National Center for Advancing Translational Sciences

2014 REPORT

National Center for Advancing Translational Sciences

NCATS' Definitions of Translation and Translational Science:

Translation is the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public — from diagnostics and therapeutics to medical procedures and behavioral changes.

Translational science is the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process.

NCATS studies translation on a system-wide level as a scientific and operational problem.

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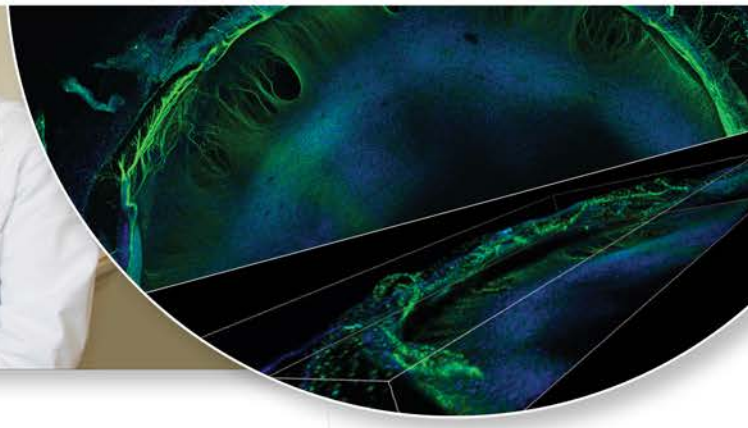
Front cover, left: The Biorepository at the Einstein-Montefiore Institute for Clinical and Translational Research is a quality-assured facility for acquisition, processing, storage and secure distribution of specimens with patient-specific annotations from the electronic medical record (Courtesy of Albert Einstein College of Medicine). Front cover, middle: Lisa Guay-Woodford, M.D., principal investigator at Clinical and Translational Science Institute at the Children's National Medical Center, talks with patient Michael Lewis during his visit to the Clinical Research Center. Lewis has mucopolysaccharidosis IVA (Morquio A syndrome) (Stephen Bobb Photo/Paula Darte). Front cover, right: Technician Christopher O'Donnell working with samples in the Genetics Translational Technology Lab, one of the cores of the Johns Hopkins Institute for Clinical and Translational Research (Johns Hopkins University/J. Franzos).

Director's Message



Christopher P. Austin, M.D.

The National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) is dedicated to getting more treatments to more patients more quickly. Thanks to our growing understanding of human biology, along with the increased availability of innovative technologies, there is an unprecedented opportunity to translate scientific discoveries more efficiently into new, more effective and safer health interventions. I am delighted to share this report of the Center's activities in 2014, which outlines how NCATS is creating technological and scientific advances in translation and building a robust, collaborative, science-based translational ecosystem to deliver health breakthroughs in new, faster ways.

Rather than focusing on a specific disease, NCATS seeks insights into what is common among diseases and the accompanying translational science processes. This approach entails advancing studies on how seemingly disparate conditions can share an underlying molecular basis and how research targeting that foundation may treat more than one disease. The Center's emphasis on studying translation on a system-wide level as a scientific and operational problem provides the potential to accelerate development of treatments and preventions for many diseases. Through its projects, initiatives and support, NCATS develops new approaches, technologies, resources and models; demonstrates their usefulness in a specific disease or use case; and disseminates the data, analyses and methodologies to the entire scientific community.

One example of NCATS' system-wide approach is the Tissue Chip for Drug Screening initiative, which supports the development of 3-D human tissue "chips" that mimic the structure and function of human organs, such as the lungs, liver and heart. Scientists supported by this program are collaborating to combine the organ chips into integrated systems that can mimic the complex functions

Left: John N. Clore, M.D., director of Virginia Commonwealth University's Center for Clinical and Translational Research (CTTR), speaks with patient Colleen A. Thoma, as she undergoes a test to monitor brain wave activity. CTTR is one of more than 60 medical research institutions supported by NCATS' Clinical and Translational Science Awards program (Virginia Commonwealth University Photo). Right: Top figure depicts neurons (shown in green) and nuclei for all cells (shown in blue). Bottom figure is layered structure that resembles early brain development. Tissue Chip investigator, James Thomson, V.M.D., Ph.D., from Morgridge Institute for Research at the University of Wisconsin–Madison, and other researchers engineered 3-D vascularized neural tissues (Morgridge Institute Photo/James Thomson Laboratory).

of the human body. Once fully developed and integrated, these systems could be used to help quickly, accurately and cost-effectively predict whether a candidate drug, vaccine or biologic agent is toxic to or effective in humans. Read more on p. 10.

Another basic NCATS principle is to recognize that translation is a team sport, requiring investigators with a wide variety of expertise to work together toward a common goal. This teamwork approach led to the biopharmaceutical company Baxter International acquiring an experimental drug, Aes-103, that was developed by our Therapeutics for Rare and Neglected Diseases (TRND) program researchers and their collaborators. As described on p. 18, this advance was a crucial milestone for the TRND program and NCATS. Most importantly, it offers patients new hope as Baxter works to complete the drug's clinical development.

NCATS also is committed to improving the efficiency and effectiveness of the clinical research conducted in the U.S. as an integral part of our goal of bringing treatments to patients more quickly. One example of how NCATS-supported researchers already have made strides toward this goal is the rapid launch of a clinical trial in the days following the horrific Boston Marathon bombing in April 2013. Researchers at the Massachusetts Eye and Ear Infirmary, which is affiliated with Harvard Medical School, set out to study the extent of these injuries. Fortunately, with support from NCATS' Clinical and Translational Science Awards (CTSA) program, Harvard already had an institutional review board (IRB) reliance network in place with regional hospitals. This network enabled the study to be launched very quickly at seven different research sites, and preliminary findings were published in November 2014. In September 2014, NCATS released a new CTSA funding opportunity announcement designed to build on this and other past program successes while aligning it more directly with NCATS' overall goal to transform the translational science process. Read more on p. 15.

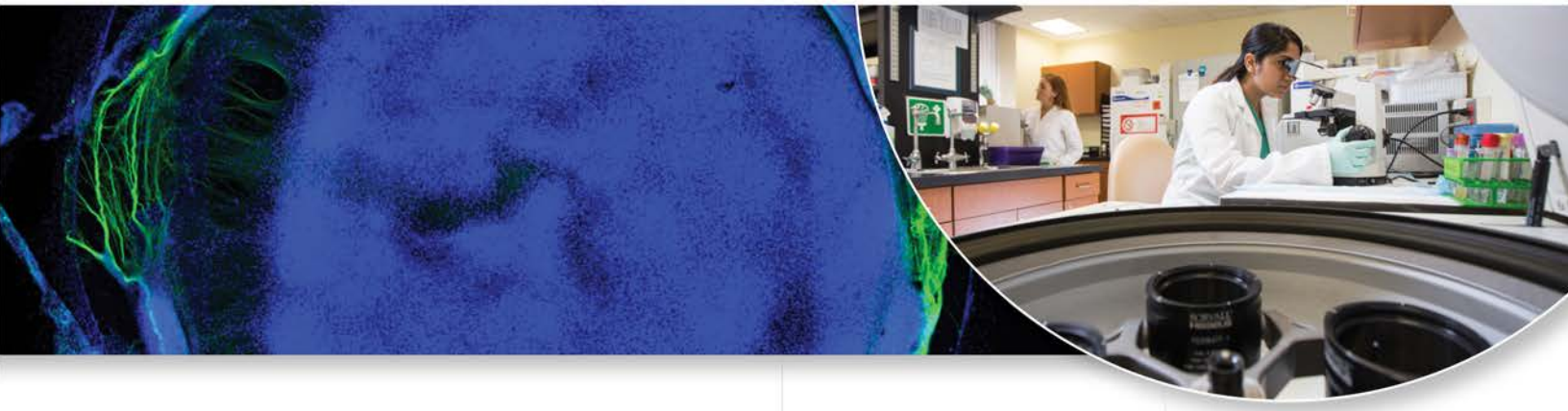
Engaging patients at every step of the translational science process plays a critical role in NCATS' work. Patient participation on the research team facilitates the translational process by providing essential connections to the patient community and disease experts as well as insights into aspects of a disease that interventions should target. NCATS has myriad collaborations with such groups — including those for Charcot-Marie-Tooth (CMT) disease, Niemann-Pick disease type C and Parkinson's disease, among many others — which ensure that NCATS-supported research addresses patients' real-life concerns, encourages clinical research participation, and garners input about study design and recruitment activities. Learn more on p. 19.

In the past year, NCATS expanded the Rare Diseases Clinical Research Network (RDCRN), which brings researchers and patient advocates together to advance medical research on rare diseases through collaboration on observational and interventional studies and data sharing. Read on p. 17 how the RDCRN supported a team that catalyzed the development and approval of three drugs to treat urea cycle disorders, providing patients with treatments for these life-threatening conditions.

There is much more in this report about NCATS' work and achievements in solving some of the most challenging problems in translational science. I hope you enjoy learning more about our Center, and I look forward to sharing more with you as we continue to evolve and innovate to bring the promise of science to patients and health.

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

Pre-Clinical Innovation



Pre-clinical research, which connects basic scientific discoveries with initial testing of therapies in humans, is a failure-prone stage of translation. (See box for key definitions.) Pre-clinical programs at NCATS are designed both to develop new technologies to make this translational stage more predictive and efficient, and also to "de-risk" targets and disease projects so that they will be more attractive to potential partners. NCATS works with academic, nonprofit and industry investigators and with patient groups to provide pre-clinical drug development expertise and resources to advance their research, and in addition, assists in generating data needed for regulatory approval. The Center employs a variety of agreements and mechanisms to establish formal partnerships and collaborations that enable sharing of research resources between partners and with the public.

Left: Engineered 3-D vascularized neural tissues are formed within 24-well transwell inserts and are characterized by complex morphological features, including neural processes that extend several millimeters (neurons shown in green, nuclei for all cells shown in blue) (Morgridge Institute Photo/James Thomson Laboratory). Right: The Biomarker and Analytic Research Core at the Einstein-Montefiore Institute for Clinical and Translational Research, a CTSA-supported institute, provides high-throughput assays for a wide range of studies (Albert Einstein College of Medicine).

The Research Spectrum

- The therapeutics development pipeline builds upon and informs **basic research** discoveries that can reveal fundamental mechanisms of biology, disease or behavior.
- **Pre-clinical research** connects basic science and human medicine. During this stage, scientists apply fundamental discoveries made in the laboratory or the clinic to further understand the basis of a disease or disorder and ways to treat it. Testing is carried out using cell or animal models; samples of human or animal tissues; or computer-assisted simulations of drug, device or diagnostic interactions within living systems.
- **Clinical research** is research with human subjects that is patient-oriented, such as research on mechanisms of human disease, therapeutic interventions, clinical trials and the development of new technologies. It also includes epidemiological and behavioral studies and outcomes and health services research.

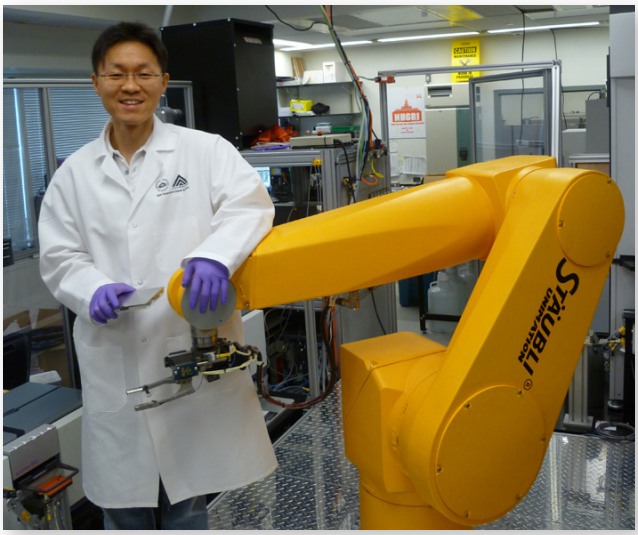
Improving the Drug Development Process

Assay Development and Screening Technology

One of the first steps in the drug development process is creating test systems (assays) in which to assess the effects of chemical compounds on cellular, molecular or biochemical processes of interest. Investigators from the biomedical research community submit ideas for assays to NCATS scientists, who help to optimize them for high-throughput small molecule screening (see box for definition). The results of these screens, called probes, can be used to further explore protein and cell functions and biological processes relevant to human health and disease. In addition, these probes can be developed further to become potential therapeutic candidates in the drug development pipeline.

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

NCATS experts pursue innovations in assay technology to expand understanding of diseases and possible treatment targets. In one example, researchers developed an assay technique to screen chemical libraries for compounds that have therapeutic potential to treat a neurological disorder called Charcot-Marie-Tooth (CMT) disease. CMT is the most commonly inherited disorder of the peripheral nervous system, affecting more than 2.6 million people worldwide. It is incurable and slowly damages the nerve cells leading to the arms, hands, legs and feet, resulting in pain, muscle loss and loss of sensation. CMT is caused by overproduction of a gene called *PMP22*. Finding ways to block this overexpression could lead to potential treatments for CMT.

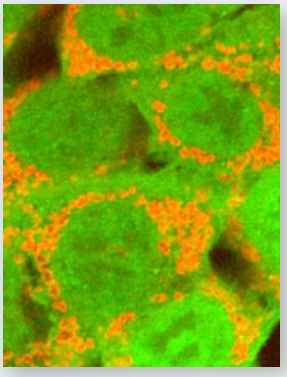


CMTA-supported postdoctoral fellow Sung-Wook Jang, Ph.D., stands next to the high-throughput screening robotic system used to identify potential treatments for CMT disease.

The NCATS group, with support from the CMT Association (CMTA) disease foundation, teamed with collaborators at the National Human Genome Research Institute (NHGRI), the University of Wisconsin and Sangamo BioSciences to carry out the research. To create an assay for this screen, the scientists used a technique called genome editing to insert biological tools known as reporter genes into the DNA sequence of *PMP22* in cells grown in culture. The reporter genes then produced detectable signals — in this case, light — when *PMP22* was expressed. For the first time, the group combined the genome-edited assay with high-throughput screening of the NCATS Pharmaceutical Collection (NPC), a library of 3,000 approved and investigational small molecular entities. The screen confirmed a number of known target pathways involved in blocking *PMP22* overexpression and revealed a pathway not previously known. This new technique represents an advance over past methods, broadening the number of potential treatment targets discovered. The scientists and CMTA have partnered with pharmaceutical company Sanofi-Genzyme to provide the new assay for screens of compound libraries that include more than 2 million small molecules. CMTA experts will pursue further testing of promising candidates that emerge from these screens and those conducted at NCATS, validating them in animal models and refining them for eventual studies in humans.

The work was published in the Nov. 21, 2014, issue of *ACS Chemical Biology*.

Using Assay and Screening Resources to Find Potential Therapies for Parkinson's Disease and Related Conditions



RNAi is used to find genes that interact with parkin (green), a protein that tags damaged mitochondria (red). Mutations in parkin are linked to Parkinson's disease and other mitochondrial disorders (NINDS Photo/ Youle Laboratory).

With support from the Michael J. Fox Foundation for Parkinson's Research, James Inglese, Ph.D., director of NCATS' Assay Development and Screening Technology Laboratory, and Richard Youle, Ph.D., of the National Institute of Neurological Disorders and Stroke (NINDS), are leading a project that showcases how the Center's assay production and chemical screening resources can advance development of potential therapeutics for a broad range of diseases.

Parkinson's disease is a brain disorder marked by shaking (tremors) and problems with walking, movement and coordination. The progressive death of neurons (brain cells) in an area of the brain that controls movement leads to these symptoms. Scientists believe that one cause of this neuronal death is dysfunction in cellular mitochondria, which generate the energy that cells need to function. Defective mitochondria leak toxic substances that have the potential to damage or destroy the cell. Youle and his group have found that under normal circumstances, a protein called parkin signals the cell to destroy and remove faulty mitochondria. For patients with Parkinson's disease, this maintenance mechanism is disrupted.

Youle's team recruited Inglese and accessed assay development and chemical screening resources at NCATS to find an agent that could enhance parkin activity, potentially preventing mitochondrial-induced damage and neuronal death. Inglese and his group developed an assay using neuron-like cells grown in a lab. With this assay, the team is now conducting high-throughput screens with the Center's chemical libraries to identify compounds that increase parkin activity. They also are conducting genome-wide RNAi screens (see definition on p. 13) to find genes that interact with parkin.

Eventually, a promising candidate from this process could be tested for its ability to treat people with Parkinson's. Additionally, the compounds identified could be used to treat a number of rare diseases also marked by damaged mitochondria.

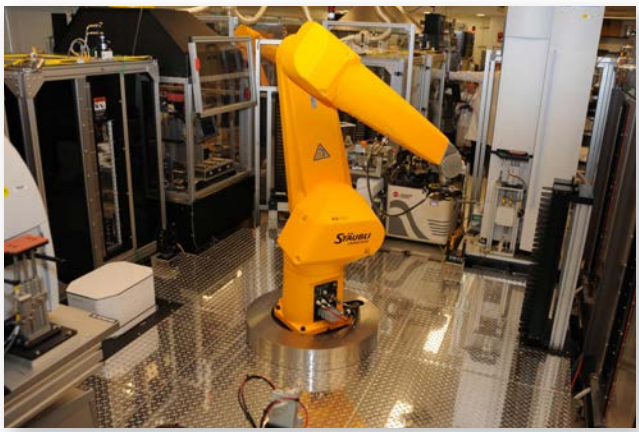
Moreover, the parkin research has provided Inglese's team the opportunity to work on an innovative process for improving screening and assay methods, which they and other scientists could use to solve many other translational research problems.

NCATS Chemical Genomics Center

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 world-leading collaborative services to meet these needs. The NCATS Chemical Genomics Center (NCGC, and formerly known as the NIH Chemical Genomics Center) collaborates with more than 200 investigators in the NIH extramural, intramural, biopharmaceutical and nonprofit sectors 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, using probes to understand diseases and validating targets to treat diseases.

In a recent example of this type of work, NCGC experts teamed with NHGRI investigators to develop a potential treatment for patients with Gaucher disease, a rare, inherited condition marked by enlargement of the liver and spleen, anemia, nose bleeds, easy bruising and bleeding, bone problems, and — occasionally — neurological problems. In patients with the disorder, a defective enzyme impairs the functioning of cells called macrophages. The research group performed a series of large-scale screens of NCGC's small molecule library, yielding several promising molecules called chemical chaperones that enhanced the function of the faulty enzyme. The chaperone molecules were particularly promising because they were the first "non-inhibitory" chaperones identified. Up until that point, the group had found only compounds that were inhibitory: At low doses, they helped the enzyme function, but at higher doses, they could inactivate it, making proper dosing a tricky balancing act. The non-inhibitory chaperones, on the other hand, presented none of these problems.

The next step was to test the molecules in patient-derived macrophages. However, the cells — especially diseased ones — are hard to keep alive in a laboratory environment, requiring researchers to continually draw large amounts of blood from Gaucher patients. NHGRI's Elma Aflaki, Ph.D., found a way around this obstacle by turning patient-derived adult stem cells into macrophages. The stem cells provided the team with a continuous supply from which to create macrophages, eliminating the need to draw blood from patients.



A robot arm retrieves compound plates from storage incubators and brings them to a transfer station where compounds are transferred to assay plates using a pin tool.

One of the chemical chaperones identified from the screens reversed the cells' disease features, returning the macrophages to normal function. The team is now working to optimize the molecule for testing in Gaucher patients. A small biotech company is exploring the possibility of licensing the compound. The molecule also could potentially benefit people with Parkinson's disease, which is linked to the same defective enzyme. The group's work not only represents a major advance in the understanding and treatment of Gaucher disease but also provides a cell model more closely resembling human physiology that scientists can use to study and explore other conditions — a major part of the NCATS mission. The non-inhibitory chaperones identified by the team could also be used to treat other disorders with similar enzyme defects. The team's findings were published in the June 11, 2014, issue of *Science Translational Medicine*.

Bridging Interventional Development Gaps (BrIDGs)

The BrIDGs program makes available, on a competitive basis, resources that investigators need to develop new therapeutic agents, including small molecule drugs, biologics and gene therapy. Successful applicants receive access to NCATS expertise and contract resources to conduct crucial pre-clinical studies necessary for regulatory approval for first-in-human trials. These resources include compound synthesis, formulation, pharmacokinetic studies and toxicology studies in support of investigator-held Investigational New Drug (IND) applications to the Food and Drug Administration (FDA).

In 2014, BrIDGs actively supported 20 projects, initiated two new ones and successfully completed three projects. During this period, BrIDGs support enabled three IND filings with the FDA. In one of these projects, BrIDGs scientists worked with investigators at the University of California, San Francisco, on a potential therapy for aromatic l-amino acid decarboxylase (AADC) deficiency, a rare, inherited disorder that appears in the first year of life. Children with the condition may have severe development delays, weak muscle tone, problems moving and uncontrollable movements of the arms and legs. The compound under study, AAV2-AADC, acts to relieve symptoms by restoring the brain's AADC enzyme, which is deficient in patients with this condition.

In addition, one therapeutic agent developed using program resources entered into first-in-human clinical trials in

2014. BrIDGs experts worked with Parion Sciences of Durham, North Carolina, to advance a potential treatment for chronic dry eye. This serious condition is one of the most frequently diagnosed diseases of the eye, affecting more than 5 million people in the United States. Only a few treatments currently exist for the condition, and they provide only temporary or partial relief. The investigators developed a compound, P-321, that appears to keep the surface of the eye hydrated by preventing the absorption of salt and water, an effect that persists over time. Parion is now conducting a phase I/IIA trial to test P-321 in humans with chronic dry eye. The company signed an exclusive option agreement with Santen Pharmaceutical for the development and commercialization of the compound.

Previously, BrIDGs experts helped Lehigh University investigators develop a potential drug for treating stress-related depression and anxiety. The compound, SRX-426, blocks a hormone called vasopressin that drives the brain's response to chronic stress. After successfully filing an IND, the researchers began testing the agent in clinical trials.

Catherine Chen, Ph.D., a biologist in the Therapeutics for Rare and Neglected Diseases program, loads a microplate containing cells that model a rare disease onto the pintool machine to allow high-throughput screening of small molecules.

It is now entering phase II clinical trials of intermittent explosive disorder, a condition related to anxiety and depression that is marked by frequent, angry outbursts.

Repurposing Drugs

A single drug or specific combination may be effective in treating several distinct disorders. "Repurposing" refers to studying drugs that are already approved to treat one disease or condition to see if they are safe and effective for treating other diseases. For every drug that is approved by the FDA, many others are abandoned after initial clinical testing but before FDA approval due to lack of effectiveness or for business reasons. Drug "rescue" refers to research involving such partially developed molecules. NCATS focuses on drug rescue and repurposing because of the potential for rapid therapeutic advances and lower costs.

NCATS Pharmaceutical Collection (NPC)

To enable such "repurposing" on a broad scale, researchers can tap the NPC, a comprehensive database and compound screening library of drugs and investigational medicines approved for clinical use by regulatory authorities in the United States, Europe, Canada and Japan. NPC is available in two forms: as a free electronic resource that lists the drugs and their regulatory status, and as a compound library used in high-throughput screening assays at NCGC.

Testing of NPC drugs already has generated new 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 — wanted to understand whether drugs used to treat other conditions might also be used to better treat hepatitis C. In a drug repurposing screen, the team identified a compound called chlorcyclizine that inhibited the ability of the hepatitis C virus to infect cells. Chlorcyclizine is an antihistamine that was 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. Scientists could use similar strategies to protect patients against other viruses that are poorly understood. In early 2014, the FDA approved chlorcyclizine for clinical trials to test whether it can be used to treat hepatitis C.

Repurposing an Approved Drug for Multiple Sclerosis

In September 2014, NCATS awarded Transparency Life Sciences, LLC, a $1.4 million Small Business Innovation Research (SBIR) grant to fund a phase IIA proof-of-concept study testing the effectiveness of an approved blood pressure drug for treating multiple sclerosis (MS). The condition is a progressive disease in which the body's immune system attacks the brain and spinal cord, leading to fatigue, pain, weakness and problems walking.

The project advances the Center's mission to innovate in both the scientific and operational aspects of translation. The researchers are repurposing an already approved drug that may be effective as an add-on to current MS therapies. Repurposing drugs is a cost-effective way to speed the development process, because these compounds have previously been proven safe and effective in treating at least one human disease. The company's approach also involves a novel method of measuring patients' responses through telemonitoring. Researchers interact with patients mostly through video, minimizing the need for in-person site visits during their clinical trial participation. This new clinical trial process will serve as a model for future studies, paving the way for more efficient and cost-effective methods.

In collaboration with Electron Kebebew, M.D., FACS, of the National Cancer Institute (NCI), NCATS scientists set out to discover novel therapeutics for anaplastic thyroid cancer (ATC), an aggressive form of cancer that is particularly resistant to existing chemotherapy. Patients diagnosed with ATC have a very poor prognosis and short survival time. NCATS scientists implemented a biological assay to look for drugs from the NPC that selectively kill ATC cells. Through their research, the scientists were able to identify four key drugs — carfilzomib, YM155, Torin-2 and CUDC-101 — that were further validated in follow-up assays and that worked in animal models. Each drug works through different biological mechanisms and can be evaluated as combination treatments. The collaborative findings will invite consideration of these drugs for ATC clinical trials and may lead to important treatment options for patients with this devastating disease.

New Therapeutic Uses

Launched in 2012, Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) is a collaborative initiative designed to facilitate partnerships between pharmaceutical companies and the biomedical research community to advance therapeutics development. This innovative program matches pharmaceutical 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 is creating new and rapid ways to test novel treatments

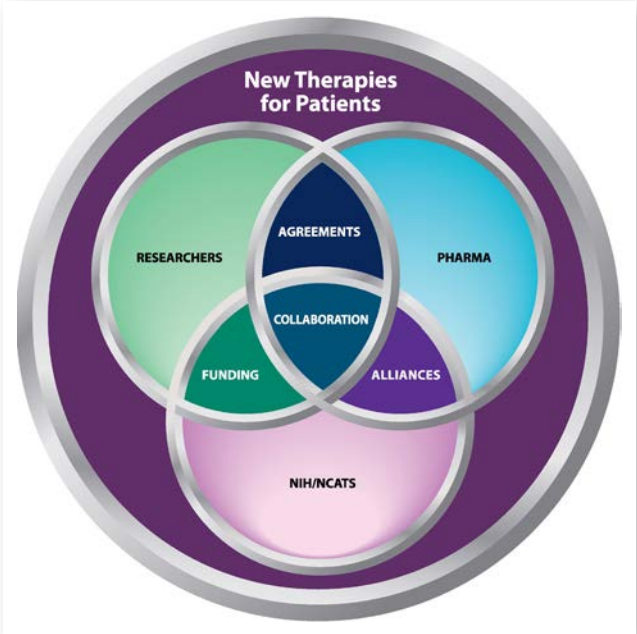


Diagram of collaboration structure for the New Therapeutic Uses program

for diseases with unmet medical needs. Through the program, the Center provides researchers with a selection of pharmaceutical industry agents that have cleared many key steps in the drug development process, including safety testing in humans, with the ultimate goal of identifying promising new treatments for patients. Repurposing these agents for a new use offers the potential for rapid completion of development and ultimate regulatory approval. NCATS crowdsourced these agents through New Therapeutic Uses, providing scientists nationwide with a strong starting point from which to engage in therapeutics development.

New Therapeutic Uses is designed to streamline the legal and administrative process for research collaboration across organizations through template partnership agreements, which are 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. In June 2013, as part of the pilot phase, NIH awarded $12.7 million to nine academic research groups for projects to explore new treatments for patients in eight disease areas. Within three months, one-third of the project investigators were testing compounds in humans for new uses, including potential treatments for schizophrenia (two agents) and Alzheimer's disease.

In one ongoing New Therapeutic Uses project, Mayo Clinic scientists have teamed with the pharmaceutical company Sanofi to test one of the firm's drugs as a potential treatment for patients with aortic valve calcification. This condition occurs when calcium deposits build up in the heart's aortic valve, which narrows and reduces blood flow. Aortic valve calcification can lead to the development of heart disease. Currently, no effective treatments exist for this disease aside from invasive and expensive surgery to replace the aortic valve. Less than 40 percent of affected patients with this disease live five years without experiencing cardiac events such as heart attacks.

Sanofi originally developed the drug being tested — called Ataciguat — as a therapy for chest pain and peripheral artery disease, but it proved to be an ineffective treatment

Expanding New Therapeutic Uses Agents to Benefit Children

A medical student at The University of Texas Health Science Center at San Antonio celebrates new life with a mother and baby while on obstetrics rotation at the Regional Academic Health Center, a campus of the Health Science Center in the Lower Rio Grande Valley of Texas (UT Health Science Center at San Antonio Photo).

With the New Therapeutic Uses funding opportunities announced in May 2014, participating pharmaceutical companies have made available, for the first time for this program, agents that scientists can use to explore for pediatric uses. For those agents, NCATS will provide an extra year of support — as compared to agents for adult indications — to complete additional studies evaluating safety, dosage and side effects in healthy volunteers as well as pre-clinical juvenile toxicity studies, which are required before pediatric clinical trials can begin. This expansion of available agents reflects the robust responses to the pilot phase from both the pharmaceutical industry and the research community, indicating a high level of enthusiasm for the program and a desire to make agents available for both adults and children.

for these conditions. The New Therapeutic Uses team is testing Ataciguat in a clinical trial of 100 patients with aortic valve calcification to assess the drug's effect. If the current trial and subsequent phase III trial is successful, Sanofi will have the first option to license Ataciguat for this new therapeutic use — a rapid pathway to delivering a novel treatment to patients in need.

In May 2014, NCATS announced new funding opportunities to build on the pilot phase of the program. For the new opportunities, NCATS is collaborating with AstraZeneca; Janssen Research & Development, LLC; Pfizer; and Sanofi to make 26 agents available, including, for the first time for this program, some that are suitable for exploring pediatric indications as well as agents that are in active development. Funding for successful applicants is expected to begin in July 2015. In addition to NCATS, multiple NIH Institutes and Centers (ICs) and the FDA's Office of Orphan Products Development are supporting this program.

Testing and Predictive Models

Predicting biological effects of drugs, chemicals and interventions is fraught with hazard. Approximately 80 percent of candidate drugs fail in human clinical trials because they are found to be unsafe or ineffective. More than 30 percent of promising medications have failed in clinical trials because they are found to be harmful to human health (i.e., they have high toxicity), despite promising and costly pre-clinical studies in animal and cell models. Because these models often do not adequately represent human biology, they do not always accurately reflect how patients will react to an experimental compound.

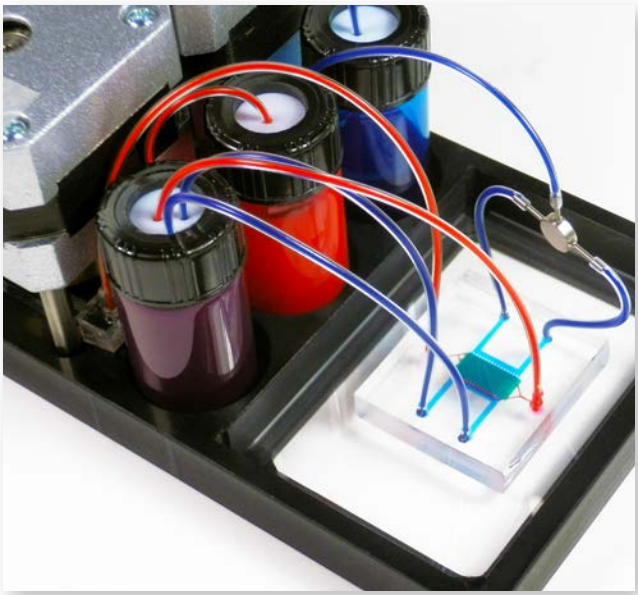
A major area of emphasis at NCATS is the development of model systems for drug and toxicity testing that more closely resemble human physiology. Such advances could save enormous amounts of time and expense by preventing patients from being exposed to potentially harmful or ineffective candidate drugs in clinical studies. In addition, these models have the potential to provide useful information about the basic biology of disease and serve as improved testing platforms for predicting toxicity or other physiological processes as well as evaluating environmental chemicals.

Tissue Chip for Drug Screening

NCATS, the Defense Advanced Research Projects Agency (DARPA) and FDA are leading the Tissue Chip for Drug Screening program, an initiative to revolutionize the process for predicting drug safety. Researchers use microchips as platforms to support human "tissue chips" that serve as miniature models of living organs, such as the lung, liver and heart. About the size of a thumb drive, the chips are lined with living cells and contain features designed to replicate the complex biological functions of specific organs.

In the first two years of the program, which was launched in 2012, researchers developed individual human tissue chips that demonstrated organ functionality, mimicked human biological responses and generated more accurate data when compared with conventional cell and animal testing methods. Tissue chips include those for the heart, liver, blood-brain barrier, blood vessels, kidney, gastrointestinal system, nervous system and models of adipose (fat) as well as tumors and metastases (the spread of cancer). In addition, chips mimicking male and female reproductive systems will be critical to evaluating differences in response to drug exposure.

As part of the new integration phase of the Tissue Chip program, several teams of scientists are working together to ensure that the organ systems will function with one another. In September 2014, NIH awarded funds to



Blood-brain barrier on a chip being developed by Vanderbilt University researchers (Vanderbilt University Photo/John Wikswo).

Danilo A. Tagle, Ph.D., M.S, Associate Director for Special Initiatives at NCATS, holds a tissue chip.

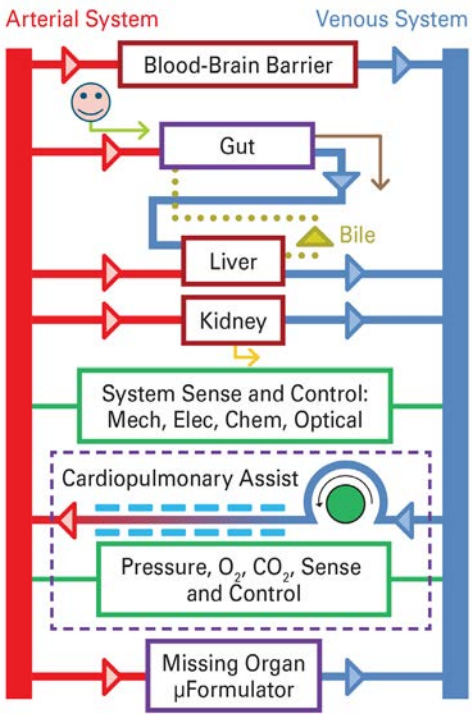
support this next phase of the program. Researchers will collaborate to refine existing chips and integrate them into a system that can mimic the complex functions of the human body. This integration will enable real-time measurement of drug activity within and across various organs and tissues, such as the liver and digestive system. It also will allow monitoring of drug effectiveness in the target organ, such as the kidney or heart. For example, in one of these collaborative efforts, a multi-investigator, multi-institution group is working to integrate the liver, gut, kidney and blood-brain barrier chips.

Two more project teams funded by DARPA will work with NIH-funded researchers to develop platforms that mimic the human body's natural environment and that can support 10 organ systems.

Because these tissue chip systems closely mimic human function under controllable conditions, scientists can manipulate the tissue chips in ways that they cannot in people. An unpredicted yet fortuitous additional outcome of the project is that the chips are becoming platforms for modeling disease. The knowledge gained may provide critical clues to disease progression, leading to better ways to treat and prevent a variety of conditions.

Toxicology in the 21st Century (Tox21)

Throughout our lives, we are exposed to thousands of chemicals in our food, household cleaning products,



A schematic representation of a plan for linking up individual organs on chips by NIH-funded investigators. Blood-brain barrier (John Wikswo, Ph.D., Vanderbilt University); Gut (Mark Donowitz, M.D., Johns Hopkins University); Kidney (Jonathan Himmelfarb, M.D., University of Washington); Liver (D. Lansing Taylor, Ph.D., University of Pittsburgh).

medicines and environment. However, scientists know little about the level of toxicity of these substances.

A unique collaboration among NIH (including NCATS and the National Toxicology Program of the National Institute of Environmental Health Sciences [NIEHS]), the Environmental Protection Agency (EPA), and the FDA, Tox21 is designed to develop better 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 (Tox21 10K library) on a wide variety of cellular and molecular pathways and functions that may lead to negative health effects. These data are being used to identify chemicals to study in greater depth, 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.

Heart-On-A-Chip Serves as Model for Heart Syndrome

Barth syndrome is an inherited condition in which defective mitochondria (the energy powerhouses of cells) damage the functioning of heart muscle cells. The syndrome is caused by a mutation in *TAZ*, the gene that tells the body to produce the enzyme tafazzin. This enzyme helps make a protein called cardiolipin, which is essential for producing normal mitochondria. Features of Barth syndrome include a weak and enlarged heart, vulnerability to infections, muscle weakness, fatigue and growth delays. Currently, no treatment exists, and scientists need a better understanding of the condition to develop effective therapies.

In a study published in the June 2014 issue of *Nature Medicine*, scientists supported by NCATS' Tissue Chip for Drug Screening program transformed adult stem cells from Barth syndrome patients into heart cells and grew them on a microchip. The resulting heart tissue contained abnormally structured cells and exhibited weak contraction (beating), characteristics that simulated the condition. Using genetic engineering, the researchers demonstrated the molecular mechanism by which the *TAZ* mutation leads to a lack of cardiolipin in the mitochondria of heart muscle. When the team applied a compound to boost production of cardiolipin, the heart muscle cells' functioning improved.

The organ-on-a-chip Barth syndrome model enabled scientists to gain a better understanding of the underlying disease mechanisms and to identify potential new treatment approaches. The findings also may apply more broadly than Barth syndrome, because cardiolipin deficits appear to underlie other, more common heart conditions.

The Harvard heart-on-a-chip that can be used to model Barth syndrome, a rare disorder that affects heart tissue (Kevin Parker, Ph.D., Harvard University).

The Tox21 program has evolved into a highly integrated, collaborative consortium, building on recent advances in the areas of genomic toxicology, gene expression analysis, human tissue stem cell technology and integrated pathway information. For example, one goal of the Tox21 program is to collect a list of all human pathways and to design assays that can measure the chemical responses of these pathways. Tox21 researchers currently are designing an integrated pathway database, called the NCGC Bioplanet, to enable researchers to systematically analyze and model toxicity responses. The Bioplanet resource will annotate pathways by source, species, biological function and process, disease and toxicity relevance, and availability of probing assays. Defining molecular mechanisms in this way is important for evaluating toxicity and also may be relevant to developing a better understanding of disease processes.

Tox21 scientists published the first results from screening the Tox21 10K library in the July 11, 2014, issue of *Scientific Reports*. This library consists of substances to which people are regularly exposed, including pesticides, industrial chemicals, food additives and drugs. The group developed an assay to test the effects of the approximately 10,000 chemicals on estrogen receptors, which convey signals to the body that regulate reproductive functioning when they are activated by the estrogen hormone. Some chemicals may cause certain cancers or birth defects by mimicking estrogen and turning its receptors on or off. The Tox21 group used the Center's high-throughput robotic screening capabilities to test the 10K library and identified some previously unknown chemical classes that interacted with estrogen receptors.

Tox21 investigators broadly disseminate their data by depositing results into the National Library of Medicine's PubChem website, making them freely available to the public and other scientists. Investigators around the world can use the data to inform their own research.

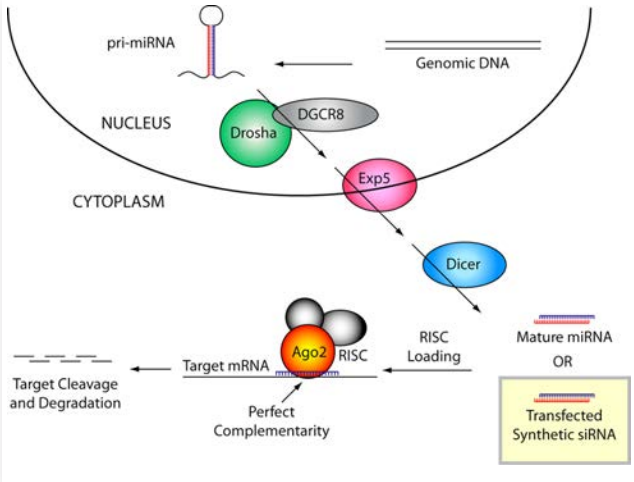
In the near future, Tox21 experts plan to publish similar data sets from screens of the Tox21 10K library in assays of stress response pathways, which are designed to identify compounds that can damage or kill cells. The team will continue to test chemicals from the library and release screening data,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

RNA Interference (RNAi)

Small interfering RNA (siRNA) molecules are pieces of RNA that block the activity of genes through a natural process called RNA interference (RNAi). RNAi has emerged as a powerful tool used in thousands of labs worldwide to understand gene function. Because each siRNA molecule can block a different gene, RNAi can tell us about the role of any gene in maintaining health or causing disease.

RNAi's potential usefulness has been limited by the lack of methodologies that can properly interpret RNAi experiments to reliably query the entire genome, the lack of collaborative expertise to perform genome-wide RNAi screens, and the absence of comprehensive RNAi data in public databases for researchers to reference. To address these problems, NCATS operates a state-of-the-art RNAi screening facility. 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, NCATS 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 genes involved in a particular biological function or disease process, which is an invaluable step in target identification and validation.



RNAi is a cellular process that can control the expression of genes by regulating mRNA levels and protein synthesis. This pathway is naturally used by miRNAs. Scientists can take advantage of this pathway to interrogate gene function by introducing synthetic siRNAs which will then turn off genes that they target (Scott E. Martin, Ph.D., Leader, Trans-NIH RNA Interference Screening Facility).

Scientists also can use these techniques to understand how genes affect drug efficacy. In a recent collaboration, NCATS and NCI investigators conducted large-scale RNAi screens to identify genes that could affect the activity of a class of cancer drugs called TOP1 inhibitors. Through these studies, the scientists discovered a number of genes whose silencing by RNAi led to a dramatic enhancement of TOP1 inhibitor activity in cell and animal models. These efforts may enable investigators to identify biomarkers that predict the activity of TOP1 inhibitors. They also may lead to the development of new combination therapies for cancer patients. To that end, NCI investigators were able to demonstrate that small molecule inhibition of one of the genes identified through RNAi screening reduced tumor growth in animal models. The improvements made by NCATS in genome-wide RNAi screening technology, combined with the public release of siRNA screening data, promise to increase understanding of the role of individual genes in basic cell functions as well as to speed up the identification of new targets for drug development.

Clinical Innovation

In the clinical stage of the translational process, medications, devices, diagnostic products and other treatment regimens developed in the pre-clinical stage are tested for safety and effectiveness in humans, disseminated to broader patient populations, and studied for their capacity to improve public health. As with those before it, this stage is fraught with scientific uncertainties and operational inefficiencies that limit our ability to test new treatments in humans and deliver interventions to patients more quickly.

NCATS is directly addressing clinical translation problems in a system-wide manner by developing, demonstrating and disseminating more efficient collaborative approaches to the clinical enterprise. The aim is to improve procedures in areas such as clinical training, institutional review board (IRB) operations and patient recruitment methods for multisite studies, and evaluation and accountability of investigators. Streamlining these processes can accelerate the transformation of laboratory discoveries into new treatments for patients.

Left: Frank McCormack, M.D., director of the CTSA-supported University of Cincinnati's pulmonary division, discusses the rare lung disorder lymphangioleiomyomatosis (LAM). Collaborative research has already led to major discoveries about the progression and treatment of LAM (University of Cincinnati Photo/Dan Davenport). Right: Jessica Mast, R.N., assists during an ultrasound performed by Zhaohui Gao, Ph.D., on study volunteer Josh Miller for one of many heart research studies at Penn State Hershey, a CTSA-supported institute (Penn State College of Medicine Photo/Darrell Peterson).

An **institutional review board (IRB)** — made up of scientific, nonscientific and community members — must review and approve new studies or trials. IRB oversight ensures that the investigators have safeguards in place to protect human participants from harm, and that the research is conducted safely and ethically.

Clinical and Translational Science Awards (CTSA) Program

The CTSA program is designed to improve the efficiency and effectiveness of clinical and translational research by supporting the development and dissemination of improved tools, operational models and training. Under NCATS leadership, the program supports a national consortium of medical research institutions — called CTSA hubs — that work together to transform how translational research is conducted. Examples of program successes include developing a single IRB model for multisite studies, enabling more efficient data collection and tools for sharing and mining data, developing innovative

methods for enhancing patient recruitment, facilitating engagement of communities, and forming efficient and effective strategic alliances with research partners and patient groups.

NIH launched the CTSA program in 2006 to help strengthen the spectrum of biomedical research. In 2013, the Institute of Medicine (IOM) convened an independent committee of experts to "evaluate the CTSA program and recommend whether changes to the current mission are needed." The committee's report, *The CTSA Program at NIH: Opportunities for Advancing Clinical and Translational Research*, was released in June 2013 and articulated seven broad recommendations. NCATS leadership then asked its Advisory Council to address the IOM's recommendations and provide measurable objectives that could be used in implementing the recommendations. A working group of the Council issued a report in May 2014. NCATS is considering these reports as well as input from CTSA program stakeholders, including investigators, patient groups, and the broader clinical and translational research community as the program evolves.

IRB Reliance: A New Model for Accelerating Translational Research

Launching multisite clinical trials can be complicated and time-consuming, in part due to the complex IRB review and approval process at multiple sites. Such a lengthy review process may discourage some researchers from initiating important studies.

Several CTSA grantees have achieved significant progress in overcoming this roadblock using a concept called IRB reliance on a single IRB. With this model, institutions develop networks in which each of the institutions in a multisite study agrees to rely on a single IRB of record for initial approval and continuing review as it relates to adverse events, amendments, deviations and other incidents. So far, CTSA grantees have formed regional groups with IRB reliance agreements in Massachusetts, Ohio, California, Texas, Wisconsin and Minnesota.

Participating institutions have shown that efficient and centralized oversight can accelerate translational science. For example, after the April 2013 Boston Marathon bombing, dozens of patients sustained blast-related ear injuries, and Boston-area clinicians found themselves attempting to treat large numbers of patients with injuries rarely seen outside combat zones. Doctors at Massachusetts Eye and Ear Infirmary (Mass. Eye and Ear) realized that studying these patients' injuries could provide an opportunity to develop improved treatments and better prepare the medical community to respond to such tragedies.

The investigators quickly formed a team with four other Harvard-affiliated hospitals and three other sites to design a high-quality multisite study. They also needed rapid IRB approval due to the unusual opportunity to study a large number of ear injuries from the same blast and to observe patients as they healed. The IRBs at each of the seven research sites agreed to use the Harvard CTSA's IRB reliance agreement to rely on Mass. Eye and Ear as the IRB of record. The Mass. Eye and Ear IRB immediately reviewed and approved the study, and patients began enrolling at all sites soon thereafter. Study investigators began collecting data on the characteristics of blast trauma ear injuries, how they heal, how they respond to treatments such as steroids and how hearing loss persists or improves over time. This data collection and analysis is ongoing, with preliminary results published in *Otology & Neurology*. Without the IRB reliance agreement, launching the study in a timely manner would have been challenging, if not impossible.

One major step was the issuance of a CTSA funding opportunity announcement (FOA) in September 2014. With this FOA, there is new emphasis on:

- Aligning the CTSA program more directly with NCATS' overall goals.
- Building a collaborative, national network to achieve strategic translational science goals.
- Developing the overall workforce to train a new generation of clinical and translational scientists.
- Emphasizing evaluation and accountability, with defined criteria for measurement and metrics.

CTSA training programs are specifically designed to equip young investigators with the tools and knowledge to appropriately and successfully address the unique challenges inherent in clinical and translational research. As an assistant professor and master's student in the Clinical Research Program at the University of Texas, CTSA trainee Andrew Barreto, M.D., devised a novel method to reduce complications from stroke. He currently is leading a phase II clinical trial to assess the safety and effectiveness of a device that sends ultrasound waves into the brain to break up stroke-related blood clots. His team is evaluating the technology as an add-on to a standard clot-reducing medication for stroke patients to enhance its effect. So far, the study's stroke patients have shown impressive rates of restored blood flow into the stroke area, an outcome that is promising for recovery. Within the past year, these results have led Barreto, who now has completed his master's degree, to apply for an R01 grant and to be promoted to associate professor.

Accelerating Rare Diseases Research

NCATS' emphasis on clinical innovation extends to conducting and supporting research aimed at accelerating new treatments for rare diseases. A rare disease is defined in the United States as one affecting fewer than 200,000 persons in the United States.[1] There are several thousand rare conditions that affect an estimated 25 million Americans and their families. According to the FDA's Office of Orphan Products Development, only about 5 percent of these diseases have an approved treatment.

The burden of rare diseases can be devastating and costly for patients and their families. This is due in part to disease severity and in part to diagnosis often being more difficult and thus taking longer — frequently, well after symptoms have appeared. Because of these variables, rare diseases can represent a disproportionate share of health care spending and a substantial unmet medical need. In addition, a limited number of drug companies conduct research into rare diseases since it may be difficult to recover the costs of developing treatments for small, geographically dispersed populations.

New discoveries about the molecular basis of rare diseases offer unprecedented opportunities to improve the diagnosis and treatment of these conditions. In addition, new scientific insights, genetic data, modeling approaches and experimental therapeutics for rare diseases promise to shed light on more common diseases that share characteristics or biochemical pathways. NCATS is capitalizing on these opportunities through its rare diseases research programs and its dedicated Office of Rare Diseases Research (ORDR).

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

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

The GRDR program is designed to advance research for rare diseases and, by applying scientific insights gained through the program, to further research into common diseases as well. The aim is to develop a Web-based resource that aggregates, secures and stores de-identified patient information from many different registries for rare diseases, all in one place.

The program began as a pilot project, which concluded in September 2013 and included 12 patient advocacy groups' registries. The project involved validating and implementing Common Data Elements (CDEs) and gauging general interest from the rare diseases

1 Amendments to the Orphan Drug Act of 1983, P.L. 97-414, and the Rare Diseases Act of 2002, P.L. 107.

community. As a result, the following tools were developed and made available:

- CDEs for patient registries
- Patient registry Informed Consent form template
- Global Unique Identifiers (GUIDs)
- Patient registry software (in collaboration with Marshfield Clinic)

The ultimate goal of the program is to improve therapeutic development and quality of life for the many millions of people suffering from rare diseases.

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 participating consortia, physician scientists and their multidisciplinary teams at hundreds of clinical sites around the world work together with representatives of nearly 100 patient advocacy groups to study more than 200 rare diseases.

The RDCRN facilitates clinical research in rare diseases through support for (1) collaborative activities, including longitudinal studies of individuals with rare diseases, clinical studies and clinical trials; (2) training of clinical investigators in rare diseases research; (3) pilot and demonstration projects; (4) uniform data collection protocols; (5) cost-sharing 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. It also includes a novel Web-based contact registry for patients who are considering participating in RDCRN clinical studies.

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

Since its launch, the RDCRN has enrolled 29,000 participants in multisite clinical research studies. Ninety-one studies are currently underway. In October 2014, NIH announced nearly $29 million in awards to expand the RDCRN to support 22 consortia and a Data Management and Coordinating Center.

Since the inception of the RDCRN in 2003, investigators have made progress in many aspects of clinical and translational research on rare diseases. For example, studies conducted at the Urea Cycle Disorders Consortium at Children's National Medical Center in Washington, D.C., in collaboration with the biopharmaceutical industry and patient groups, led to the FDA's approval of three drugs to treat these serious disorders in 2014.

Boston Children's Hospital physician-scientist Mustafa Sahin, M.D., Ph.D., explains brain imaging findings to his 8-year-old patient with tuberous sclerosis complex, which can cause epilepsy, autism and intellectual disability. Sahin leads an RDCRN consortium exploring genetic conditions associated with mutations in the TSC1/2, SHANK3 and PTEN genes (Boston Children's Hospital Photo).

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

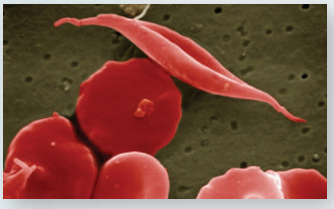
Therapeutics for Rare and Neglected Diseases (TRND)

The TRND program goal is to speed the development of treatments for rare and neglected diseases. The program operates via collaborative research partnerships with public and private entities, which leverage the unique strengths and capabilities of each party to develop new technologies and models that improve the efficiency of therapeutic development. TRND staff provide drug development expertise and resources, working with research partners to move potential therapeutics through pre-clinical testing. This also includes guiding the design of clinical trials and submitting IND applications to the FDA. These efforts effectively "de-risk" therapeutic candidates and make them more attractive for adoption by outside business partners. The TRND Annual Report can be found in the Appendix of this report, and clinical trials that received TRND support can be found at clinicaltrials.gov.

NCATS utilizes a set of rigorous criteria to enhance the evaluation of applications for TRND collaboration. The detailed checklist is posted online, thus ensuring that all potential applicants know exactly how their projects will be evaluated. The first milestone for all projects selected by the NCATS TRND program is verification of the results on which the project is based. This could involve reproducing the exact data submitted by the collaborator or conducting additional experiments to verify the key findings.

At the end of 2014, TRND had a portfolio of 14 active projects targeting drug development for some of the most devastating diseases affecting either small populations in the United States or large populations in the developing world. Four projects targeting chronic lymphocytic leukemia, Niemann-Pick disease type C1, sickle cell disease and GNE myopathy yielded successful IND applications to the FDA and have entered human clinical trials.

A TRND First: Drug Candidate Acquired by Biopharmaceutical Company



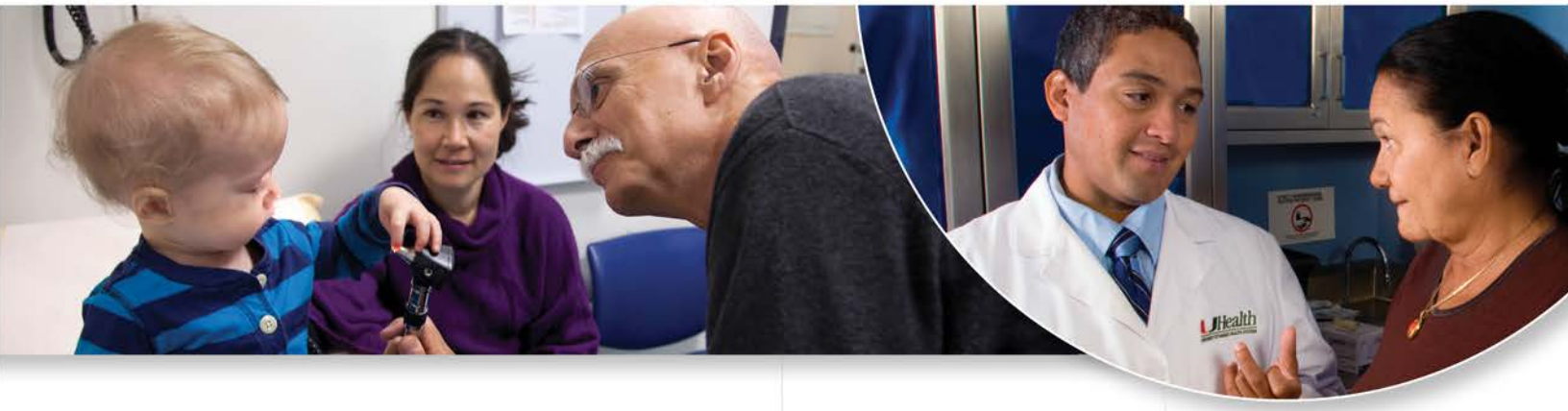
Sickle cell with other cells.

Sickle cell disease is an inherited blood disorder that affects millions worldwide and approximately 100,000 in the United States, including one in every 500 African-American births. People with the disease have defective hemoglobin (the protein in red blood cells that carries oxygen), which causes cells to become rigid and crescent-shaped, leading to blocked blood vessels, inflammation, pain and strokes.

To date, the only drug approved by the FDA to treat sickle cell disease is hydroxyurea, an anticancer drug that can only be used in adults, has modest efficacy and has unpleasant side effects that severely limit its use. A drug candidate, called Aes-103, developed under a collaborative agreement by researchers at TRND and AesRx, LLC, Newton, Massachusetts, is the first to target the disease's underlying molecular defect. Aes-103 works by attaching to hemoglobin and changing its structure, thereby reducing the sickling of red blood cells.

Prior to the collaboration with NCATS and despite promising data on Aes-103, AesRx was unable to secure private financing because potential investors lacked interest in an early-stage project that was considered too risky. The NIH collaboration to develop the compound began in 2010 and included scientists from the National Heart, Lung, and Blood Institute (NHLBI). In less than one year, the team completed the pre-clinical toxicology, chemistry, manufacturing, controls and regulatory studies necessary to support an IND application. After IND clearance by the FDA, from 2011 to 2013, Aes-103 moved successfully through phase I and II clinical trials to evaluate safety and effectiveness in healthy volunteers and patients. In July 2014, Baxter International's BioScience business acquired AesRx and its Aes-103 program to perform the clinical development activities required for regulatory approval and commercialization. The move was the first time a company has acquired a drug candidate developed with TRND program resources.

Patient/Community Engagement and Health Information



NCATS believes it is vital to engage patients in every step of the research process. Incorporating the patient perspective builds trust and improves the quality of the research by enabling investigators to design studies measuring outcomes that are important to patients. It also provides researchers with better access to patients for studies. Alliances with patient groups facilitate this engagement. The open lines of communication also can provide patients and their families with a resource for accessing accurate, up-to-date information on health conditions and the latest research progress.

Engaging with patient advocacy groups is a crucial step for rare diseases researchers in particular. These groups often seek guidance in translating basic science knowledge about a disease's biology into tangible interventions that can benefit patients. As one way to help address this need, James Inglese, Ph.D., director of NCATS' Assay Development and Screening Technology Laboratory, has formed collaborative relationships with a number of rare disease foundations to launch early-stage drug discovery efforts. These agreements involve foundation support for postdoctoral researchers who work in Inglese's laboratory. For example, Hannah's Hope Fund, an advocacy organization for giant axonal neuropathy (GAN), an inherited nervous system disorder, supported the work of Melissa Mendez, Ph.D., to search for potential GAN treatments in 2014. Her efforts included creating assays (tests) based on patient cells for screening thousands of potential therapeutic compounds as well as for studying the molecular characteristics of GAN.

Another advocacy group, the Alpha-1 Foundation, also will fund a two-year postdoctoral fellowship position in Inglese's laboratory. The organization supports research on alpha-1 antitrypsin deficiency, a rare, inherited disorder affecting the lungs and liver. The fellow will focus on drug discovery, including developing assays and conducting small molecule screens to find compounds that curb the effects of the abnormal protein that causes alpha-1 antitrypsin deficiency.

NCATS experts also have been working with the Friedrich's Ataxia Research Alliance (FARA) to identify strategies for improving clinical research on Friedrich's

Left: Leader of the RDCRN-supported Primary Immune Deficiency Treatment Consortium, Morton J. Cowan, M.D., sees patient Everett Schmitt, 18 months, and his mother Anne Klein at the University of California, San Francisco (UCSF) (UCSF Photo). Right: Olveen Carrasquillo, M.D., M.P.H., director of community engagement and cultural diversity in the Miami Clinical and Translational Science Institute, a CTSA-supported institute, is pictured with a study participant in an NHLBI study examining the role of community health workers in improving the health status of Latinos with diabetes (John Zillioux Photo).

Patient Lindsey Ross, who has Rett syndrome, interacts with Clinic Associate Anna Lane at the Rett syndrome travel clinic in Chicago (UAB Rett Syndrome Clinic).

ataxia, a debilitating, life-shortening neuromuscular disorder. NCATS and FARA hosted a meeting in 2014 at which dozens of Friedrich's ataxia experts discussed opportunities for finding biomarkers, which are biological indicators of the presence, absence or stage of a disease. Identifying Friedrich's ataxia biomarkers could help in developing therapeutics and conducting clinical trials of potential treatments.

Engaging patients and patient groups can accelerate the pace of research and improve understanding of diseases and potential new treatments. The NCATS-supported RDCRN requires that applicants to the program partner with at least one patient advocacy group. Previous experience has demonstrated that RDCRN consortia that both engage and integrate patient advocacy groups into their research program achieve greater success in study enrollment. Similarly, applicants to the current New Therapeutics Uses program are encouraged to involve patient advocacy groups in their projects.

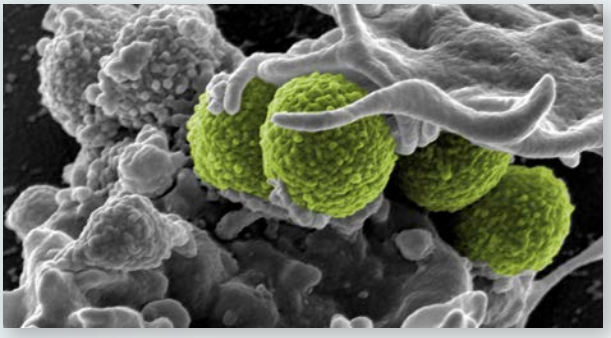
NCATS' emphasis on patient engagement extends to making a difference in the lives of patients and families through its Genetic and Rare Diseases Information Center (GARD), which provides accurate information about thousands of genetic and rare conditions. Through this program, NCATS provides patients, their families, health care providers, researchers and the public with information via the website, e-mail, telephone and traditional mail. Through GARD, NCATS also disseminates research findings from around the world, which is a key part of the translational process.

Over the past 12 years, GARD information specialists have responded to questions regarding approximately 6,400 different rare or genetic diseases. Each month, the GARD website receives approximately 200,000 unique visitors, and specialists respond to an average of 563 inquiries. These numbers increase each year, reflecting expanded awareness and growing demand for GARD's resources. GARD responds to Spanish-language inquiries and launched Spanish-language disease pages to its website in March 2014.

In addition, GARD staff:

- Dynamically maintain a list of approximately 6,400 terms related to rare and genetic diseases.
- Provide access to NIH and other resources and information about FDA-approved medical products for rare diseases, ongoing rare diseases research and select patient registries.
- Develop patient-friendly guides, such as "How to Find a Disease Specialist" and "Tips for the Undiagnosed," to address frequently asked questions.

Using Community Engagement to Tackle a Hard-to-Treat Bacterial Infection



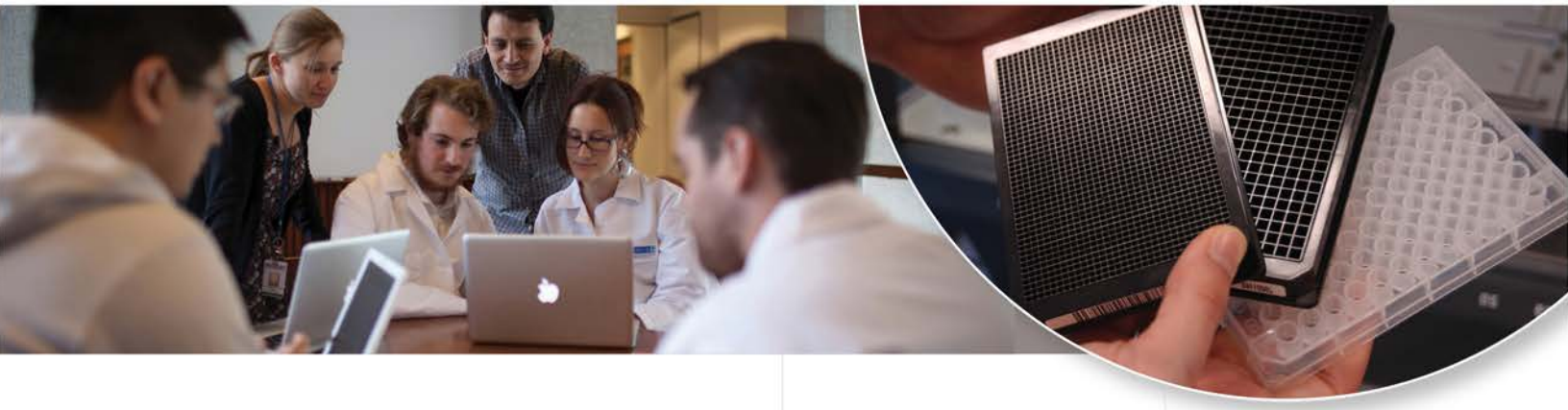
Interaction of MRSA (green bacteria) with a human white cell. The bacteria shown is strain MRSA252, a leading cause of hospital-associated infections in the United States (National Institute of Biomedical Imaging and Bioengineering Photo).

Community and patient engagement are priorities for the CTSA program. The Rockefeller University CTSA's Community Engagement (CE) Core teamed with the Clinical Directors Network, a primary care practice-based research network that works with Federally Qualified Health Centers (FQHCs), to conduct a study on the significance of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection in the health care setting. For the initiative, called the Community Acquired MRSA Project (CAMP), clinicians were engaged around the unmet clinical need related to MRSA, and basic scientists were involved to gain a better understanding of the molecular basis of MRSA bacteria. Using a team science-based approach and combining expertise in basic science with patient and community-driven research can simultaneously advance discovery that translates into improved patient care.

MRSA bacteria are resistant to many commonly used antibiotics and cause several hard-to-treat infections in humans. Although MRSA traditionally infects hospital patients, CA-MRSA also can infect healthy people who have not been hospitalized. Community clinicians identified CA-MRSA skin infection as an emerging problem in the FQHCs' patient population. The Rockefeller CE group provided training to community clinicians on best practices for treating CA-MRSA. Following the training, clinicians helped the project's MRSA scientific expert to design research questions related to the molecular biology of MRSA. In addition, the team developed a protocol for carrying out best practices and met regularly to advance the project at continuing medical education workshops.

The clinicians engaged MRSA patients at Community Health Center town hall meetings, focus groups and information sessions to learn about their MRSA experiences and identify patients' priorities. Patients were most concerned about increasing their knowledge of MRSA infection. As a result, the interdisciplinary CE team developed a MRSA education and outreach project with local barbershops, an initiative that significantly increased community awareness and knowledge about MRSA infection and its prevention. The outcomes of this effort resulted in a second grant that began in November 2014. In the second phase of the project, patients, clinicians, scientists and local community health workers will be engaged to conduct household visits to test the effectiveness of strategies for preventing MRSA recurrence and reducing household transmission.

Partnerships and Collaborations



Working together to solve challenges in biomedical science is crucial to accelerating the translational research process and therefore is vital to all NCATS programs and initiatives. The Center encourages partnerships and collaborations across all disciplines and sectors, including NIH-funded investigators, other federal agencies, business and industry, and patient groups and advocacy organizations. Among other benefits, this approach helps maximize public and private resources, expand scientific knowledge, and increase participation in clinical research — all of which can speed the drug development process and get treatments to patients faster.

Examples of NCATS alliances include the following:

- Tox21, an initiative aimed at developing better ways to predict and evaluate toxicity of environmental chemicals and compounds, is a federal collaboration involving NIH (including NCATS and the National Toxicology Program of the National Institute of Environmental Health Sciences), the EPA, and the FDA. See p. 11 for more details on Tox21.
- Tissue Chip for Drug Screening, a program led by NCATS aimed at developing 3-D human tissue "chips" to improve the process of predicting drug safety in humans, is a five-year collaboration among NIH (including 15 ICs), DARPA, and the FDA. For the second phase of the program, launched in September 2014, pharmaceutical companies Pfizer and GlaxoSmithKline also are contributing funding. See p. 10 for more details on the Tissue Chip program.
- New Therapeutic Uses is a collaborative program designed to facilitate partnerships between pharmaceutical companies and the biomedical research community to advance therapeutics development. In the new round of funding opportunities announced in May 2014, NCATS, along with other NIH ICs and the FDA's Office of Orphan Products Development, will contribute funding for new projects. See p. 8 for more details on the New Therapeutics Uses program.
- TRND stimulates drug discovery and development research collaborations among NIH and academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies working on rare and neglected conditions. See p. 18 for more details on TRND.

Left: Education and training programs offered by the Einstein-Montefiore Institute for Clinical and Translational Research equip young investigators with skills they need to embark on careers in translational research (Albert Einstein College of Medicine Photo). Right: Photo of 96-well, 384-well and 1,536-well plates. With improved technology, the plates can be reused, reducing waste and cost.

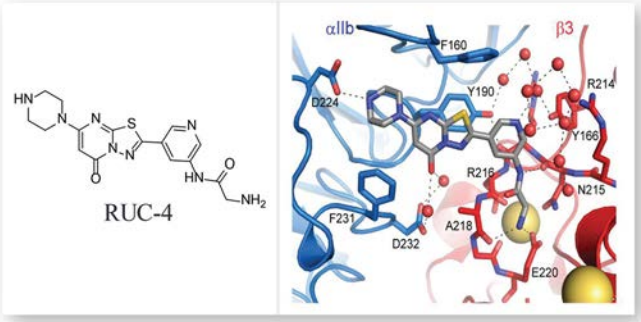
NCATS-FDA Partnership Produces Award-Winning, Globally Recognized Ingredients Database

As part of its mission to ensure food and drug safety, the FDA tracks the ingredients in all the products it regulates. One purpose of this tracking system is to integrate safety data from around the world to identify emerging issues as early as possible. The FDA recently needed to update its existing system to the current global standard and approached NCATS. The agencies teamed to repurpose NCATS' chemical ingredient information system to fit the FDA's requirements. Through a collaborative research and development agreement, NCATS experts demonstrated that they could extend the system to serve the FDA's broad ingredient tracking needs, from simple molecules like aspirin to biological products and even whole organisms. The team currently is working to deploy the software and transfer data to the new system.

The project, called the Global Ingredient Archival System (GINAS), has attracted attention within the Department of Health and Human Services (HHS) and internationally for the rapid development of software to handle the complex International Organization for Standardization requirements. The collaborators received an award from the HHS Ignite program, which praised the project's innovative, agile development process. Several national drug agencies, including European entities, also have expressed interest in adopting the software for their own needs and have recognized GINAS as the current de facto standard for ingredient information systems worldwide. The open, collaborative development of this platform presents a unique opportunity for global cooperation that can have a significant impact on patient health and safety worldwide.

An example of how NCATS' commitment to partnerships can speed the drug discovery process is the recent development of a potential therapeutic for patients experiencing heart attacks. This advance emerged from a recent collaboration among Craig Thomas, Ph.D., Leader, Chemistry Technologies, NCATS; and researchers at The Rockefeller University, Harvard University and Icahn School of Medicine at Mt. Sinai. Rockefeller's Barry Coller, M.D., a biologist, originally discovered the molecule and sought NCGC's drug development expertise to optimize and further develop the molecule. The agent works by inhibiting a protein involved in blood clotting.

The group of academic and NIH scientists carried out a series of studies to determine the molecule's structure and function, ultimately creating a new version called RUC-4. The updated agent blocked clotting through a newly discovered mechanism and possessed the appropriate pharmacological properties to be considered for use by emergency medical service providers before reaching the hospital. This work received support in the form of expertise and resources from NCATS' BrIDGs program and NCGC as well as from NHLBI. These programs and their collaborative approaches enabled Coller and his multidisciplinary team to navigate the complexities of readying a compound for testing in humans. The researchers will use the data generated from these efforts to apply for an IND from the FDA.



The chemical structure of the small molecule RUC-4 (left image) and model of the crystal structure of RUC-4 (right image) illustrating how it binds to the αIIbβ3 receptor to prevent blood clot formation. This agent, a product of a long-standing collaboration between Barry Coller, M.D., of the Rockefeller University and NCATS scientists, was awarded support in October 2014 from the BrIDGs program and the Harrington Discovery Institute for advancement into clinical evaluation in a pre-hospital therapy of patients with ST segment elevated myocardial infarction. (Li, J., Vootukuri, S., Shang, Y., Negri, A., Jiang, J.-k., Nedelman, M., Diacova, T. G., Filizola, M., Thomas, C. J., Coller, B. S. RUC-4: A novel aIIbb3 antagonist for pre-hospital therapy of myocardial infarction. (2014) *Arterioscl. Throm. Vas.* 34, 2321–2329.)

Resources for Small Businesses

NCATS' collaborative mission includes forming partnerships with other NIH ICs and federal agencies to support business and industry. NCATS supports small business participation in federally funded research and development as well as the private-sector commercialization of technology developed with federal support. The Center supports these aims through the federal government's SBIR and Small Business Technology Transfer (STTR) programs. By funding technologies that address the translational process from pre-clinical to clinical, the SBIR program is one of the many ways NCATS catalyzes innovation at various stages of translation. (See p. 8 article, "Repurposing an Approved Drug for Multiple Sclerosis," for more information on the SBIR project.)

For example, NCATS SBIR contractor IonField Systems successfully developed an automated system for cleaning microtiter plates, which contain hundreds or thousands of tiny wells used as small test tubes. Researchers commonly use microtiter plates in high-throughput screening for drugs or other research compounds. The technology, which uses cold plasma cleaning, will enable the plates to be used multiple times, which is an eco-friendly alternative as well as a huge cost-saving measure for companies involved in drug development.

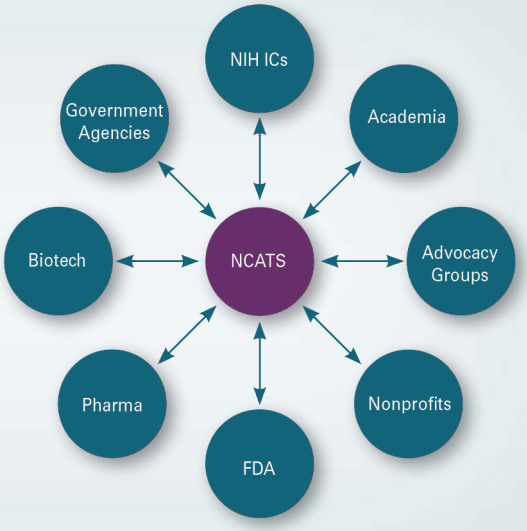
NCATS, along with NCI, NHLBI and NINDS, has formed a collaboration with the National Science Foundation (NSF) to support the training of SBIR/STTR-funded academic researchers and entrepreneurs to overcome key obstacles along the path of innovation and commercialization. The program, called I Corps at NIH, is a pilot of the NSF Innovation Corps program and is specially tailored for biomedical researchers, aiming to accelerate innovations for applied health technologies.

Small business grantees with SBIR/STTR phase I awards — which establish feasibility of proof of concept for commercializable technology — from the four participating NIH ICs were eligible to apply to I-Corps at NIH in the summer of 2014. The training curriculum involves a 10-week boot camp in which experienced, business-savvy and technically savvy instructors work closely with teams of researchers to help them explore potential markets for their federally funded innovations. The 21 selected teams, two of which were supported by NCATS, received supplemental funding from NIH to support entrepreneurial training, mentorship and collaboration opportunities. The pilot program is designed to better equip biomedical researchers to enter the business arena, speeding the commercialization of their biomedical research to the marketplace.

Catalyzing Collaborations

NCATS:

- Complements the work of other organizations
- Revolutionizes the process of translation by targeting and overcoming barriers
- Galvanizes and supports new kinds of partnerships
- Supports and augments regulatory science and its application
- Expands the precompetitive space



Tools for Accelerating Translational Science

NCATS aims to advance the process of developing and deploying solutions that can be used by all translational researchers. NCATS is interested in the application of clinical technology, instruments, devices and related methodologies that may have broad application to clinical research. In particular, NCATS funds applications that enhance clinical research and patient care.

Enabling Public Access to Data

One way NCATS arms the scientific community with translational science resources is by enabling the public release of new methods and data. NCATS and Life Technologies Corp. announced that, for the first time, large-scale data on the biochemical makeup of small interfering RNA (siRNA) molecules are available to the public. Each siRNA molecule can block a different gene and thus can tell researchers about the role of any gene in maintaining health or causing disease. See p. 13 for more information on siRNA.

Left: NCATS Kalypsys robot enables ultra high-throughput screening of small molecules against diverse types of assays. Right: DNA illustration.

Until recently, a major limitation for RNAi researchers has been the lack of publicly available data on the chemical sequences for siRNAs. Historically, the companies that own these molecules have not published this information. To address this obstacle, NCATS and Life Technologies have provided all researchers with access to siRNA data from the company's Silencer Select siRNA library, which includes 65,000 siRNA sequences targeting more than 21,000 human genes. At the same time, NCATS released complementary data about the effects of each siRNA molecule on biological functions. These data are available to the public free-of-charge through the National Library of Medicine's PubChem database.

Tox21 researchers also submit their chemical toxicity data to PubChem and other public databases. The available information includes results from the completed first phase of the project, which used the high-throughput robotic screening system at NCATS to test 2,800 compounds in more than 50 assays. Data generated so far from the second phase, which is testing the Tox21 10K library, also are available in PubChem. 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 in-depth studies to define their effects on human health.

To spur such participation from outside investigators, the Tox21 program also launched a crowdsourcing competition in July 2014 to develop computational models that can better predict chemical toxicity. The competition harnesses the power of crowdsourcing, the practice of soliciting ideas from a large group of people — in this case, the scientific community. The large amount of information produced by the Tox21 team is more than its own scientists can realistically analyze and understand without additional collaboration. Thus, data generated from 12 of the assays form the basis of the challenge. NCATS will showcase the winning models in January 2015.

Appendix

Therapeutics for Rare and Neglected Diseases (TRND) Program

2013–2014 ANNUAL REPORTS

Appendix Contents

Brief Overview of Accomplishments

TRND began its fourth first-in-human clinical trial at the NIH Clinical Center for a rare metabolic condition (Cyclodextrin for Niemann-Pick Type C1 Disease) in early 2013. This clinical trial is in addition to continued support for ongoing trials arising from TRND's preclinical efforts for sickle cell disease (SCD), chronic lymphocytic leukemia (CLL), and hereditary inclusion body myopathy (HIBM). TRND continued its natural history study of disease progression in HIBM patients and began planning for a second natural history study and registry for creatine transporter defect (CTD) patients.

TRND completed two solicitations for new collaborative projects through 2013 and 2014. After rigorous scientific evaluation and an in-depth due diligence process, seven new projects were selected: four initiated in 2013 and three initiated in 2014. These projects address a range of rare and neglected conditions and represent a mix of small chemical compounds and biologics, including the first cell-based treatment adopted by TRND. The subjects of these projects include a hormone deficiency, a heart failure syndrome, two tropical infectious diseases, two novel approaches to treat a hereditary eye disease that leads to blindness, and a therapeutic candidate with the potential to treat a family of rare blood disorders.

Comprehensive operational teams have been formed for all projects, including the most recently initiated projects adopted in 2014. All previously initiated projects are achieving interim milestones and progressing according to schedules, with a number of projects having reached completion throughout 2013 and 2014. These completed projects include those that met all agreed-upon preclinical endpoint milestones, projects that failed to achieve milestones set forth in the project plan, and projects that were sufficiently de-risked such that the collaborators were able to retake full control to advance development without additional TRND support.

As a demonstration of the success of the catalytic preclinical de-risking model of TRND, two of the completed projects were sufficiently de-risked so as to attract biopharmaceutical industry adoption. These include the collaborations with AesRx, LLC, whose sickle cell disease candidate was acquired by Baxter International, and BIKAM Pharmaceuticals, whose retinitis pigmentosa candidate was acquired by Shire Pharmaceuticals.

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, St. Louis, MO

Initiated: September 2009

Description: Niemann Pick Type C1 (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 Food and Drug Administration (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 initial safety, efficacy and biomarker reliability in NPC1 patients.

Outcomes: TRND established an interdisciplinary project team of academic and industrial scientists from nine different organizations and received ongoing input from patient advocacy groups in order to accomplish the clinical evaluation of HPBCD most efficiently. TRND scientists conducted the animal toxicology studies necessary to file an Investigational New Drug (IND) application with the FDA and helped support biomarker studies. TRND provided regulatory support to achieve clearance of the IND application with the FDA in November 2012, and first-in-human clinical trials began in January 2013 at the NIH Clinical Center. 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, 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 complete the IND filing to gain FDA approval to lift the clinical hold preventing initiation of human trials. The collaborative team has initiated a natural history study of disease progression, as well as a phase IA clinical trial in HIBM patients. The results from these studies will help enable the design of pivotal phase II trials that will examine whether DEX-M74 is efficacious in treating HIBM patients.

Developing New Treatments for Giardiasis

Lead Collaborator: Osnat Herzberg, Institute for Bioscience and Biotechnology Research, University of Maryland, Rockville, MD

Initiated: September 2009

Description: *Giardia lamblia* is the causative agent of the human intestinal disease giardiasis. It is the most common cause of waterborne outbreaks of diarrhea in the United States, and it is responsible for significant mortality and morbidity in developing countries. Current treatments have undesirable side effects, and there are concerns about the emergence of drug-resistant strains. The aim of this project is to identify new anti-giardiasis therapeutics that are more effective, cause fewer side effects than current therapies and counteract the emergence of resistant strains of the pathogen.

Outcomes: As a pilot project, an initial screening effort identified 43 drugs that demonstrated potential anti-giardia activity. TRND supported the development of an animal model of disease to allow for efficacy testing and refinement of the list of candidate drugs. A focused set of 11 compounds were further evaluated, resulting in identification of three novel compounds with anti-giardia activity. After reaching this agreed-upon endpoint milestone in the TRND project plan, the project was completed in 2013 and returned to the lead collaborator to continue development.

Aes-103 for Sickle Cell Disease

Lead Collaborator: Stephen Seiler, AesRx, LLC, Newton, MA

Initiated: April 2010

Description: Sickle cell disease (SCD) is a genetic blood disorder affecting millions worldwide and approximately 80,000 patients in the United States, in particular one in every 500 African-American births. A defect in hemoglobin causes red blood cells to become rigid and sickle-shaped, blocking small blood vessels, causing decreased blood flow, inflammation, pain and strokes in children. To date, the only drug approved by the FDA to treat SCD is hydroxyurea, an anti-cancer drug, which is only indicated for use in adults, has modest efficacy and has undesirable side effects that severely limit its use. The novel compound Aes-103 is the first drug candidate to directly target the cause of SCD. This project seeks to develop Aes-103 as an effective treatment for both adults and children with SCD.

Outcomes: TRND established a project team including TRND staff, AesRx and a leading sickle cell clinical researcher at the National Heart, Lung, and Blood Institute (NHLBI). In less than a year of signing the collaborative agreement with AesRx, preclinical toxicology, chemistry, manufacturing, controls and regulatory studies were completed. The IND was filed and cleared, and Aes-103 was moved into phase I clinical trials in both healthy volunteers and SCD patients, progressing to subsequent phase IIA studies at the NIH Clinical Center. After

TRND's involvement with this project, AesRx was able to obtain a Massachusetts Life Science Accelerator Grant to support additional studies necessary to complete clinical development of Aes-103. In July 2014, the biopharmaceutical company Baxter International acquired Aes-103 for further clinical development, representing the first time a company has acquired a drug candidate developed in part by TRND researchers.

Auranofin for Chronic Lymphocytic Leukemia

Lead Collaborator: Scott Weir, University of Kansas Medical Center, Kansas City, KS

Initiated: June 2010

Description: Approximately 15,000 people in the United States are diagnosed with chronic lymphocytic leukemia (CLL) each year. Patients ultimately become resistant to current chemotherapies, and their disease recurs, leading to death. During a previous collaboration between the lead collaborator and the NIH Chemical Genomics Center (NCGC), part of NCATS, the drug auranofin, previously approved by the FDA as a treatment for rheumatoid arthritis, was found to selectively kill CLL cells. The goals of this TRND project are to develop auranofin as a treatment for refractory CLL and to develop a novel collaborative paradigm that is broadly applicable to repurposing drugs for rare diseases.

Outcomes: A unique collaboration called The Learning Collaborative was established between TRND, the University of Kansas and the non-profit Leukemia & Lymphoma Society in which each organization contributes expertise and funding to the development of auranofin for CLL. All preclinical studies necessary for IND application with the FDA were completed by the team in less than a year, and the IND was filed and cleared. Phase I-IIA clinical trials of auranofin were conducted in patients at three sites (NIH, University of Kansas and The Ohio State University). In the past several months, four quite promising new treatments for CLL have been introduced. As such, the perceived unmet medical need for this blood cancer is much less than when the TLC team embarked on this project. As a partnership, TLC has closed the ongoing CLL clinical trial evaluating auranofin.

Development of VBP15 for Treatment of Duchenne Muscular Dystrophy

Lead Collaborator: Erica Reeves, ReveraGen BioPharma, Inc., Rockville, MD

Initiated: June 2011

Description: Duchenne muscular dystrophy (DMD) affects approximately 10,000 patients in the United States and 40,000 worldwide. Characteristic muscle deterioration results in confinement to wheelchairs by age 12 and death by age 30 due to cardio-respiratory failure. Current therapy, glucocorticoid steroid injection, acts in a non-specific manner to lessen the severity of symptoms, but does not treat the muscle-specific effects of DMD. Glucocorticoids can only be used for a short time due to serious toxic side effects, including bone fragility, suppression of the immune system and suppression of growth hormone production. This project seeks to develop a modified steroid treatment that will be specific to the muscles, potentially avoiding the toxic side effects of current therapy.

Outcomes: After TRND's acceptance of the project, ReveraGen was able to secure additional funding from the Muscular Dystrophy Association (MDA) to speed the team's collaborative work. TRND completed confirmatory studies demonstrating the effectiveness of the candidate molecule in both cell-based assays and animal models of DMD disease. TRND also successfully designed and executed a novel synthetic route for manufacturing the candidate molecule for human testing under FDA guidelines. TRND prepared for and participated in a pre-IND meeting with the FDA to receive guidance regarding clinical endpoints and other regulatory issues. TRND support generated the data package necessary for filing an IND application for VBP15. However, in late 2014, the molecule failed to meet a key preclinical safety milestone within the TRND project plan. For this reason, the project has been discontinued.

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 are conducting preclinical pharmacokinetic studies, animal efficacy studies, synthesis, formulation and manufacturing of the lead compound, and toxicology studies in rodents and non-rodents. Collaborative studies were completed with the Centers for Disease Control and Prevention (CDC) to test the in vitro efficacy of the molecule against 400 fungal strains from Africa. These studies will form the basis for an IND submission with the FDA.

A Novel Compound for Targeted Treatment of CBF Leukemia

Lead Collaborator: Paul Liu, NHGRI Intramural Research Program, National Institutes of Health, 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 non-specific chemotherapy and/or bone marrow transplantation, which are frequently associated with significant side effects, including life-threatening infections, bleeding, kidney dysfunction and even death. This project seeks to develop a drug targeted to the specific causal genetic abnormality responsible for CBF leukemia, with the aim of significant improvement in survival and reduced complications compared with current treatments.

Outcomes: TRND researchers have successfully optimized the animal disease model and confirmed the efficacy of a lead molecule. TRND will perform additional efficacy studies to the lead compound, optimize the formulation, and perform pharmacokinetic and toxicology tests that will lead to clinical trials.

Inhaled GM-CSF Therapy of Autoimmune Pulmonary Alveolar Proteinosis

Lead Collaborator: Bruce Trapnell, Cincinnati Children's Hospital Medical Center, Cincinnati, 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), which 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 with the disease. 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 has been developed by TRND and the collaborating partners at Cincinnati Children's Hospital. TRND has supported the extensive primate toxicology studies necessary to demonstrate the safety of using GM-CSF in an inhaled formulation. The toxicology and clinical trial protocols were shared under confidential disclosure agreement with Genzyme Corporation, and negotiations were completed to sign a three-way Materials Cooperative Research and Development Agreement (M-CRADA) to allow provision of essential research materials to TRND. TRND prepared for and participated in a pre-IND meeting with the FDA to receive guidance regarding clinical endpoints and other regulatory issues.

BMP Inhibitors to Treat Fibrodysplasia Ossificans Progressiva

Lead Collaborator: Kenneth Bloch, Massachusetts General 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 insufficient to advance further in preclinical development. As such, TRND scientists are performing medicinal chemistry optimization to identify a compound more suitable for formal preclinical development.

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 owing to the high doses required, current production makes it impossible to treat more than 10 percent of affected patients. 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 has selected a PZQ analog for further development. TRND is conducting studies to assess the pharmacokinetics and confirm the anti-schistosomal activity of this PZQ analog.

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 this group of 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: TRND scientists are performing pharmacokinetic studies in animal models of the disease to better understand brain uptake of CincY, and they are working with Lumos to generate all data needed to file an IND with the FDA. This includes chemistry and manufacturing of CincY, toxicology studies, and development of appropriate formulations for human drug dosing. In addition, TRND is developing a prospective natural history study of the disease course in humans along with a registry system for identifying and recruiting patients with the disease, both of which will be necessary for a clinical trial.

AVI-4038 for Treatment of Duchenne Muscular Dystrophy

Lead Collaborator: Peter Sazani, Sarepta Therapeutics, Inc., Bothell, WA

Initiated: September 2011

Description: Duchenne muscular dystrophy (DMD) affects approximately 10,000 patients in the United States and 40,000 worldwide. Mutations in the dystrophin gene result in loss of the dystrophin protein, which causes deterioration of muscle cells. Patients are confined to wheelchairs by age 12 and die by age 30 due to cardio-respiratory failure. Sarepta has developed an injectable biologic (oligonucleotide) drug that allows the DNA-RNA machinery to effectively "skip over" the mutated portion of the dystrophin gene so that functional dystrophin protein can be produced. This project seeks to develop this technology into a potential disease-modifying, life-saving therapy. The technology being developed for this DMD project will be applicable to many other rare genetic disorders, amplifying the impact of this project.

Outcomes: The TRND team performed preclinical efficacy studies to select the best candidate molecule for development. After TRND confirmed the lead molecule, Sarepta reclaimed full control of the project in 2013, utilizing internal corporate resources to continue development. This TRND project is complete.

Long-Acting Parathyroid Hormone Analog for the Treatment of Hypoparathyroidism

Lead Collaborator: Henry Bryant, Eli Lilly & 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. Hypoparathyroidism represents one of the few remaining hormone deficiencies for which an approved replacement therapy does not exist. 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: Negotiations were completed to sign a Research Collaboration Agreement (RCA) with Eli Lilly & Company, the first large pharmaceutical entity to initiate a collaboration with the TRND program. TRND, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and Eli Lilly teams will execute the full preclinical and clinical development plan as milestones are met. TRND will support the preparation and filing of the IND application with the FDA as well as phase I and phase II proof-of-concept clinical trials in hypoparathyroidism 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. These results, in addition to known toxicology and other supporting information, will determine what further studies are needed to support development of the clinical plan and IND filing.

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 develop these retina-derived cells as a transplantable treatment to stop the cellular damage that leads to blindness in RP patients.

Outcomes: TRND researchers are performing initial preclinical pharmacology, pharmacokinetic and toxicology studies. The results of these initial studies will inform the formal development and execution of the IND-enabling studies that will support IND filing with the FDA.

Small Molecule Pharmacological Chaperone for the Treatment of Autosomal Dominant Retinitis Pigmentosa

Lead Collaborator: William Brubaker, BIKAM Pharmaceuticals, Inc., Cambridge, MA

Initiated: September 2013

Description: Autosomal dominant retinitis pigmentosa (adRP) is a rare genetic disease of the eye characterized by the 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 adRP. Researchers have investigated many genes associated with adRP. The most common genes have changes in the protein opsin. The lead collaborator for this project has identified and begun developing compounds that correct abnormal forms of opsin. The purpose of this project is to fully develop one of these candidate compounds into a drug that may be taken orally and to perform the studies needed for testing in adRP patients.

Outcomes: TRND confirmed the chaperone activity of the lead molecule in cells and significantly improved the throughput of the key assay, which can be applied to the screening for new lead compounds. TRND contributed to de-risking the lead molecule by completing a dose range-finding toxicology study to support a future IND filing. After completion of these activities, BIKAM Pharmaceuticals was acquired by Shire Pharmaceuticals in 2014 to continue the development of the de-risked lead molecule for the treatment of adRP. 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: A comprehensive TRND project team has been created to conduct a rigorous initial gap analysis. This gap analysis will enable the team to formalize the development plan that will guide full conduct of the collaborative project.

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 compound suitable for further evaluation and development. A comprehensive TRND project team has been created to conduct a rigorous initial gap analysis. This gap analysis will enable the team to formalize the development plan that will guide full conduct of the collaborative project.

Development of a Therapeutic for Lassa Fever

Lead Collaborator: Sean Amberg, Kineta, Inc., Seattle, WA

Initiated: September 2014

Description: Lassa fever is a viral, hemorrhagic (causes bleeding) disease found in tropical regions of Africa. Each year, an estimated 300,000 people are infected, and severe cases can be fatal. It is classified as a "Category A Priority Pathogen" by the CDC and the National Institute of Allergy and Infectious Diseases (NIAID). Symptoms include fever and damage to multiple organs and the circulatory system. Current treatment options are inadequate, relying primarily on supportive care. The purpose of this project is to develop an antiviral drug to treat and prevent Lassa fever.

Outcomes: A comprehensive TRND project team has been created to conduct a rigorous initial gap analysis. This gap analysis will enable the team to formalize the development plan that will guide full conduct of the collaborative project.

Table 1. TRND Projects and Scientific Resources

See text for outcomes. Glossary for terms listed below can be found on p. 37.

Project	Collaborating Institutions	Scientific Resources
Cyclodextrin for Niemann-Pick Type C1 Disease	Ara Parseghian Medical Research Foundation; Niemann-Pick Type C Support of Accelerated Research (NPC-SOAR); Washington University; Albert Einstein College of Medicine; University of Pennsylvania; Johnson & Johnson; 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
Developing New Treatments for Giardiasis	University of Maryland, Institute for Bioscience and Biotechnology Research	Project Management, Pharmacology, ADME/PK, Toxicology
Aes-103 for Sickle Cell Disease	AesRx, LLC; NHLBI	Project Management, ADME/PK, Toxicology, Formulation, Process Chemistry, Regulatory, Clinical
Auranofin for Chronic Lymphocytic Leukemia	University of Kansas Medical Center; Leukemia & Lymphoma Society; NHLBI	Project Management, Pharmacology, ADME/PK, Regulatory, Clinical
Development of VBP15 for Treatment of Duchenne Muscular Dystrophy	ReveraGen BioPharma, Inc.	Project Management, Medicinal Chemistry, Pharmacology, ADME/PK, Toxicology, Formulation, Process Chemistry
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	Project Management, Toxicology, Formulation
BMP Inhibitors to Treat Fibrodysplasia Ossificans Progressiva	Massachusetts General 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

Table 1. TRND Projects and Scientific Resources (continued)

Project	Collaborating Institutions	Scientific Resources
AVI-4038 for Treatment of Duchenne Muscular Dystrophy	Sarepta Therapeutics, Inc.	Project Management, Pharmacology
Long-Acting Parathyroid Hormone Analog for the Treatment of Hypoparathyroidism	Eli Lilly & Company	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
Small Molecule Pharmacological Chaperone for the Treatment of Autosomal Dominant Retinitis Pigmentosa	BIKAM Pharmaceuticals, Inc.	Project Management, Pharmacology, Toxicology
Repurposing an EU Therapeutic for Hemoglobinopathies	Phoenicia Biosciences, Inc.	Project Planning
Development of Malaria Transmission-Blocking Drugs	Loyola University of Chicago	Project Planning
Development of a Therapeutic for Lassa Fever	Kineta, Inc.	Project Planning

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 in order to improve its efficacy and safety in treating a disease.

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

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

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

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

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

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

For More Information

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