to treat diseases.

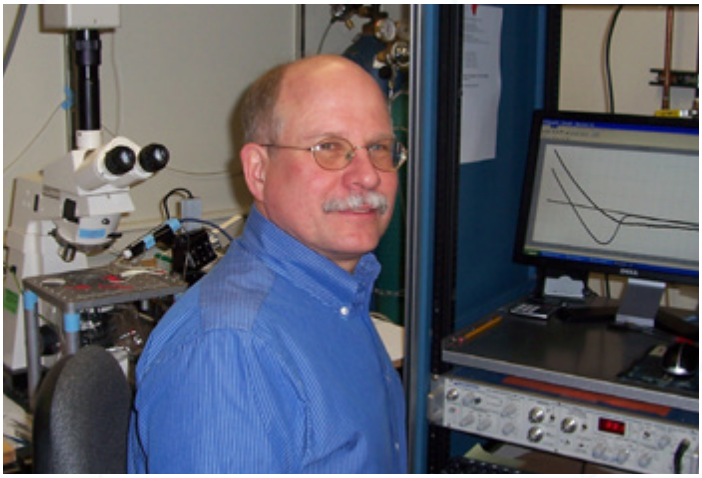
Bridging Interventional Development Gaps (BrIDGs)

NCATS provides resources that investigators need to develop promising therapies for both common and rare diseases. Through its BrIDGs program, NCATS makes such resources available to scientists on a competitive basis for the development of drugs, biologics and gene therapy. Successful applicants have access to NCATS' expertise to conduct the crucial pre-clinical studies necessary for regulatory approval for first-in-human trials. This expertise includes compound synthesis, formulation, pharmacokinetic studies and toxicology studies in support of investigator-held Investigational New Drug (IND) applications to the FDA.

In one NCATS project supported through its BrIDGs program, researchers at the Children's Hospital of Philadelphia are working to develop a drug called exendin-(9-39) for the treatment of congenital hyperinsulinism, a rare inherited disorder in which too much insulin production leads to low blood sugar in infants. These researchers are developing the drug to treat a type of congenital hyperinsulinism that does not respond to any current medication and is typically treated by near-total removal of the infant's pancreas. BrIDGs data enabled the investigators to amend a pre-existing IND to evaluate the effects of longer intravenous infusions and higher doses of the drug in patients. Soon, they also will test a formulation of the drug that can be injected just under the skin (i.e., subcutaneously). NCATS staff ensured that manufacturing of the drug, developing a subcutaneous formulation, and evaluating its safety effects in animal models all were in compliance with regulatory standards.

Another BrIDGs-supported project team is developing a new drug for epilepsy, a neurological disorder characterized by recurring seizures caused when a group of brain cells begins to fire in an abnormal way. While current therapies — called anticonvulsants — help about half of all epilepsy patients, the other half may continue to have seizures despite treatment. The researchers are developing a new anticonvulsant drug called 2DG that acts by stopping the bursts of brain cell activity that trigger seizures. The drug also may modify the disease so that more patients are amenable to treatment.

Although 2DG has been produced synthetically, a robust manufacturing method that would enable large-scale production and avoid potential intellectual property (IP) pitfalls was needed. NCATS scientists, in collaboration



NCATS BrIDGs-supported neurologist Thomas Sutula, M.D., Ph.D., of the University of Wisconsin-Madison, is exploring the anti-seizure actions of 2DG studied in the laboratory as a potential new therapy for epilepsy. (Photo credit: University of Wisconsin-Madison)

with a contract manufacturing organization, developed a practical, robust process for manufacturing 2DG that was suitable for human clinical studies. This manufacturing process enabled further clinical development while avoiding IP concerns typically encountered when using an existing, patented method of production. In addition, NCATS scientists conducted studies of the drug's safety in animal models. Previously published research had revealed that 2DG might cause heart damage (cardiotoxicity), and the FDA requested the development of a biomarker for cardiotoxicity as part of the 2DG pre-clinical safety evaluation effort. NCATS scientists successfully identified a potential biomarker of early cardiotoxicity; this finding could enable clinicians to monitor patients for early signs of heart injury in clinical trials and intervene before 2DG causes heart damage. The BrIDGs data enabled the research team to file an IND application in 2015.

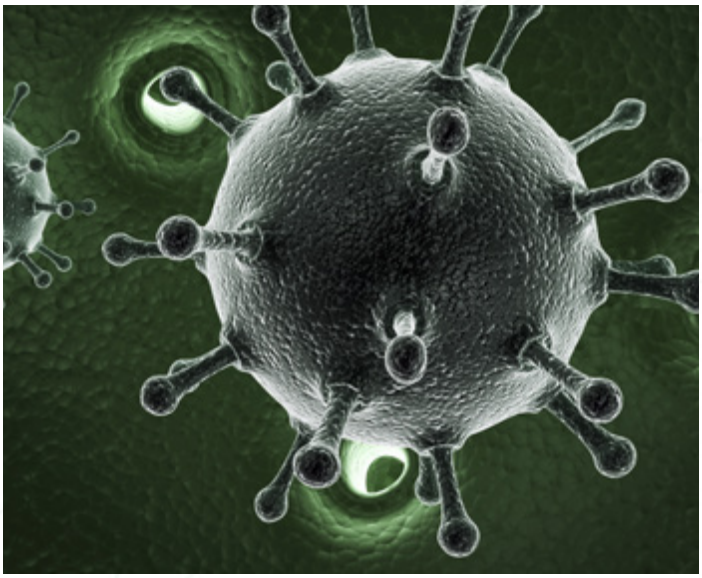
Repurposing Drugs

A single drug or specific combination of drugs may be effective in treating several distinct disorders. One way to shorten the process of developing new treatments and cures for diseases is to find new uses for drugs that already have been approved or that have cleared several key steps along the development pathway; this is called drug repurposing. NCATS focuses on repurposing because of the potential for therapeutic advances that will help get more treatments to more patients more quickly.

NCATS Pharmaceutical Collection

To enable repurposing on a broad scale, researchers can tap into the NCATS Pharmaceutical Collection (NPC), a comprehensive database and screening library of investigational medicines and drugs approved for clinical use by regulatory authorities in the United States, Europe, Canada or Japan. The NPC 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 NCATS.

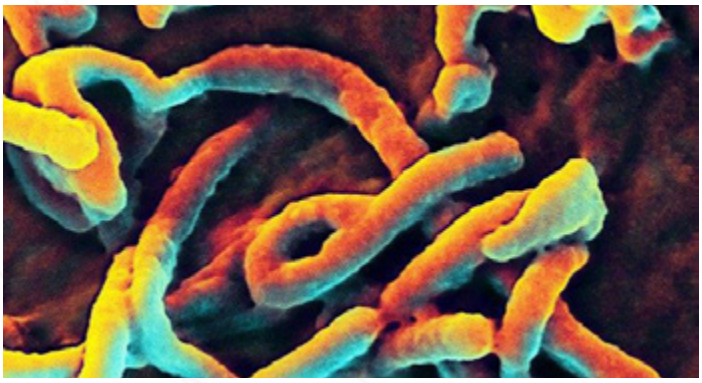
Testing of NPC drugs already has generated new and unexpected potential treatments. One group of NCATS scientists — in collaboration with Jake Liang, M.D., at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) — wanted to understand whether drugs used to treat other conditions might also be used to treat hepatitis C virus infection. Through a drug-repurposing



The hepatitis C virus. NCATS and NIDDK scientists discovered that an over-the-counter drug used to treat allergy symptoms also limited hepatitis C virus infection in human liver cells.

screen, the team identified a compound called chlorcyclizine that blocked the ability of the hepatitis C virus to infect cells. Chlorcyclizine is an antihistamine originally developed to treat seasonal allergies. Its activity against the hepatitis C virus provides important clues about how cells protect themselves against viruses in general. The results were published in the April 2015 issue of *Science Translational Medicine*, and the NIH Clinical Center has initiated a clinical trial for chlorcyclizine.

Tapping into the NPC also has yielded compounds that may combat Ebola virus infection. Currently, there is no FDA-approved medication for Ebola infection. Time- and resource-saving efforts become critical during public health



The Ebola virus. NCATS and Icahn School of Medicine at Mount Sinai researchers screened existing drugs and found 53 drugs that may block Ebola infection. (Photo credit: National Institute of Allergy and Infectious Diseases)

crises, and drug repurposing is a viable option that offers great potential. A team of researchers from NCATS and the Icahn School of Medicine at Mount Sinai developed a miniaturized assay for high-throughput screening to find compounds that block the ability of Ebola virus-like particles (VLPs) to enter and infect cells. A screen using 2,816 compounds from the NPC identified 53 drugs with entry-blocking activity against Ebola VLPs. Although further testing is needed before any of these drugs could be used to treat Ebola infection, the findings, which were rapidly published in *Emerging Microbes and Infections* in the midst of the Ebola outbreak, may jump-start the development of such treatments.

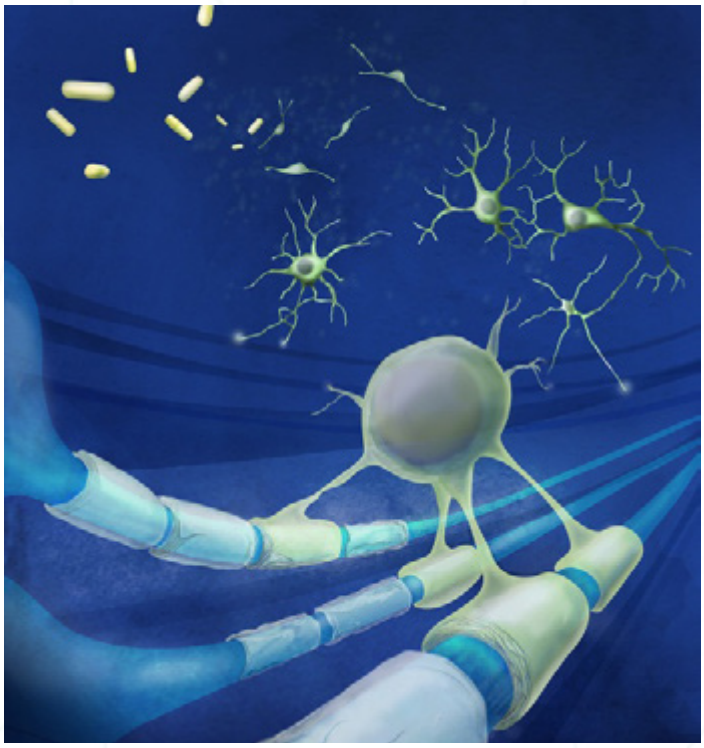
In a third scientific advance that involved screening using the NPC, scientists at Case Western Reserve University School of Medicine, who were funded in part by the National Institute of Neurological Disorders and Stroke (NINDS), found that two drugs currently used to treat fungal skin infections and eczema hold promise as therapies for multiple sclerosis. The drugs may activate stem cells in the brain to repair damage caused by the disease. The results were published in *Nature*, and the investigators are continuing to work with NCATS to expand the library of drugs screened to identify other promising compounds.

New Therapeutic Uses

Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) is a collaborative program designed to facilitate partnerships between pharmaceutical and academic research communities to advance therapeutics development. This innovative program matches companies that have investigational drugs or biologics with academic investigators who have new ideas for disease indications in which the drugs could be tested.

Through New Therapeutic Uses, NCATS is re-engineering how the public and private sectors collaborate, and it is creating new and faster ways to test novel treatments for both neglected and common diseases where there are unmet medical needs. Facilitated by NCATS, pharmaceutical companies provide their academic partners with investigational drugs, along with knowledge and data gathered from previous studies. The researchers use the compounds to test their hypotheses in pre-clinical experiments, and because of the agents' prior development, promising ones can advance to clinical trials much more quickly than usual.

New Therapeutic Uses also is designed to streamline the legal and administrative process for research collaboration across organizations through template partnership agreements, which are freely available on the NCATS website. During the program's pilot phase, these agreements reduced the time required to establish collaborations between industry and academia to about three months, far less than the more typical nine months to one year. The template agreements also are designed to address in advance common bottlenecks in drug development, such as patents and IP issues, to enable the research projects to proceed unimpeded. In July 2015, NCATS announced awards totaling nearly $3 million to fund cooperative agreements with four additional academic research groups to explore treatments for acute myeloid leukemia, an aggressive blood cancer; glioblastoma, one of the deadliest brain tumors in adults; Chagas disease, a neglected tropical disease causing heart, digestive and neurological problems; and type 2 diabetes, also known as adult-onset diabetes.



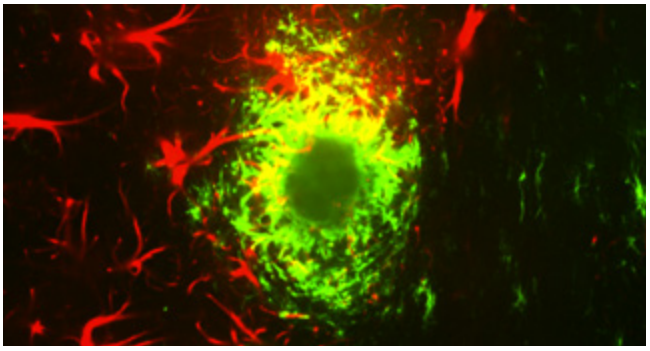
The image illustrates an oligodendrocyte depositing myelin, an insulating substance, on several nerve cells. In multiple sclerosis, the myelin sheaths of nerves are damaged, which impairs or blocks messages sent across the nervous system. Researchers from NCATS and Case Western Reserve University School of Medicine collaborated to identify and test approved drugs that could stimulate myelin production. (Photo credit: Case Western Reserve University Illustration/Megan Kern)

New Therapeutic Uses researcher Steven Grant, M.D., of the Massey Cancer Center at Virginia Commonwealth University (VCU), investigates novel combinations of drugs that cooperate to kill leukemia cells. (Photo credit: VCU Massey Cancer Center)

Repurposing a Cancer Drug to Treat Alzheimer's Disease

In 2015, NCATS announced one of the first promising results from the New Therapeutic Uses program: Scientists at Yale University School of Medicine have found that an experimental compound originally developed by the pharmaceutical company AstraZeneca as a cancer therapy potentially could be used to treat Alzheimer's disease. In mouse models of the disease, the compound successfully reversed memory and recognition problems as well as physiological signs of the disorder, and now the researchers are testing it in humans. The results of the animal study were published in the *Annals of Neurology*.

Alzheimer's disease is the most common form of dementia, a group of disorders that causes progressive loss of memory and other mental functions. Current drug therapies can only ease symptoms, not stop the disease's progression. New treatments — so-called disease-modifying therapies — are needed to halt Alzheimer's by targeting its underlying mechanisms.



Astrocytes, in red, surround amyloid beta clusters (green) located in the brain of a mouse that exhibits Alzheimer's-like symptoms. NCATS-supported scientists at Yale University School of Medicine have found that an experimental compound originally developed as a cancer therapy potentially could be used to treat Alzheimer's disease. (Photo credit: Strittmatter Laboratory, Yale University Photo/ Adam Kaufman)

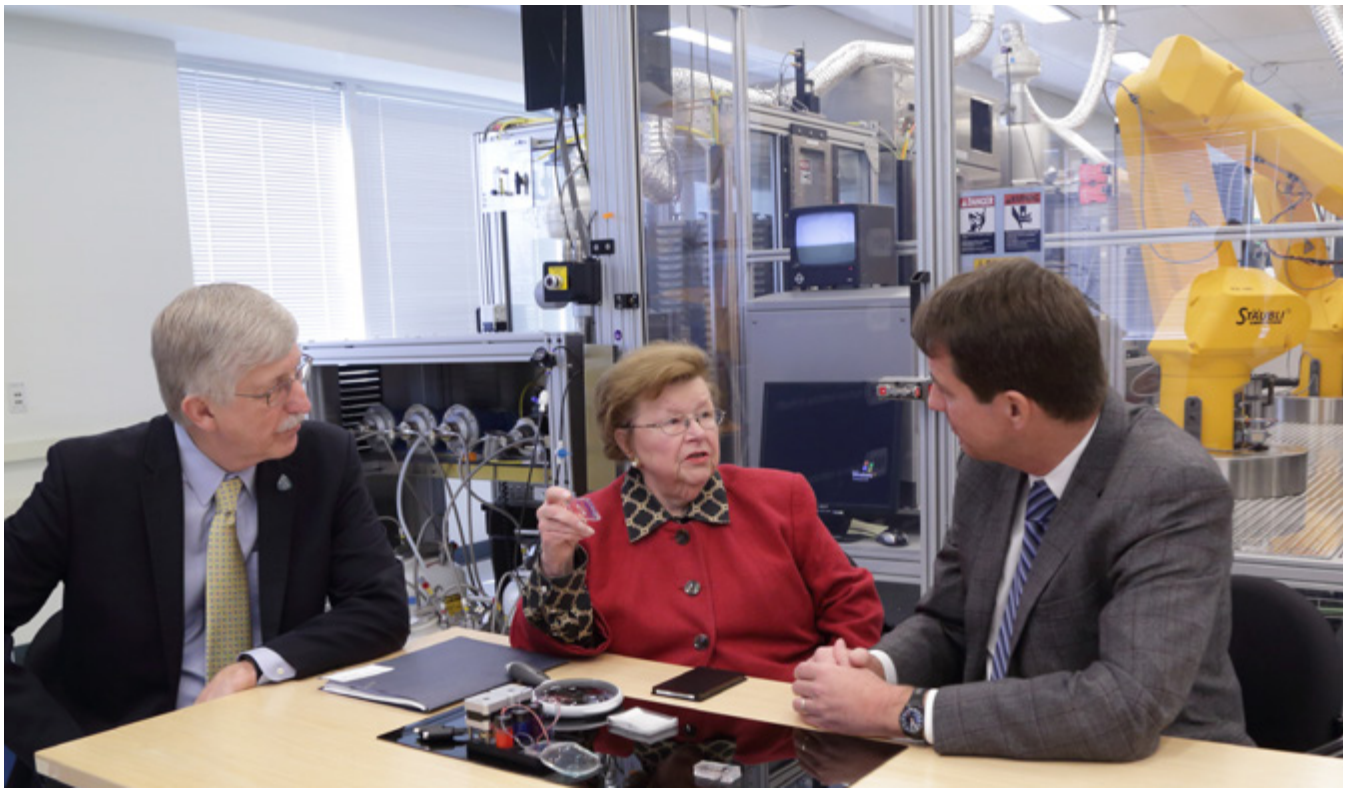
Abnormal clumps of amyloid beta protein build up in the brains of Alzheimer's disease patients. These protein clusters damage brain cells (neurons), eventually killing them.

Repurposing a Cancer Drug to Treat Alzheimer's Disease (continued)

The Yale team, which had previously discovered that a protein called Fyn kinase is central to this process, hypothesized that a compound that blocks Fyn activity might represent a potential disease-modifying therapy for Alzheimer's.

In 2013, the Yale team, led by Stephen Strittmatter, M.D., received one of the first New Therapeutic Uses program awards to test its hypothesis using saracatinib (AZD0530), originally developed by AstraZeneca to treat cancer. The researchers gave the drug to mice with Alzheimer's-like symptoms, and after six weeks, these models showed complete reversal of spatial learning problems, memory loss and brain cell abnormalities. The Yale research team also has completed a successful Phase IB safety study of saracatinib in humans with Alzheimer's disease.

Saracatinib's prior development and the Yale team's successful completion of animal and human studies enabled the compound to advance rapidly into a larger, multisite Phase IIA trial in Alzheimer's patients that is ongoing. Study investigators currently are enrolling older adults with Alzheimer's disease to participate in the trial and expect to have results in about two years.



NIH Director Francis S. Collins, M.D., Ph.D. (left), and NCATS Director Christopher P. Austin, M.D. (right), talk with U.S. Senator Barbara A. Mikulski (Maryland) about the New Therapeutic Uses Program and other NCATS-supported research during her tour of NCATS' high-throughput robotic screening facility.

Testing and Predictive Models

Predicting biological effects of investigational drugs is fraught with uncertainty. Two-thirds of candidate drugs fail because they are found to be ineffective for treating the intended disease or are frankly harmful to human health (i.e., have toxicity) despite costly pre-clinical studies in cell and animal models that suggested they would be safe and effective.

To address this obstacle, NCATS focuses on the development of more reliable ways to predict toxicity and effectiveness. Such advances could save enormous amounts of time and expense by more accurately predicting which drug candidates are potentially harmful or may be ineffective in humans. In addition, these models have the potential to provide useful information about chemical toxicity and the basic biology of disease and to serve as improved testing platforms for evaluating environmental chemicals.

Toxicology in the 21st Century (Tox21)

Throughout our lives, we are exposed to thousands of chemicals in our food, household cleaning products, medicines and environment. However, scientists know little about the level of toxicity to humans of many of these substances.

Tox21 is a collaboration among the Environmental Protection Agency (EPA), the FDA, and NIH, including NCATS and the National Institute of Environmental Health Sciences' National Toxicology Program. The initiative is designed to develop more reliable methods of assessing the potential toxicity of drugs and environmental chemicals. High-throughput screening technologies developed by chemical probe specialists at NCATS were adapted to enable researchers to measure the effects of more than 10,000 different drugs and chemicals (the "Tox21 10K library") at different levels of exposure on a wide variety of cellular and molecular functions. These data help researchers identify chemicals to study in greater depth so they can define their effects on human health, develop computational programs that will better predict toxicity of new drugs and chemicals, and improve the efficiency and accuracy of new drug and chemical development.

Tox21 investigators broadly disseminate their data through the National Library of Medicine's PubChem website, making the findings freely available to the public and to other scientists. To date, the team has produced nearly 50 million data points from screening the Tox21 10K library against cell-based assays. This public release of data enables scientists in the general community to prioritize chemicals for further study. Importantly, in an unprecedented experimental effort in chemical quality control, in 2015 the Tox21 team released a first-in-kind dataset detailing the chemical identity and purity of each of the compounds in the 10k library.

Because the Tox21 researchers produce such large amounts of information, they often look for creative ways to engage scientists around the world to devise innovative ways to mine the data. For example, the Tox21 program launched a global crowdsourcing prize competition in July 2014 to develop computational models that can better predict chemical toxicity. In January 2015, NCATS announced the winners of the challenge. To determine the winners, Tox21 staff had tested the submitted models' accuracy. All of the winning models displayed good predictive power, achieving greater than 80 percent accuracy, with several models exceeding 90 percent. The models from the seven winning teams will become part of Tox21's arsenal of tools that help researchers assess how various chemicals might disrupt biological processes in the human body and thus lead to negative health effects. Additional information about the winning models will be published in the scientific literature.

Tox21 experts now are planning to publish additional datasets from screens of the Tox21 10K library in assays of stress response pathways, which are designed to identify compounds that can damage or kill cells. The team will continue to test chemicals from the library and release screening data, moving Tox21 closer to its goal of transforming toxicity testing into a more efficient and effective enterprise.

A robot arm at NCATS' Tox21 laboratory retrieves compound plates from storage incubators (right) and brings them to a transfer station (foreground), where compounds are transferred to assay plates using a pin tool.

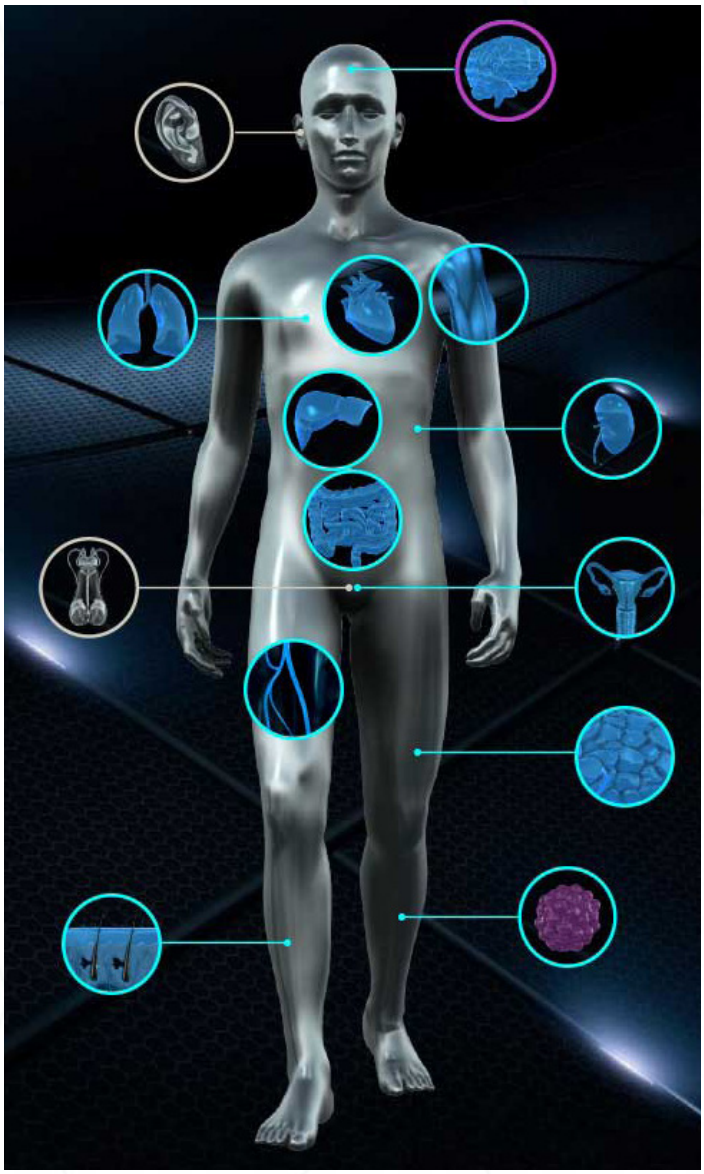
Tissue Chip for Drug Screening

NCATS, the Defense Advanced Research Projects Agency (DARPA) and the FDA are the leading partners in the Tissue Chip for Drug Screening program, an initiative to revolutionize the process of predicting drug safety and efficacy. Researchers use the chips as miniaturized platforms to grow 3-D representations of human tissues that serve as models of living organs, such as the lung, liver and heart. The chips are lined with living cells and contain features designed to replicate the complex biological functions of specific human organs.

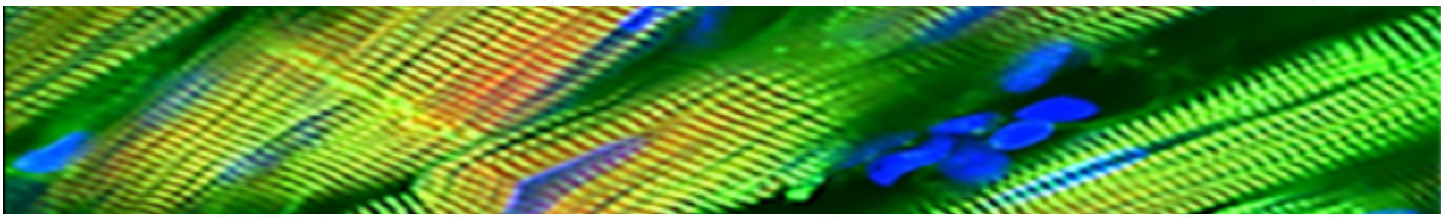
In the first two years of the program, which launched in 2012, researchers developed individual human tissue chips that demonstrated organ functionality, mimicked human biological responses, and generated data more representative of the human physiological response than conventional cell and animal testing methods. Currently, there are tissue chips for the heart, liver, blood-brain barrier, blood vessels, kidney, gastrointestinal system, nervous system and female reproductive system, as well as models of adipose (fat) tissue, tumors and metastasis.

In the current phase of the Tissue Chip program, teams of scientists are joining forces to connect individual organ chips. Researchers are collaborating to refine the chips and integrate them into a system that can mimic the complex functions of the human body. This integration promises to enable real-time measurement of drug activity within and across various organs and tissues, such as in the liver and digestive system.

Because these tissue chip systems closely mimic human physiology under controllable conditions, scientists can design experiments using them in ways that would not be feasible in research involving humans. One important evolution of the Tissue Chip project has been the rapid adoption of the technology to mimic diseases, with the hope of finding better ways to prevent and treat them.



"Chip" is a whole-body representation of the tissues and organ systems that Tissue Chip program researchers are developing and testing. The ultimate goal of the program is to integrate all of the systems to produce a "human body on a chip," enabling researchers to test the potential effects of a substance across the entire body before involving human participants in clinical studies.

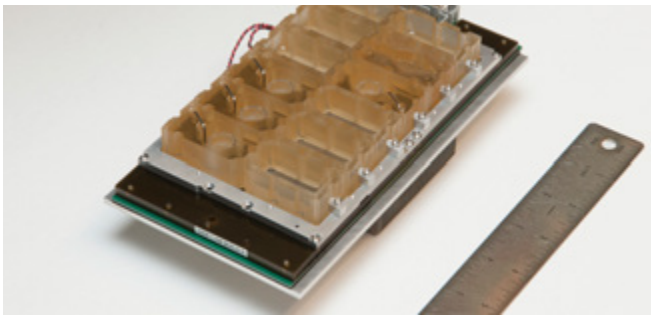


This image shows mature cardiac cells properly aligned and functional on a heart chip that was developed by Columbia University researchers. (Photo credit: Columbia University)

Modeling the Female Reproductive Tract in 3-D: The Birth of EVATAR™

A team of scientists from Northwestern University, the Charles Stark Draper Laboratory and the University of Illinois at Chicago (UIC) have built EVATAR™, a miniaturized 3-D representation of the female reproductive tract plus the liver on an integrated tissue chip platform. Prior to joining the Tissue Chip program, the Northwestern and UIC scientists were working separately on 3-D models of the organs in the female reproductive system: the ovaries, fallopian tubes, uterus, cervix and vagina.

Through the Tissue Chip program's first round of funding in 2012, these researchers collaborated to build a platform that integrates all of the separate reproductive organs, modeling the entire female tract and providing the opportunity to explore how the organs function together as a system. The device they created allows the female reproductive tissues to interact over periods of a month or more, much like they do in the human body. This advance solved a major technical challenge in the field: enabling organ models to communicate with each other via secreted factors, including hormones, to more closely resemble human physiology. Miniaturized pumps and tubes (called microfluidics) carry liquids and hormones through each of the tissues on the chip. The hormone fluctuations and the behavior of the cells recreate the physiological changes during a woman's 28-day reproductive cycle. The group plans to use EVATAR™ to better understand the basic hormonal and cellular functioning of the reproductive tract. At present, the effects of hormonal changes in women in drug metabolism are largely understudied and have led to gender-specific adverse drug reactions. When coupled with other tissue chips, EVATAR™ will be an invaluable tool in optimizing drugs and therapies for women.



EVATAR™, the female reproductive tract and liver tissue chip, was developed with support from NCATS. (Photo credit: Northwestern University)

The EVATAR™ team at Northwestern University. (Photo credit: Northwestern University)

RNA Interference (RNAi)

Small interfering RNA (siRNA) molecules are pieces of ribonucleic acid (RNA) that block the activity of genes through a natural process called RNAi. Scientists have harnessed this process as a powerful tool used in thousands of laboratories worldwide to understand gene function. Because each siRNA molecule can block a different gene, RNAi informs researchers about the role of any gene in maintaining health or causing disease.

What is RNA?

Ribonucleic acid is a molecule that conveys information about our genes to determine cell structure and function. RNA is created from the genetic blueprint of deoxyribonucleic acid (DNA).

RNAi's potential usefulness has been limited by a lack of methods to properly interpret RNAi experiments and reliably query the entire genome, a lack of collaborative expertise to perform genome-wide RNAi screens, and a lack of comprehensive RNAi data in public databases for researchers to reference. To address these systemic problems, NCATS operates a state-of-the-art RNAi Screening Facility. Here, NCATS staff assist NIH intramural investigators with all stages of project planning and execution, including assay development through genome-wide siRNA screens, informatics and pathway analysis, and rigorous confirmation.

NCATS researchers have developed and shared several new techniques that enable reliable genome-wide RNAi screens. To perform such tests, scientists use high-tech robots to introduce siRNAs into human cells to block the activity of each gene, one at a time. This process can produce a complete list of all the genes involved in a particular biological function or disease process, an invaluable step in target identification and validation.

Extracellular RNA Communication

Until recently, scientists believed RNA worked mostly inside the cell that produced it. Some types of RNA help translate genes into proteins that are necessary for organisms to function. Other types of RNA control which proteins and how much of those proteins the cells make. Now, investigators have shown that cells can release RNA — in the form of extracellular RNA (exRNA) — to travel through body fluids and affect other cells. ExRNA can act as a signaling molecule, communicating with both neighboring and distant cells and carrying information from cell to cell throughout the body. A better understanding of basic exRNA biology could open doors to improving the diagnosis, prognosis and treatment of many diseases and conditions, such as cancer, kidney disorders, heart disease, Alzheimer's disease and multiple sclerosis.

To better address opportunities, NIH launched the cross-cutting Extracellular RNA Communication program in 2013 with its Common Fund support. The program is led by a trans-NIH team that includes NCATS; the National Cancer Institute (NCI); the National Heart, Lung, and Blood Institute (NHLBI); and the National Institute on Drug Abuse (NIDA).

The goals, which span the entire spectrum of translational research from discovery to treatment, are to discover:

- How cells make and release exRNAs;
- How exRNAs move through the body;
- How exRNAs target specific cells and affect other cells;
- How the amount and types of exRNA can change in disease; and
- How scientists can use exRNAs to develop new therapies.

At the time of the launch, NIH awarded approximately $130 million over six years to scientists nationwide for first phase projects to improve our understanding of exRNA communication through 30 multidisciplinary research projects that address a number of critical scientific areas. The first phase of the projects focused on discovery, feasibility and proof of concept.

In September 2015, NCATS announced it would spearhead the second phase of the program to test and validate exRNA molecules for their potential as disease biomarkers and treatments. Specific focus areas include Alzheimer's disease; multiple sclerosis; kidney disease; brain injury; complications of pregnancy; heart disease, heart attack and stroke; and

liver, stomach and brain cancers. Funded exRNA researchers disseminate data and resources via the exRNA Research Portal to keep the scientific community informed of the most recent developments in the field.

In one NCATS-funded project, researchers at the University of California, Los Angeles (UCLA) are exploring how exRNAs in saliva could be used as biomarkers to detect gastric (stomach) cancer. The team announced its findings in January 2015 in *Clinical Chemistry*. While previous studies described only some of the exRNAs found in saliva, this study was the first to catalog all small noncoding exRNAs in this oral fluid.

The UCLA team found that saliva contains many of the same exRNA molecules found in blood; the molecular profiles of different people varied in the same way that molecular profiles of blood do. This finding suggests that saliva may be as useful as blood for finding indicators of stomach cancer. The researchers now are developing a noninvasive diagnostic test for stomach cancer, which is quite deadly because most people do not notice its symptoms until the disease has advanced. This work could enable clinicians to perform simple tests to detect this cancer at earlier stages.

A research team led by Huang-Ge Zhang, Ph.D., at the University of Louisville, Kentucky, has shown that large amounts of exosome-like particles from grapes and other edible plants can deliver therapeutic mitochondrial RNA and chemotherapy drugs for the potential treatment of cancer. (Photo credit: University of Louisville)

Clinical Innovation

Through clinical research, investigators assess whether interventions (e.g., medications, devices, diagnostics, behavioral and other treatment regimens) developed during the pre-clinical phase are safe and effective in people. NCATS accelerates the transformation of laboratory discoveries into new treatments for patients through the development and implementation of solutions that address system-wide scientific and operational issues that limit the efficiency and effectiveness of clinical research.

Clinical and Translational Science Awards (CTSA) Program

NCATS' CTSA Program supports an innovative national network of medical research institutions to improve the clinical phases of the translational research process from the first time a new intervention is tested in humans to dissemination into medical practice in communities. CTSA Program research centers serve as hubs locally and regionally to catalyze innovation in clinical research and training. Program support enables researchers to share best practices and build an increasingly robust national capacity for rapid and effective translation of newly developed interventions into improved health outcomes.

CTSA Program goals include:

- Innovating to create processes that increase the quality and efficiency of translational research, particularly for multisite clinical trials;
- Promoting the integration of special and underserved populations in translational research across the human lifespan;
- Developing new ways to engage patients and communities as partners in every phase of the translational process;
- Training and cultivating the translational science workforce; and
- Advancing the creation and implementation of cutting-edge approaches to informatics that enable discovery and catalyze more rapid translation.

In October 2015, NCATS announced new funding for 18 CTSA Program hubs, including two new hubs: the State University of New York at Buffalo and Wake Forest University Health Sciences.

Michael V. Homer, M.D., (left) examines clinical trial participant Yanping Huang at the University of California, San Diego Clinical and Translational Research Institute (CTRI), Center for Clinical Research. Todd May (right), a clinical coordinator at the CTRI, assists with studies. (Photo credit: UC San Diego CTRI Photo/Patti Wieser)

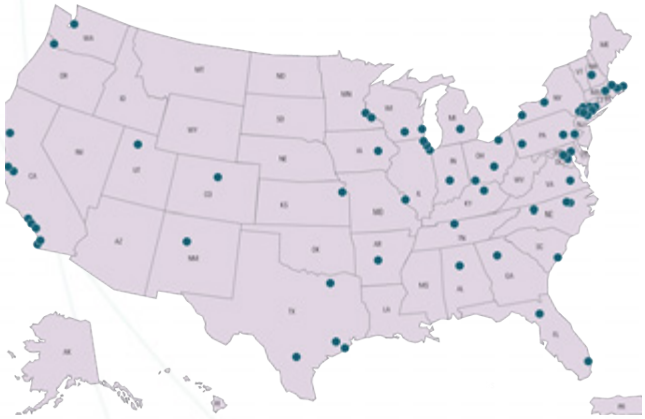
2015 CTSA Program: Building Network Capacity

NCATS continues to build on the strong foundation of the CTSA Program to tackle system-wide scientific and operational problems to make the clinical and translational research enterprise more efficient, initiating several new efforts in 2015. For example, in April 2015, NCATS released two new funding opportunity announcements (FOAs) for Collaborative Innovation Awards, which are designed to stimulate team-based research across the CTSA Program consortium. Through these FOAs, NCATS solicited proposals for innovative studies designed to involve three or more CTSA Program hubs that would collaborate to improve translational research methods at any step in the translational research spectrum. NCATS' intent is to enhance the ability of the CTSA Program consortium to address systemic translational science problems by encouraging teams from multiple hubs to work together to overcome roadblocks.

Two other new initiatives are aimed at overcoming critical challenges to the planning and conduct of multisite clinical trials:

- **Trial Innovation Centers (TICs)** will serve as lead centers of excellence to streamline and harmonize innovative approaches, such as obtaining approval for and relying on a single institutional review board (IRB) of record for a clinical trial, establishing master agreements for executing research contracts, qualifying clinical sites and initiating study start-up procedures.
- **Recruitment Innovation Centers (RICs)** will increase the likelihood of success for multisite clinical trials in two ways: (1) by developing informatics-driven approaches to assessing the site-specific availability of potential participants during trial planning, and (2) by developing innovative approaches to recruit participants for trials.

By building these new components of the CTSA Program and interfacing them with the CTSA hubs, NCATS is catalyzing the creation of a national network for translational medicine that will enable clinical researchers to conduct their studies more effectively, efficiently and creatively.



• = CTSA Program Hubs

Building an innovative national network for clinical and translational science: This map depicts the locations of the more than 50 medical research institutions designated as CTSA Program hubs. Program investigators have established collaborations with more than 60 formal partners and are adding more each year. The national research capacity of the network will be further enhanced by the establishment of CTSA Trial Innovation Centers and Recruitment Innovation Centers to be funded in 2016.

CTSA Program Accrual to Clinical Trials (CTSA ACT)

Led by CTSA Program investigators from the University of Pittsburgh in collaboration with Harvard University; University of California, San Diego; and University of Texas Southwestern Medical Center investigators, the CTSA ACT initiative is underway to develop a nationwide network of sites that will share electronic health record data to identify and enroll participants who meet criteria for a given clinical study. The ACT team is building on existing informatics platforms and operating models to create a "federated" network with common standards, data terminology and shared resources. The investigators have created standard categories and terminology for demographic and clinical visit data as well as for medications and laboratory results. They conducted a successful demonstration of the technology at more than 20 CTSA Program hubs in 2015 and are continuing to integrate information into a technology platform that converts data into de-identified and searchable participant information that is stored in a central, open-source database.

Institutional Review Board Reliance

The difficulty of recruiting participants is only one of many obstacles to conducting efficient clinical studies. Another major hurdle for initiating a trial conducted at multiple sites is the separate IRB review and approval process that is conducted at each site. This can potentially delay trial launch for months and even years after the trial was initially funded. Several CTSA Program hubs have achieved significant progress in overcoming this roadblock using a concept called IRB reliance. With this model, researchers develop networks in which each of the institutional participants in a multisite study agrees to rely on a single IRB of record for initial approval and for continuing review relevant to adverse events, amendments, deviations and other events. NCATS is building on the existing successful track record of its CTSA Program's regional IRB models, and in 2015, supported the development of an IRB reliance agreement template, operating procedures and workflows, as well as testing these items in a pilot study.

Good Clinical Practice (GCP)

Before investigators can enroll participants in a clinical trial, those involved in conducting the study should be appropriately qualified, with the necessary competencies to carry out the research. To prevent delays in ensuring

Lauren Jones, R.N., assistant nurse manager (front left), Shelley Stanton, R.N., and Donald A. McClain, M.D., Ph.D., of the University of Utah Center for Clinical and Translational Science, prepare a patient for a positron emission tomography scan as part of a clinical trial. (Photo credit: University of Utah)

appropriate qualification before a trial can begin, NCATS and CTSA Program principal investigators (PIs) are working together to implement a network-wide Good Clinical Practice training initiative. GCP incorporates established ethical and scientific quality standards for the design, conduct, recording and reporting of clinical research involving the participation of human subjects. The goals are to streamline and standardize GCP training for clinical study personnel across the CTSA Program consortium, eliminate redundant training requirements, and measure the impact of the changes. CTSA Program hubs will demonstrate the effectiveness of the GCP training standards within their institutions and then disseminate the standards broadly.

Clinical Diagnostics

Innovations in diagnostics improve clinical research and treatments. In one such example, in April 2015, the Michigan Institute for Clinical and Health Research (MICHR) announced that a diagnostic device that tests extremely small blood samples helped save the life of a young cancer patient whose organs were shutting down due to a catastrophic immune system reaction during treatment. The device was developed by a University of Michigan research team with CTSA Program as well as NHLBI support. The device, which is still in the research phase, supplied critical information to support adjustments made to the treatment protocol that rapidly improved the patient's condition. This successful emergency

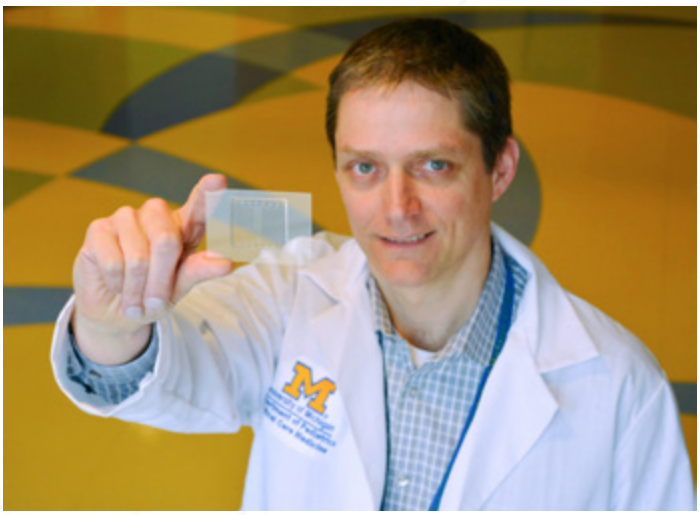
use provided real-life evidence of the device's potential. The MICHR team plans to continue development of the device and is exploring commercial and regulatory pathways that could lead to approval for its routine use in medical practice.

Accelerating Rare Diseases Research

One of the most remarkable and unexpected scientific revelations since the completion of the Human Genome Project is that genes and biological pathways are not unique to the functioning of any particular type of cell, organ or even disease. Rather, genes and pathways can play a role in different diseases in different organs. This insight has profound implications for the understanding and treatment of all diseases, but particularly for rare diseases, which are frequently caused by mutations in particular genes and can affect many different organ systems simultaneously. NCATS, therefore, is accelerating rare diseases research by focusing on what is *common* among diseases.

This systematic approach is critical for translation of rare diseases research, since of the more than 6,500 rare diseases that have been defined, only a few hundred have any FDA-approved treatment. Although rare diseases by definition affect relatively small numbers of people (usually defined as fewer than 200,000 in the United States), these diseases collectively affect an estimated 25 million Americans and are the source of enormous suffering, premature death and financial burden. Both the large number of currently untreatable rare diseases and the scarcity of insights into the connectedness of their causes render the prevailing "one disease at a time/one organ at a time" translational model to be operationally impractical and scientifically inappropriate.

Given the unique challenges associated with rare diseases research, NCATS' team approach is particularly important. NCATS supports collaborative models for advancing discovery and therapeutics development for rare diseases via partnerships among academia, government, industry and patient advocacy groups.



Timothy Cornell, M.D., of the Michigan Institute for Clinical and Health Research, a CTSA Program hub, holds the life-saving blood analysis device he helped develop to test extremely small blood samples. (Photo credit: University of Michigan)

Rare Diseases Clinical Research Network (RDCRN)

The RDCRN is designed to advance medical research on rare diseases by facilitating collaboration, study enrollment and data sharing. Through the network of 22 multisite consortia — in which each consortium focuses on at least three related rare diseases — and a Data Management and Coordinating Center (DMCC), physician-scientists and their multidisciplinary teams at hundreds of clinical sites around the world collaborate with representatives of more than 130 patient advocacy groups to study almost 300 rare diseases. NCATS collaborates with 10 NIH ICs to fund, manage the awards and work with RDCRN consortia. The RDCRN-DMCC enables uniform data collection and analysis and facilitates the sharing of information across the network. With a focus on natural history studies (see box on page 22), RDCRN investigators develop data sources for scientists to better understand the common elements of rare diseases so they may apply that knowledge to improve diagnosis and treatment for these and other related conditions.

The RDCRN facilitates clinical research in rare diseases through support for (1) collaborative activities, including

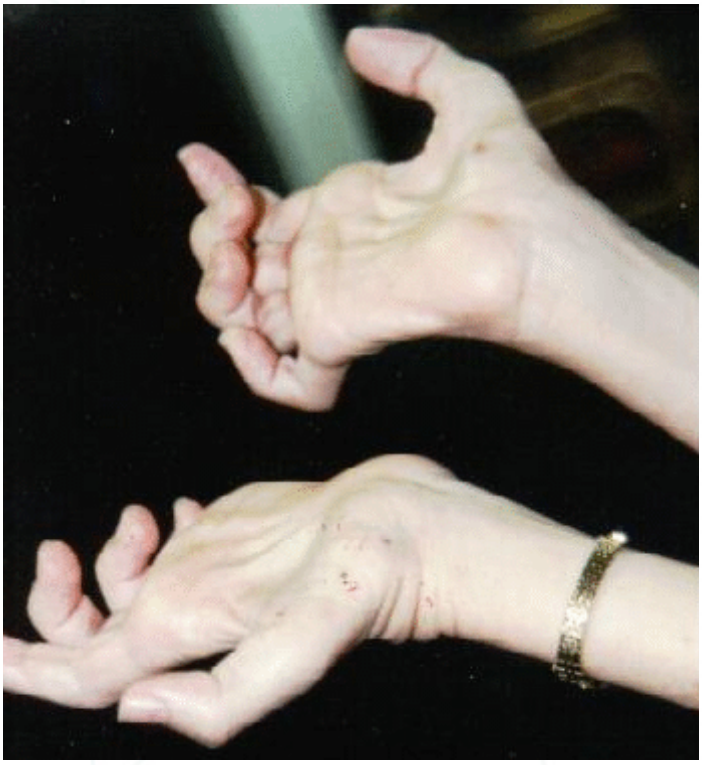
clinical trials and longitudinal studies of individuals with rare diseases; (2) training of clinical investigators in rare diseases research; (3) innovative pilot and demonstration projects that leverage new rare disease clinical research opportunities (e.g., novel high-throughput analyses of patient biospecimens); (4) uniform data collection protocols; (5) an integrative trans-consortium infrastructure; and (6) access to information about rare diseases for basic and clinical researchers, academic and practicing physicians, patients, and the public.

The RDCRN website is a resource for health care providers, researchers, patients and caregivers, and the general public. Since its inception in 2003, RDCRN investigators have enrolled 40,000 participants in multisite clinical research studies. Ninety-one studies are currently underway.

Natural history studies

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

A 2-year-old girl with Charcot-Marie-Tooth disease walks to her father. (Photo credit: Jill Selby)



Charcot-Marie-Tooth (CMT) disease affects the peripheral nerves (i.e., the nerves outside the brain and spinal cord), and individuals with the CMT1A subtype, which affects approximately 1 in 2,500 people in the United States, experience progressive muscle weakness, movement problems, chronic pain and fatigue. RDCRN investigators in the Inherited Neuropathies Consortium are working to find treatments for CMT. (Photo credit: charcotmarietoothdisease.org)

Rare Lung Diseases Consortium (RLDC)

In May 2015, thanks to work done in the RLDC of the RDCRN, the FDA approved a supplemental new drug application (sNDA) for the treatment of lymphangioleiomyomatosis (LAM), a rare, progressive, often fatal lung disease that primarily affects women of childbearing age. Approval of the sNDA for the use of Rapamune (sirolimus), a drug previously approved to prevent rejection by the immune system of kidney transplants, was based on the results of the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) trial. Rapamune is the first drug approved for the treatment of LAM. The MILES trial, led by Francis McCormack, M.D., of the RDCRN RLCD Consortium, was a collaborative effort among the consortium, the pharmaceutical industry and the LAM Foundation. NHLBI co-funded the effort.

Porphyrias Consortium

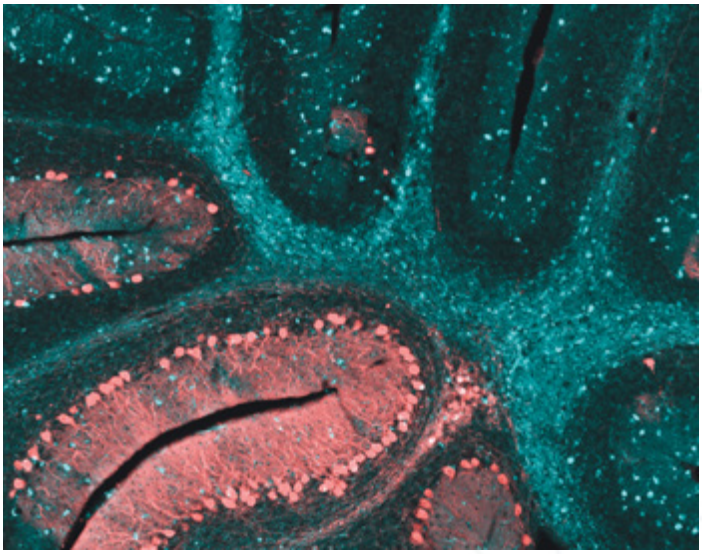
The porphyrias are a group of rare, inherited disorders caused by problems with substances necessary for the function of hemoglobin, a protein in red blood cells that carries oxygen to tissue and organs. Until recently, the clinical and laboratory features of patients with acute porphyrias in the U.S. were not well described. To address this lack of knowledge, the RDCRN's Porphyrias Consortium published an important natural history study in the *American Journal of Medicine*. This report characterizes and documents the largest group of porphyrias patients assembled to date in North America. Consortium investigators concluded that the acute porphyrias often remain undiagnosed for more than a decade after the first symptoms develop. They also identified a drug called hematin as the most effective therapy for treating these conditions and for preventing the recurrence of symptoms.

Therapeutics for Rare and Neglected Diseases (TRND)

The goal of the TRND program is to speed the development of treatments for rare and neglected diseases with high unmet medical needs. This NCATS intramural program operates via collaborative research partnerships with public and private entities to leverage the unique strengths and capabilities of each party to develop new technologies and models that improve the efficiency of therapeutics development. NCATS scientists provide project management and drug development expertise and resources, working with research partners and seeking regulatory perspective from FDA to move potential therapeutics through pre-clinical testing. The program also may support first-in-human studies. These efforts effectively "de-risk" therapeutic candidates and make them more attractive for adoption by outside business partners.

TRND program staff employ a milestone-driven, team-based operational model to conduct the collaborative projects. They rigorously evaluate each project to determine its specific development needs and to outline a formal project plan. As a common first milestone, these scientists verify the results on which the project was initially based. This could involve reproducing the exact data submitted by the collaborator or conducting additional experiments to verify the key findings. TRND staff also periodically determine whether to continue projects based on whether they successfully meet critical milestones or timelines.

Through its TRND program, NCATS supports a diverse portfolio of projects targeting drug development for some of the most devastating diseases affecting either small populations in the U.S. or large populations in the developing world. Two ongoing projects targeting rare, inherited diseases — Niemann-Pick type C1 disease and GNE myopathy — yielded successful IND applications to the FDA, enabling the pre-clinical therapeutic candidates to advance to clinical trials in humans. Clinical studies supported through TRND can be found at clinicaltrials.gov, and the TRND Annual Report is provided as an appendix to this report.



Through its TRND program, NCATS supports research on Niemann-Pick type C1 disease (NPC). This image shows the cerebellum of a brain affected by NPC at the end stage of the disease. The blue staining shows the dense pockets of lipid accumulations throughout the brain. (Photo credit: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development)

Have TRND and BrIDGs Worked?

A financial analysis of 28 TRND and BrIDGs projects, published Feb. 25, 2015, in *Science Translational Medicine*, demonstrates that the answer to this question is a resounding "yes."

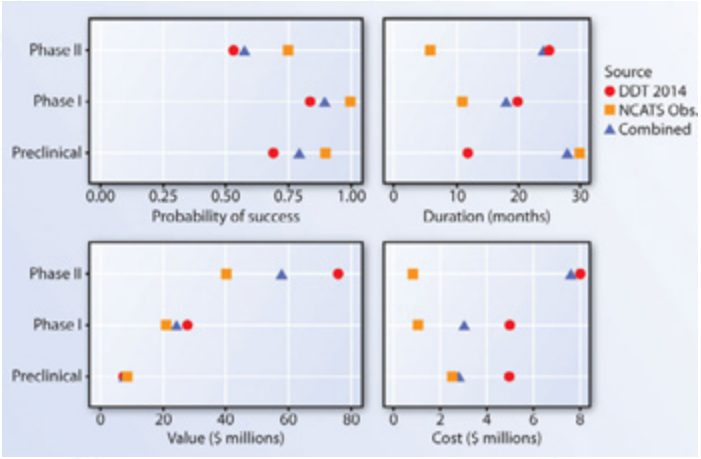
Andrew Lo, Ph.D., the Charles E. and Susan T. Harris Professor of Finance at the Massachusetts Institute of Technology (MIT) Sloan School of Management, and Nora Yang, Ph.D., director of portfolio management and strategic operations for the NCATS Division of Pre-Clinical Innovation, led a collaborative research team in a financial analysis of the two programs' projects related to rare diseases.

Lo and Yang found that the scientific and operational processes used in TRND and BrIDGs projects reduced the cost of developing new drugs, lowered financial risks and provided an effective way to develop promising therapeutics to the point where they could be handed off to the private sector for final testing and marketing.

TRND and BrIDGs projects' greater success rates were accompanied by longer pre-clinical development times than the industry average, however. This was due to the programs' methodical, step-by-step "sequential approach." Notably, the sequential approach differs from the industry standard, which undertakes multiple investigations into a new drug simultaneously. The industry approach moves successful therapeutics more quickly through the pipeline to market, but it also can cost more if a drug fails, because there is more up-front investment.

For each project, NCATS and outside investigators form a team that develops a project timeline and milestones and defines deliverables and go/no-go milestone criteria. If projects meet all of the milestones, there is greater potential for the therapeutic agent to succeed and for private financing to be secured from pharmaceutical companies, biotechnology companies or venture capitalists. When a project does not meet its milestones, it may be closed out.

The TRND and BrIDGs model provides a way to help drug developers navigate through the so-called "valley of death," the time after a therapeutic agent emerges from pre-clinical research but before it has undergone final testing for use with patients.



Investigators at MIT and NCATS conducted an analysis of 28 NCATS projects in the TRND and BrIDGs programs for value, success, duration and cost by building analytical models and comparing NCATS projects (orange squares) with a set of industry averages (red dots). The box on the top left illustrates that NCATS' probability of success was better for pre-clinical, phase 1 and phase 2 projects, while its costs were lower (bottom-right box).

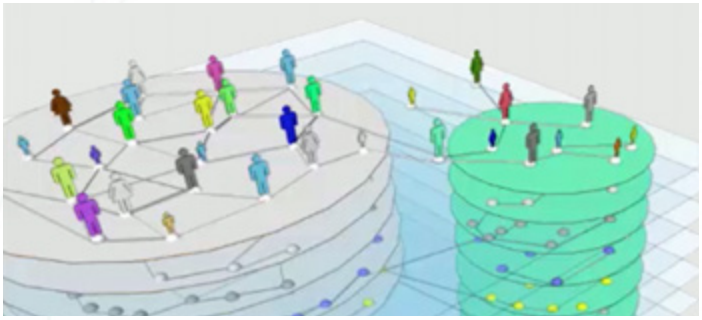
NIH/NCATS Global Rare Diseases Patient Registry Data Repository/GRDR®

Rare diseases, and the people living with them, are all best considered in relation to each other, not in isolation. The goal of NCATS' GRDR program is to build a web-based resource that sets the stage for integrating data across diseases and hopefully all the way to better treatments for patients.

Through the program, NCATS will provide patients, health care professionals and researchers with tools that enhance their ability to access and submit information such as high-quality patient and clinician-reported data.

To advance this vision for the GRDR program, in August 2015, NCATS awarded a supplemental grant to the Harvard Medical School Department of Biomedical Informatics, led by Isaac Kohane, M.D., Ph.D., and Paul Avillach, M.D., Ph.D. This project enables the integration of different patient registries within the GRDR platform to provide secure, encrypted access to these data by authorized users. Using this approach, which also builds upon NIH's Big Data to Knowledge initiative, data providers will more easily be able to share their data with the wider research community and make connections among diseases to help get more treatments to more patients more quickly.

Izzabella Mendenhall has Bardet-Biedl syndrome, a rare genetic disease that affects many parts of the body and often leads to impaired vision, chronic kidney disease and endocrine disorders. The Clinical Registry Investigating Bardet-Biedl Syndrome is a GRDR Program partner. (Photo credit: Kris Novetzke)



i2b2/tranSMART is the system currently being used for the NCATS GRDR in conjunction with Harvard Medical School's Department of Biomedical Informatics.

Patient and Community Engagement and Health Information

A key part of NCATS' ambitious translational science agenda is the development of the *science* of patient and community engagement, that is, the evidence base for best practices for making the development and deployment of interventions maximally efficient and relevant by engaging patients and communities at every stage of the translational research process.

For example, investigators at the University of Miami CTSA Program hub have developed and implemented an innovative community-based approach to increasing cervical cancer screening in the Little Haiti community in Miami. The University of Miami team recognized that women in Little Haiti have disproportionately high rates of suffering and death due to cervical cancer, a common observation in many minority and immigrant communities. They determined that this high incidence rate was derived in part from cultural and access barriers to early screening, as well as a lack of understanding of the disease. The Miami team partnered with community health workers to create an outreach and education program run by members of the community, making cervical cancer screening more culturally acceptable and locally accessible. In addition, a new and simpler diagnostic test was developed, enabling women to conduct cervical self-sampling for human papillomavirus (HPV, the primary cause of cervical cancer) outside a clinical setting. The University of Miami researchers also are working with pre-clinical investigators to develop a paper-based HPV test designed to detect high-risk strains of HPV in as little as 15 minutes, which would be much faster and more cost-effective than the current laboratory-based methods. The partnering with community health workers, combined with self-sampling and the new paper test, has been demonstrated to improve the translation of health interventions to the community in Miami and, as these techniques are disseminated, promises to improve cervical cancer outcomes in resource-poor settings in Miami and beyond.

Erin Kobetz, Ph.D., M.P.H., senior associate dean for health disparities, University of Miami Miller School of Medicine, is pictured with her GE Foundation USCREEN research collaborators. Kobetz is the director of the Miami CTSA Community Engagement and Cultural Diversity Program. Pictured from left are Krystal De Palma, Claudia Gordon, Marlene Norono, Dr. Kobetz, Ludmilla Paul, Milagros Pierre and Martine Poitevien. (Photo credit: University of Miami)

For people to benefit from new interventions, clinical research studies must test potential therapies and devices on populations that are affected by or can benefit from these research efforts. However, minority, low-socioeconomic and rural populations are typically underrepresented in clinical trials, and new approaches are urgently needed to remedy this persistent problem. Such a new approach was developed by Vanderbilt University CTSA Program hub investigators through their "Community Engagement (CE) Studio" program. The program is designed to bring together researchers and members of underrepresented groups for in-person meetings, enabling researchers to get input from community and patient stakeholders on study purposes, design, communication and recruitment. In the December 2015 issue of *Academic Medicine*, the researchers reported the results of 28 CE Studios that engaged 152 community stakeholders. They said the stakeholders' input enhanced research design and implementation, while stakeholders said they better understood the research process and were more likely to take part in it. The authors have developed a toolkit to disseminate the approach so that scientists across the country can replicate the program.

In the rare diseases research arena, RDCRN consortia members both engage with and integrate patient advocacy groups into their research programs, which helps achieve greater success in study enrollment goals. As a result, NCATS requires RDCRN consortia to include patient groups as full partners on their research teams. The RDCRN Coalition of Patient Advocacy Groups (CPAG), a collective representing patient groups affiliated with the RDCRN, shares best practices across patient groups, and the RDCRN website includes a Web-based contact registry for patients who are considering participating in any of the RDCRN clinical studies.

Information is perhaps the most empowering and certainly the most easily disseminated translational tool in the era of the Internet. Thus, NCATS provides accurate information about thousands of genetic and rare conditions to patients, their families, health care providers, researchers and the public through the Genetic and Rare Diseases Information Center (GARD), a collaboration between NCATS and the National Human Genome Research Institute (NHGRI). Via a website, e-mail listservs and telephone support services, GARD provides information on the more than 6,500 rare and genetic conditions known to date. GARD staff also work to identify gaps in information on rare diseases to continually improve the resource.

Since the inception of GARD in 2003, its information specialists have responded to approximately 60,000 questions from the public. In addition, each month, approximately 200,000 unique visitors access the GARD website, and 300 to 600 requests are answered by the information specialists, many of whom are certified genetic counselors. Year after year, the number of inquiries has increased dramatically, reflecting a growing demand for GARD's services.

CPAGs Contribute to Rare Diseases Research

In one example of its utility, the RDCRN CPAG helped build knowledge about a genetic disorder called primary ciliary dyskinesia (PCD), which leads to frequent infections of the lungs, ears, throat and sinuses and can result in serious and permanent damage to these tissues. The PCD Foundation worked with the RDCRN Genetic Disorders of Mucociliary Clearance Consortium to expand the natural history research that the consortium had conducted. This collaboration has fueled an explosion of research activity that has significantly contributed to scientists' understanding of the disease. Advances include successfully defining the clinical features of PCD, identifying 32 genes linked to this disorder, establishing diagnostic standards, and creating PCD medical centers.

GARD staff provide services in English and Spanish and respond in the inquirer's native language whenever possible. In addition, they:

- Maintain and update a list of approximately 6,800 terms related to rare and genetic diseases;
- Provide easy access to disease-specific information from NIH about available services, including clinical trials, FDA-approved medical products for rare diseases, clinical research across the nation and services available from disease-specific patient support organizations; and
- Develop and provide patient-friendly guides and videos, including "How to Find a Disease Specialist" and "Tips for the Undiagnosed," as well as fact sheets in response to frequently asked questions.

Lori Sames, founder of Hannah's Hope Fund, and her daughter Hannah, who has giant axonal neuropathy (GAN), a progressive neurological condition. Information about this and other rare conditions can be found in GARD. A Hannah's Hope fellow collaborated with the NCATS Assay Development team to create a test to identify potential therapeutics for GAN. (Photo credit: Lori Sames)

Partnerships and Collaborations

Effective translation requires many disciplines and organizations to work in concert. As a result, collaboration is a core NCATS value. Every project NCATS supports is built on a partnership, and emphasis is placed on the development of new approaches and incentives to overcome barriers to teamwork. NCATS convenes collaborative scientific teams from government, academia, industry and nonprofit patient organizations with diverse expertise — including in drug and device development, efficacy and toxicity testing, data sharing, biomarkers and clinical research — to reduce, remove or bypass significant bottlenecks across the entire continuum of translation.

Following are descriptions of just a few of the hundreds of NCATS collaborations. Each required a different and innovative partnering structure.

CTSA Program and Patient-Centered Outcomes Research Institute (PCORI)

In 2015, NCATS and PCORI staff members collaborated to improve processes in clinical trial research. Both organizations support the development of infrastructure and resources for conducting multisite clinical trials: NCATS' CTSA Program supports research for earlier-stage trials, and PCORI focuses on later-stage trials. To synergize activities and avoid redundancies, CTSA Program and PCORI experts are working in tandem on three mutual areas of interest:

- Streamlining regulatory oversight through shared IRB agreements;
- Building electronic health records and informatics tools to conduct assessments of trial feasibility and enhance capabilities for trial recruitment; and
- Improving the contracting process.

Developing shared tools and resources that will be compatible across PCORI and CTSA Program clinical trial operations will enable a more seamless infrastructure to serve all studies using these two networks.

University of California, Irvine, CTSA Program-supported research nurse Connie Parido draws blood in a regional middle school as part of an NIH-funded research effort to reduce obesity in children at high risk for developing type 2 diabetes. (Photo credit: Paul R. Kennedy)

NCATS-FDA Collaborative Use Repurposing Engine (CURE)

Around the world, clinicians frequently repurpose drugs developed for other uses to treat neglected tropical diseases, which disproportionately affect people in resource-poor regions. However, clinicians' observations in the field on the effects of drugs often are not reported. FDA staff recognized the clear need for a repository to store such information that clinicians around the world could easily access. They partnered with NCATS' pre-clinical innovation researchers and collaborated with several other research and public health organizations to develop the Web-based CURE, a platform that enables the crowdsourcing of medical information from health care providers to guide the identification of effective drugs for neglected tropical diseases.

The NCATS-FDA team received support in 2015 from the Department of Health and Human Services' Innovation Ventures Fund to enhance CURE. The highly competitive awards provided growth-stage funding and 15 months of mentoring as well as tools to help enhance and sustain the platform.

CURE collaborator Parvesh Paul, M.D., and Arnav Bhagwati, a patient at Jibhi Clinic of Lady Willingdon Hospital, Manali, Himachal Pradesh, India. (Photo credit: Food and Drug Administration/Heather Stone)

NCATS and Industry Partners

Partnering with the biopharmaceutical industry is critical for translating basic science discoveries into interventions that improve human health.

Several NCATS initiatives include industry partners:

- NCATS spearheads the Tissue Chip for Drug Screening program (read more about this program on page 14). Working with industry partners and other potential users of tissue chip technology is invaluable in determining the marketability of the devices and the widespread adoption of this technology in the research community. The International Consortium for Innovation and Quality in Pharmaceutical Development, an organization of biopharmaceutical company organizations, is working with tissue chip researchers to test and validate the devices according to industry standards and regulations. Additionally, these researchers are using proprietary compounds provided through partnerships with GlaxoSmithKline and Pfizer, Inc., to further assess the use of these bioengineered platforms for predictive toxicology. Other key partners in this program include five co-funding NIH ICs, DARPA and the FDA.

- Through a collaboration among government, academic and industry researchers and patient groups, NCATS' TRND program researchers demonstrated the therapeutic potential of a drug called cyclodextrin for treating Niemann-Pick type C1 disease. This disorder belongs to a group of lipid storage diseases, about 50 rare inherited disorders that usually affect children. In patients with these often fatal conditions, fatty materials build up in the cells and tissues of the body, which can result in damage to the brain, peripheral nervous system, liver and other organs and tissues. This TRND team developed cyclodextrin to the point of attracting biotechnology company Vtesse, Inc., of Gaithersburg, Maryland, to invest in the compound's further clinical development. Vtesse is providing funding for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to conduct clinical trials of cyclodextrin, as well as for NCATS to carry out additional pre-clinical studies on therapeutics for other lipid storage diseases. Read more about the TRND program on page 23.

- NCATS is leading an innovative collaboration between the NIH intramural program and Pfizer's Centers for Therapeutic Innovation (CTI) network. This public-private partnership program connects leading NIH intramural researchers with Pfizer resources to identify biologic compounds with activity in a disease pathway or target of interest. Together, NIH and CTI teams will work to move these compounds into the clinic for testing. Other partners in the CTI network include 25 academic institutions and four patient foundations.

Trans-NIH Partnerships

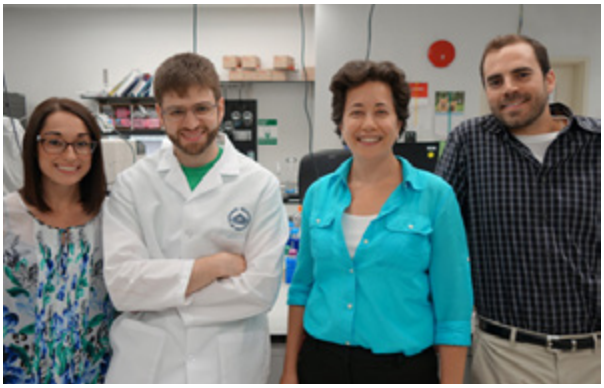
NCATS collaborates with multiple NIH ICs to provide unique resources, including technology and expertise, for numerous scientific projects. Some examples follow:

- **RNAi**
  NCATS' staff provide NIH investigators with collaborative RNAi screening resources in the form of expertise and facilities for high-throughput screening. Current projects involve collaborations with investigators from NINDS, NICHD and NCI. Read more about the RNAi program on page 16.

- **RDCRN**
  NCATS manages the RDCRN in collaboration with 10 other NIH components: NICHD; NCI; NHLBI; the National Institute of Allergy and Infectious Diseases; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the National Institute of Dental and Craniofacial Research; NIDDK; the National Institute of Mental Health; NINDS; and the NIH Office of the Director. This NIH-wide partnership provides scientific oversight and funding support for all RDCRN consortia. Read more about the RDCRN on page 21.

- **TRND** and **BrIDGs**
  These programs offer NIH intramural researchers a variety of opportunities to partner with NCATS researchers to gain access to drug development capabilities, expertise, and clinical or regulatory resources in a collaborative environment. The goal is to move promising therapeutics into human clinical trials. For example, NCATS' TRND staff worked with researchers from the NHGRI to refine an animal model for core binding factor leukemia, a rare bone marrow cancer. The team currently is working with this more optimized animal model to identify and develop a compound with therapeutic potential. This work will support the filing of an IND application with the FDA so that the compound can eventually be tested in humans. Read more about TRND and BrIDGs on page 23 and page 8, respectively.

- **Assay Development and Screening Technology**
  With support from the Michael J. Fox Foundation for Parkinson's Research, Richard Youle, Ph.D., of NINDS, recruited James Inglese, Ph.D., director of NCATS' Assay Development and Screening Technology Laboratory, to help find an agent that could enhance the activity of parkin, a protein whose function in the brain is abnormal in Parkinson's disease, a progressive movement disorder. Eventually, a promising candidate from this process could be tested for its ability to treat people with the disease. In addition, the compounds identified could be used to treat a number of other related rare diseases.



Several of NCATS' Assay Development and Screening Technology Laboratory postdoctoral fellows (from left to right): Brittany Wright, Adam Fogel, Melissa Mendez and Michael Iannotti.

Training and Workforce Development

Providing the resources to train, cultivate and sustain future leaders of the biomedical research workforce is a key NCATS goal, and both the CTSA Program and RDCRN program emphasize training and career development. CTSA Program investigators offer opportunities for practical research experience and mentorship to young scientists and clinicians. In addition, NIH and CTSA Program grantees have created a freely available set of national training resources and educational materials — including educational core competencies, best practices for research mentors and curriculum materials for courses — that many institutions have integrated into their training programs.

Training in Clinical and Translational Research Study Design

For example, Julie Shakib, D.O., M.P.H., a pediatrician, joined the University of Utah to complete a primary care research fellowship and an M.S. in clinical investigation to refine her skills in observational research design and statistics. She then earned an appointment as a faculty member at the university and conducted research on the effects of maternal immunization on infant immunity as a CTSA Program K12 scholar under the mentorship of Carrie L. Byington, M.D. Her work with Byington enabled her to become an independent researcher, and she now is evaluating strategies to improve immunization coverage among children attending child care programs statewide. Shakib cited CTSA Program training as

Drug development trainees in the laboratory of Margarita Dubocovich, Ph.D., chair of the Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo. (Photo credit: University at Buffalo)

King Li, M.D., M.B.A., director of the Clinical and Translational Science Institute at Wake Forest University Health Sciences, talks with a second-year medical student presenting a translational research project as part of the Medical Student Research Program, which provides a nine-week research experience for medical students to work with researchers to develop clinical and translational research projects. (Photo credit: Wake Forest School of Medicine)

helping her to gain the skills and hands-on experiences in study design, participant recruitment and analysis necessary to launch her research career.

NSF I-Corps Train-the-Trainer @ NCATS

Translating basic and pre-clinical research into interventions that benefit patients entails developing and testing innovations and then making them commercially available. Thus, it is important to train researchers and entrepreneurs to overcome key obstacles along the path of commercialization. NCATS, along with three other NIH Institutes, is collaborating with the National Science Foundation (NSF) to support the training of academic researchers funded through NIH's Small Business Innovation Research (SBIR) program. The new initiative, called I-Corps at NIH, is a pilot of the NSF Innovation Corps program and is tailored for biomedical researchers, aiming to accelerate innovations for applied health technologies and to speed their delivery to the marketplace.

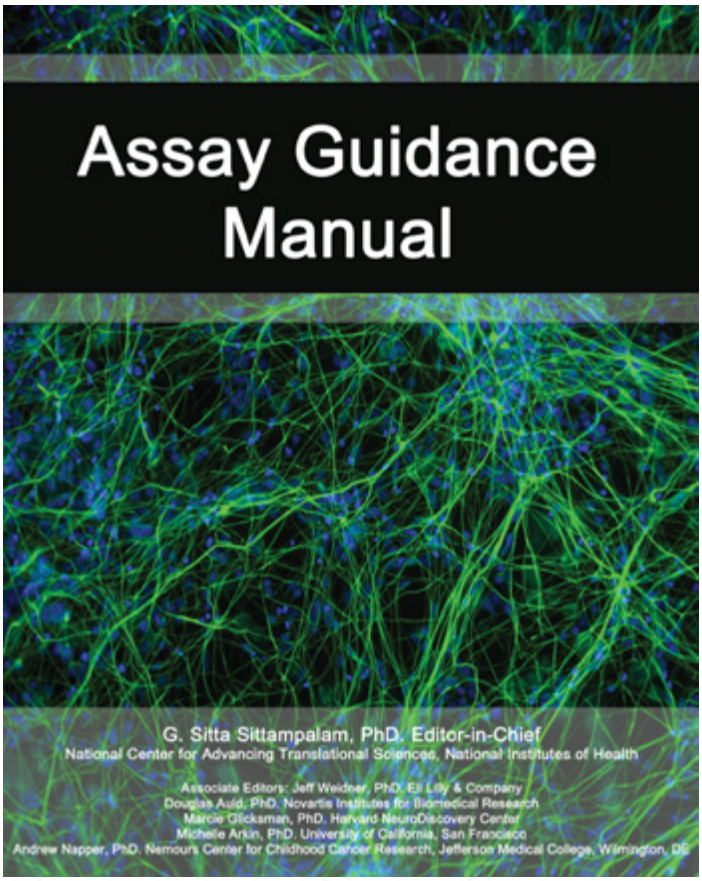
Twenty-one teams, two of which were supported by NCATS — Aclaris Medical LLC and Vivo Biosciences — successfully applied to the program in the summer of 2014. The I-Corps training curriculum, undertaken by awardees in October 2015, involved a 10-week "boot camp" in which experienced, business- and technology-savvy instructors worked closely with teams of researchers to help them explore potential markets for their NIH SBIR-funded innovations. NCATS also provided supplemental funding to the 21 awardees to support entrepreneurial training, mentorship and collaboration opportunities. NIH plans to expand the NIH I-Corps program to all NIH SBIR Phase 1-funded grantees in fiscal year 2016. The CTSA Program also will play an important role in expanding I-Corps at NIH™, as NSF's "train-the-trainer" program will be piloted by 10 CTSA Program hubs. This NSF-CTSA collaboration was among the initiatives announced by the White House during Demo Day in August 2015.

Training and Education for NIH Researchers

To guide NIH postdoctoral research fellows in translational sciences, in March 2015 NCATS and the NIH Office of Intramural Training and Education sponsored a Translational Science Training Program workshop. NCATS researchers presented on the topics of target identification and validation with RNAi technology, assay design and development for screening chemical compounds, and NCATS resources that help investigators "de-risk" drug candidates and conduct studies required to initiate clinical trials. In small group discussions, NCATS intramural researchers provided expert feedback on the participants' ideas for developing their own translational science projects. The event concluded with a tour of the NCATS intramural facilities, where the 20 participants saw the cutting-edge equipment and tools used to discover and develop new therapies and innovative technologies.

Training in Pre-Clinical Research

In July 2015, the FDA and NCATS' editors of the Assay Guidance Manual — a how-to guide written with Eli Lilly and Company on developing high-throughput screening assays — hosted a workshop on assay development for researchers from NIH, the FDA and the EPA. Experienced pharmaceutical industry scientists described best practices in drug discovery, a topic not readily found in the scientific literature. The workshop, attended by 140 scientists in person and 300 online, covered the practical aspects of developing and validating reproducible, robust assays for high-throughput screening and drug discovery projects.



The Assay Guidance Manual is an online 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.

Virtually Tour the NCATS Laboratories

The process of translation is unfamiliar to many in the scientific, patient and policy communities. To help demystify the pre-clinical stages of the translational process, NCATS produced a video tour of its intramural laboratories in 2015 that takes viewers behind the scenes to illustrate how its researchers rely on the power of data and new technologies to develop, demonstrate and disseminate improvements in translational science. https://youtu.be/FOp-IX3NY6E

The NCATS laboratories video tour provides an insider's look at the research conducted at the NCATS intramural research labs.

Appendix

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

Brief Overview of Accomplishments

Through 2015, TRND has maintained a portfolio of projects addressing a range of rare and neglected disease conditions, representing both pre-clinical stage development and human clinical trials. Pre-clinical studies have addressed rare cancers, lung disorders, neurological conditions, hormone deficiencies, heart failure syndromes, blood diseases and premature blindness as well as neglected tropical infectious diseases affecting millions worldwide.

Clinical studies are ongoing at the NIH Clinical Center for two rare genetic conditions: the pediatric neurological disease Niemann-Pick type C1 and the adult-onset muscle-wasting disease GNE myopathy. For GNE myopathy, a Phase I trial examining drug safety in healthy volunteers was completed, enabling initiation of a Phase II clinical trial in patients evaluating the effectiveness of the new therapeutic candidate to treat the disease. This is in addition to the continued GNE myopathy natural history study examining overall disease progression. For Niemann-Pick type C1 disease, a Phase I trial examining drug safety and efficacy in patients was completed. This work enabled the biotechnology industry partner Vtesse, Inc., to initiate a pivotal Phase IIB/III trial at multiple sites in the United States and Europe.

The comprehensive operational teams executing each project have successfully achieved interim milestones and are progressing according to schedules. Two collaborators exiting the portfolio in 2015 continue to demonstrate the success of TRND's catalytic pre-clinical de-risking model. Viamet Pharmaceuticals (cryptococcal meningitis) attracted sufficient venture capital funding to retake full control and continue pre-clinical development of their small molecule antifungal therapy. The University of California, Irvine, team (retinitis pigmentosa) received FDA notification that the clinical trials could proceed, enabling the collaborator's spinoff company, jCyte, Inc., to continue clinical development of this novel cell-based therapy treating hereditary blindness.

Detailed Program Accomplishments

See Table 1 for detailed listing of scientific resources provided.

Therapeutic Development Projects: Listed in order of initiation

Cyclodextrin for Niemann-Pick Type C1 Disease

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

Initiated: September 2009

Description: 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-β-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 HBPCD 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 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 Phase IIB/III trial at the NIH Clinical Center and sites around the United States and Europe. These clinical studies are currently ongoing.

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

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. HIBM has been traced to specific mutations in the *GNE* gene and the biochemical pathways this gene affects within muscle cells. There are no approved therapies for HIBM, 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 two pivotal 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 FDA 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, a Phase I clinical study was initiated in GNE myopathy patients at the NIH Clinical Center. This Phase I study has concluded, and a Phase II clinical trial is now underway.

Development of the Novel Antifungal VT-1129 for Cryptococcal Meningitis

Lead Collaborator: Edward Garvey, Viamet Pharmaceuticals, Inc., Morrisville, NC

Initiated: June 2011

Description: Cryptococcal meningitis (CM) results from fungal infections that are particularly prevalent in immune-compromised patients. CM is the second leading cause of HIV-related deaths in sub-Saharan Africa, with estimates of 500,000 deaths per year. Current therapies are only marginally effective. This project aims to develop a novel therapeutic that would greatly improve treatment of CM.

Outcomes: TRND researchers conducted validation studies for the lead compound, VT-1129, including pharmacokinetic, efficacy and toxicology studies in rodents and non-rodents, enabling selection of an optimal dosing regimen to balance efficacy and safety. The TRND team optimized a synthetic process for scaled-up production of the drug at a low cost that will support treatment of patients in the developing world. Additional collaborative studies were completed with the Centers for Disease Control and Prevention to test the *in vitro* efficacy of the molecule against 400 fungal strains from Africa. This TRND support enabled Viamet to successfully raise venture capital funding to continue development of the de-risked candidate. This TRND project was completed in 2015.

A Novel Compound for Targeted Treatment of CBF Leukemia

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

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 nonspecific 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 pre-clinical development. Once such a compound is identified, TRND will conduct the necessary studies to support filing an IND with the FDA.

Inhaled GM-CSF Therapy of Auto-immune Pulmonary Alveolar Proteinosis

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

Initiated: September 2011

Description: Pulmonary alveolar proteinosis (PAP) is a rare disease marked by accumulation of proteins and lipids in the narrow gas exchange pockets of the lung, leading to respiratory failure. As an autoimmune disease, PAP causes patients to generate antibodies that attack a 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. This project seeks 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 is providing essential research materials to the partnership. TRND supported extensive preliminary primate toxicology and dosing studies necessary to demonstrate the safety of using inhaled GM-CSF. TRND is now conducting formal IND-enabling toxicology studies and formulation development. Once an IND is in effect, TRND will support clinical pharmacology and pharmacokinetic studies.

BMP Inhibitors to Treat Fibrodysplasia Ossificans Progressiva

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

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 pre-clinical development. As such, TRND scientists are performing medicinal chemistry optimization to identify a compound suitable for formal pre-clinical development. Once such a compound is identified, TRND will conduct the necessary studies to support filing an IND with the FDA.

Deuterated Analogs of Praziquantel for Treatment of Schistosomiasis

Lead Collaborator: Julie Liu, Concert Pharmaceuticals, Inc., Lexington, MA

Initiated: September 2011

Description: Infection by the schistosoma worm (schistosomiasis) is a devastating parasitic disease, second only to malaria in impact, and affects more than 200 million people worldwide. Standard therapy involves treatment with praziquantel (PZQ), but very high doses are required to treat each patient. With the goal of global eradication of schistosomiasis in mind, this project seeks to develop a modified form of PZQ that will have improved potency and slower metabolism, thereby lowering the dose needed to clear infection and allowing much more widespread patient treatment. Concert's platform technology to increase exposure of currently approved therapeutics could be applied to other therapeutics in the rare and neglected tropical disease areas.

Outcomes: After studying the metabolic stability of modified forms of PZQ, TRND selected a PZQ analog for further development. These studies included identification of PZQ metabolites and efficacy studies in cells and animal models. During conduct of this research, Merck KGaA, as part of the Pediatric Praziquantel Consortium, announced a commitment to develop formulations of PZQ. In light of this announcement, TRND concluded that the medical need for developing modified forms of PZQ to treat schistosomiasis has been met. Consequently, this TRND project has been discontinued.

CincY as a Treatment for Creatine Transporter Defect

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

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 creatine transporter defect (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 (CincY) 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 CincY 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 CincY. Toxicology studies, formulation development, chemistry studies and manufacturing are ongoing. These studies will enable an IND application to be filed with the FDA. To support future clinical trials of CincY, TRND is developing a prospective natural history study of the disease course in patients.

Long-Acting Parathyroid Hormone Analog for the Treatment of Hypoparathyroidism

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

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. 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 and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), have further developed the animal model of hypoparathyroidism to generate robust efficacy data. With concurrence from the FDA, the team will execute the full pre-clinical development plan. TRND will support the preparation and filing of the IND application with the FDA, with NICHD providing support for subsequent clinical trials in patients.

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

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 with the FDA to enter human trials.

Use of Retinal Progenitor Cells for the Treatment of Retinitis Pigmentosa

Lead Collaborator: Henry Klassen, University of California, Irvine, CA

Initiated: September 2013

Description: Retinitis pigmentosa (RP) is a severe form of hereditary blindness characterized by progressive damage to and loss of the light-sensing cells of the retina. Most patients have night blindness in their early teens, typically progressing to legal blindness by age 40. There are no approved treatments for RP. The lead collaborator has identified an innovative approach involving cell transplantation to save the light-sensing cells of the eye. The purpose of this project is to support the development of these retina-derived cells as a transplantable treatment to stop the cellular damage that leads to blindness in RP patients.

Outcomes: Studies were performed by TRND and the collaborator to support submission of a full IND application package. TRND researchers completed a key biodistribution study of the formulated retinal cells (jCell) in animals. The results of these studies were incorporated into an IND filing by the collaborator's start-up company, jCyte, Inc. The IND was submitted to the FDA, and the FDA has allowed human clinical trials to begin. jCyte, Inc., will now be able to continue development of jCell using internal resources. This TRND project is now complete.

Repurposing an EU Therapeutic for Hemoglobinopathies

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

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 pre-clinical project plan with a primary focus on beta-thalassemia as the first indication. The team has begun pharmacology and efficacy studies to recapitulate key data generated by the collaborator, with further studies planned to support IND filing with the FDA.

Development of Malaria Transmission-Blocking Drugs

Lead Collaborator: Kim Williamson, Loyola University of Chicago, IL

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 further evaluation and development. The TRND team is performing medicinal chemistry optimization to identify a lead candidate for further development. Initial pharmacology and absorption, distribution, metabolism and elimination studies are being performed, with further studies planned to support IND filing with the FDA.

Table 1. TRND Projects and Scientific Resources

See text for outcomes. Glossary for terms listed below can be found on "Glossary of Terms" on page 42.

Project	Collaborating Institutions	Scientific Resources
Cyclodextrin for Niemann-Pick Type C1 Disease	Ara Parseghian Medical Research Foundation; Niemann-Pick Type C1 Support of Accelerated Research (NPC-SOAR); Washington University in St. Louis; Albert Einstein College of Medicine; University of Pennsylvania; Johnson & Johnson; Vtesse, Inc.; National Institute of Neurological Disorders and Stroke (NINDS); NICHD; NHGRI	Project Management, Pharmacology, ADME/PK, Toxicology, Formulation, Regulatory, Clinical
DEX-M74 for GNE Myopathy	NHGRI; New Zealand Pharmaceuticals	Project Management, ADME/PK, Toxicology, Formulation, Process Chemistry, Regulatory, Clinical
Development of the Novel Antifungal VT-1129 for Cryptococcal Meningitis	Viamet Pharmaceuticals, Inc.	Project Management, Medicinal Chemistry, Pharmacology, ADME/PK, Toxicology, Formulation, Process Chemistry
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
Deuterated Analogs of Praziquantel for Treatment of Schistosomiasis	Concert Pharmaceuticals, Inc.	Project Management, Medicinal Chemistry, Pharmacology, ADME/PK, Toxicology
CincY as a Treatment for Creatine Transporter Defect	Lumos Pharma, Inc.; Cincinnati Children's Hospital	Project Management, ADME/PK, Toxicology, Formulation, Process Chemistry
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
Use of Retinal Progenitor Cells for the Treatment of Retinitis Pigmentosa	University of California, Irvine	Project Management, Pharmacology, ADME/PK, Toxicology
Repurposing an EU Therapeutic for Hemoglobinopathies	Phoenicia Biosciences, Inc.	Project Management, Pharmacology
Development of Malaria Transmission-Blocking Drugs	Loyola University of Chicago	Project Management, Medicinal Chemistry, Pharmacology, ADME/PK

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 drug candidates up to Phase IIA to assess the candidates' safety and effectiveness in treating the intended disease, as well as non-drug studies of patients with a particular disease (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 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.

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 communications 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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