2021 — 2022
Biennial Report

NIH National Center
for Advancing
Translational Sciences

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Director's Introduction

At NCATS, our mission is to turn research observations into health solutions through translational science. We define translational science as "the field that generates scientific and operational innovations to solve long-standing challenges along the translational research pipeline." Since NCATS' beginning in 2011, we have successfully overcome many research bottlenecks through our programs and initiatives.

The NCATS team's successes spring from our organizational culture. We value innovation, collaboration, and acceleration, and our patient-driven focus is ever-present. Our programs are nimble and can pivot quickly to address public health emergencies. We creatively leverage our resources to address high-level needs across all diseases. And because the needs far exceed the scope of any one organization, we employ team science to share ideas, knowledge, and expertise.

In 2021, our staff identified an initial set of principles that characterize effective approaches for translation. The principles stem in part from in-depth case studies of successful NCATS-supported activities that addressed scientific and operational processes to make the research faster, more efficient, and more impactful. This report highlights the following principles:

Joni L. Rutter, Ph.D.

- Focus on unmet needs
- Produce generalizable solutions
- Emphasize creativity and innovation
- Leverage cross-disciplinary team science
- Focus on efficiency and speed
- Utilize boundary-crossing partnerships
- Use bold and rigorous approaches
- Prioritize diversity, equity, inclusion, and accessibility

The stories we share in this report show the translational science principles in action for an array of translational research problems we addressed in 2021–2022. As you will read, the principles shaped our approaches to tackling rare diseases, COVID-19, and the toxic effects of drugs. I am certain they will inspire us to find solutions for whatever comes next.
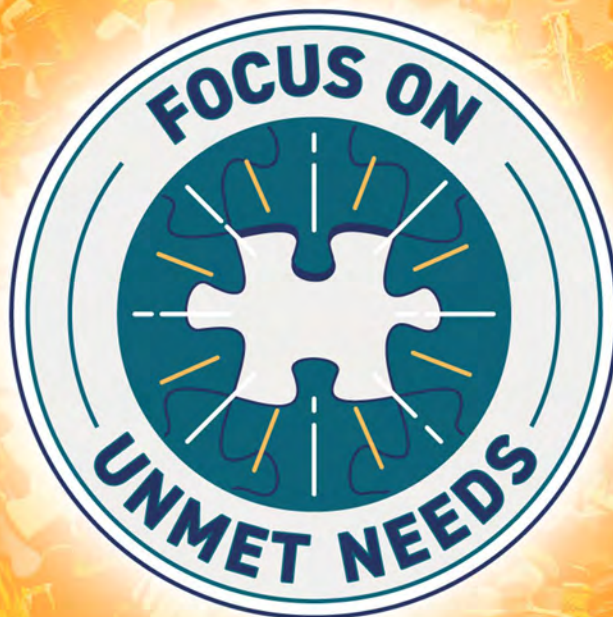
Joni L. Rutter, Ph.D.
Director
National Center for Advancing Translational Sciences

NCATS pursues scientific goals that address unmet scientific, patient or population health needs.

True Costs of Rare Diseases Underscore Urgent Need for Faster Diagnosis, Treatment

For the millions of people with a rare disease, the journey to diagnosis and treatment is neither short nor straight. Their search for answers brings not only false leads and failed treatments. Their unmet needs also bring profound health care costs.

To quantify those costs, NCATS led the Impact of Rare Diseases on Patients and Healthcare Systems (IDeaS) initiative. IDeaS researchers studied medical and insurance records to reveal that health care costs for people with rare diseases have been significantly underestimated.

Individually, most of the 10,000 known rare diseases might affect only a few hundred to a few thousand people worldwide. Collectively, rare diseases are common, affecting an estimated 25 million to 30 million people in the United States; however, only about 5% of rare diseases have an FDA-approved treatment.

IDeaS showed that direct medical costs for those with a rare disease are three to five times greater than for people without a rare disease. The costs are similar to the annual costs for people with cancer, Alzheimer's disease or heart failure.
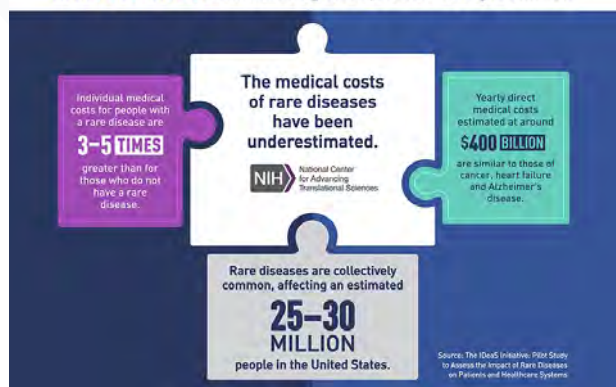
Findings in the graphic are from the publication "The IDeaS Initiative: Pilot Study to Assess the Impact of Rare Diseases on Patients and Healthcare Systems."

The IDeaS researchers looked at medical records and billing codes to identify people with rare diseases and their direct medical costs for 14 rare diseases in four health care systems. In every case, the cost per patient per year for those with a rare disease was more than the costs for non–rare diseases patients of the same age. Annual costs ranged from $4,859 to $18,994 for rare diseases patients versus an annual average cost of $2,211 for those without a rare disease.

> **We must make more rare disease treatments available faster to everyone who needs them.**

Extrapolating the average cost estimate for all the people with rare diseases in the United States results in total annual direct medical costs of approximately $400 billion.

"We need to find innovative ways, including new technologies, to help shorten the lengthy diagnostic odysseys so many patients and families experience," said NCATS Director Joni L. Rutter, Ph.D., who was an IDeaS

study co-author. "And we must make more rare disease treatments available faster to everyone who needs them."

NCATS is the heart of rare diseases research at NIH. We partner with patients, advocates, scientists and health care providers to shorten the time to diagnosis by finding early indicators of rare diseases. We collaborate with researchers to tackle many rare diseases at a time by focusing on what they have in common. We use all the translational science principles to make it easier and more efficient for scientists to discover and develop drugs for rare diseases.

Learn more about how NCATS finds rare disease solutions for those who need them most.

More Unmet Needs Stories
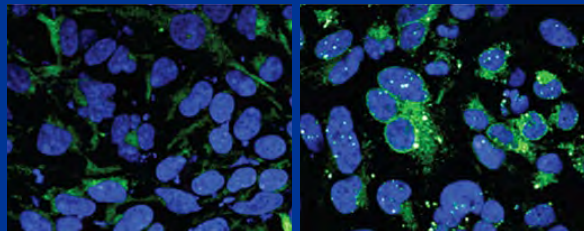
Drug Repurposing Approaches Reveal HIV Drug Holds Promise Against a Rare, Disabling Muscle Disorder

https://ncats.nih.gov/pubs/features/drug-repurposing-approaches-reveal-HIV-drug-holds-promise-against-a-rare-disabling-muscle-disorder

NIH Director's Blog: A Rare Public Health Challenge

https://directorsblog.nih.gov/2023/01/24/a-rare-public-health-challenge

Rare Disease Day at NIH 2022: Shining a Light on Patient Perspectives

https://ncats.nih.gov/pubs/features/rare-disease-day-at-nih-2022-shining-a-light-on-patient-perspectives

GENERALIZABLE SOLUTIONS

NCATS develops innovations that address persistent challenges found across multiple research initiatives or projects, or that span research on multiple diseases or conditions.

Stem Cell Cocktail Could Bring More Treatments for Many Diseases

Pluripotent stem cells are biomedical blank canvases. Capable of becoming nearly any type of cell in the body, these stem cells offer a potentially endless source of hard-to-get specialized cells that researchers need for testing new treatments for a wide range of diseases.

But stem cells have a problem: They're sensitive.

The stress of living in a laboratory culture dish can damage their DNA and trigger cell death. That fragility is a barrier to stem cells' achieving their full potential as a powerful research tool for many diseases and conditions. Too-sensitive stem cells can't easily be made in the vast quantities scientists need.

Scientists in the NCATS Stem Cell Translation Laboratory have come up with a solution that works for a range of scenarios: Pour sensitive stem cells a calming cocktail.

An NCATS research team devised a four-part cocktail of small molecules that can protect a type of stem cell called induced pluripotent stem cells (iPSCs) from stress and preserve their normal structure and function. iPSCs are made by reprogramming skin or blood cells.

To find the right mix, the NCATS team tested more than 15,000 U.S. Food and Drug Administration–approved

This video provides an overview of the SCTL lab and how NCATS is applying stem cells in translational science.

drugs and investigational small-molecule compounds from NCATS' collections. They identified a unique combination, called CEPT, that greatly improved stem cell survival and reduced cell culture stress.

"The small-molecule cocktail is the cornerstone of every protocol we have developed, spanning the establishment of new iPSC lines to the generation of various human cell types, organoids and 3D models," said Carlos Tristan, Ph.D., acting director of the NCATS Stem Cell Translation Laboratory. "It's truly exciting to see the widespread adoption of this cocktail by leaders in both the private and

public sectors within the fields of stem cell biology and regenerative medicine."

For example, the CEPT cocktail dramatically improved stem cells' survival during freezing and thawing, a key step in using the cells for biomedical research. CEPT had a similar protective effect on iPSCs that had already developed into heart cells, motor neurons and other cell types.

"Because they offer new ways to protect stem cells from damage, these results could eventually have wide-ranging implications for many different diseases, including cancer, Alzheimer's disease, neuromuscular disorders, and more," said NCATS Director Joni L. Rutter, Ph.D.

Stem cell breakthroughs like the CEPT cocktail are just one of the many therapeutic tools and technologies that NCATS has developed to work across diseases. From tissue chips

and gene therapy tools to clinical trial designs and big-data innovations, we seek what's common across health research to find generalizable solutions that can work for many challenges.

> " By finding new ways to protect stem cells from damage, these results could eventually have wide-ranging implications for many different diseases. "

Learn more about how NCATS advances stem cell technologies to speed research on a broad range of diseases and conditions.

More **Generalizable** Stories
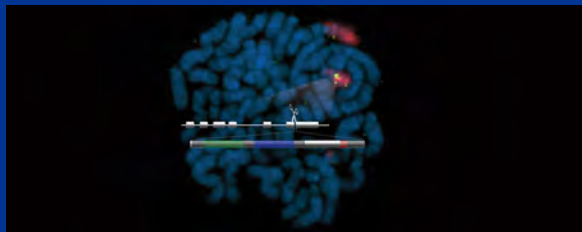
NCATS Researchers' New Approach to Measure Gene Activity Could Speed Search for Rare Disease Therapies

https://ncats.nih.gov/pubs/features/ncats-researchers-new-approach-to-measure-gene-activity-could-speed-search-for-rare-disease-therapies
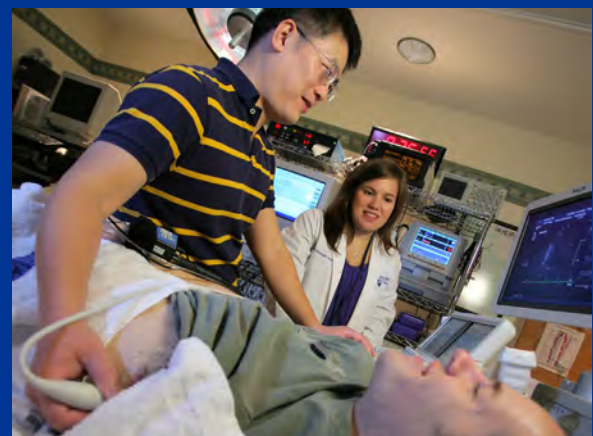
SMART IRB Agreement Reaches 1,000 Signatories, Speeds Medical Trials

https://ncats.nih.gov/pubs/features/nationwide-IRB-reliance-agreement-aimed-at-speeding-research-reaches-1000-signatories

NCATS leverages creativity and innovation to increase the impact of research.

How Llamas Could Lead to Innovative Antiviral Therapies

Llamas might seem unlikely sources for creative answers to COVID-19. But the shaggy pack animals may possess a key to unlocking innovative treatments that stop viruses like SARS-CoV-2: nanobodies.

Nanobodies are found in camelid species, which include llamas, alpacas and camels. They are one-tenth the size of a human antibody, which the immune system uses to identify and attack bacteria and viruses. Their small size lets them attach inside protein grooves on viruses. This feature could help scientists target weaknesses on the SARS CoV-2 spike protein that full-sized antibodies can't reach.

Working with colleagues at the National Institute of Environmental Health Sciences and the U.S. Naval Research Laboratory, NCATS scientists built a library of small antibodies, called synthetic nanobodies, and used it to find promising new therapeutic leads for stopping viral activity.
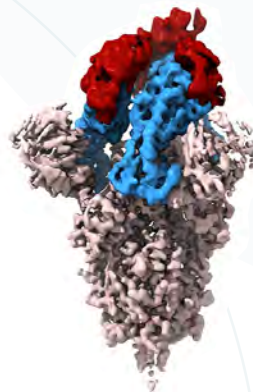
"Nanobodies make attractive building blocks for the design of new therapies," said NCATS scientist Bryan Fleming, Ph.D., who helped lead the work, along with former NCATS scientist Ying Fu, Ph.D. "We've developed a way to rapidly and efficiently discover nanobodies against SARS-CoV-2."

An NIH-led team of scientists built a library of small antibodies, called synthetic nanobodies, and used it to find promising new therapeutic leads for halting SARS-CoV-2 infection. The SARS-CoV-2 spike protein is depicted in white, and its three receptor binding domains (RBDs) are highlighted in blue. The RBD is the portion of the viral spike protein that binds to the protein receptor, ACE2, on the surface of healthy cells. SARS-CoV-2 enters cells through ACE2. Three nanobodies (red) mask the binding portion of the RBDs, preventing the spike protein from recognizing ACE2. This prevents the virus from entering the cell. (Credit: Kedar Sharma, Ph.D., and Mario Borgnia, Ph.D., National Institute of Environmental Health Sciences.)

The first step to building the library was making llama nanobodies appear more like human antibodies. The researchers "humanized" the nanobodies by using a U.S. Food and Drug Administration–approved nanobody drug backbone as the basis for the library.

Each nanobody has regions that recognize and stick to protein targets. These regions are like nanobody fingerprints and make each nanobody unique to a protein. Changing

these regions creates new nanobodies capable of targeting new proteins.

The construction of a synthetic library can yield about 10 billion possible nanobodies. These nanobodies can be studied as individual therapies or used together to create combination therapies.

NCATS' technology to develop a library of humanized nanobodies was among those that NIH licensed to the Medicines Patent Pool through the World Health Organization COVID-19 Technology Access Pool. The licenses will allow manufacturers around the world to use these technologies. For example, NCATS signed a material transfer agreement with the Weizmann Institute of Science, giving the institute's researchers in Israel access to the nanobody library.

"This is a huge library of antibodies that can be screened to identify drug candidates against almost any protein, related to almost any disease," explained Matthew

Hall, Ph.D., director of NCATS' Early Translation Branch and a study co-author. "Given that there are more than 10,000 rare diseases, most of which have no treatment, we hope this new platform will also prove useful in tackling that challenge."

> " Nanobodies make attractive building blocks for the design of new therapies. "

The synthetic nanobody library is just one of the many ways NCATS and our partners harness creativity and innovation to find answers for biomedical research challenges. Learn more about how our Division of Preclinical Innovation applies translational science principles to transform research observations into health solutions.

More **Innovative** Stories

Lung Tissue Chips Could Help Predict Future Infectious Influenza Disease Variants
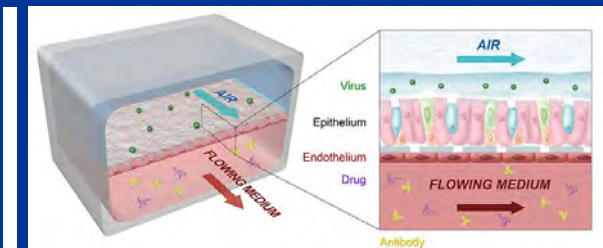
https://ncats.nih.gov/pubs/features/lung-tissue-chips-could-help-predict-future-infectious-influenza-disease-variants

Improving Manufacturing Techniques to Deliver High-Quality Biotherapeutics to the Clinic Faster

https://ncats.nih.gov/pubs/features/improving-manufacturing-techniques-to-deliver-high-quality-biotherapeutics-to-the-clinic-faster

CROSS-DISCIPLINARY
TEAM SCIENCE

NCATS engages experts across disciplines, fields and professions to advance research.

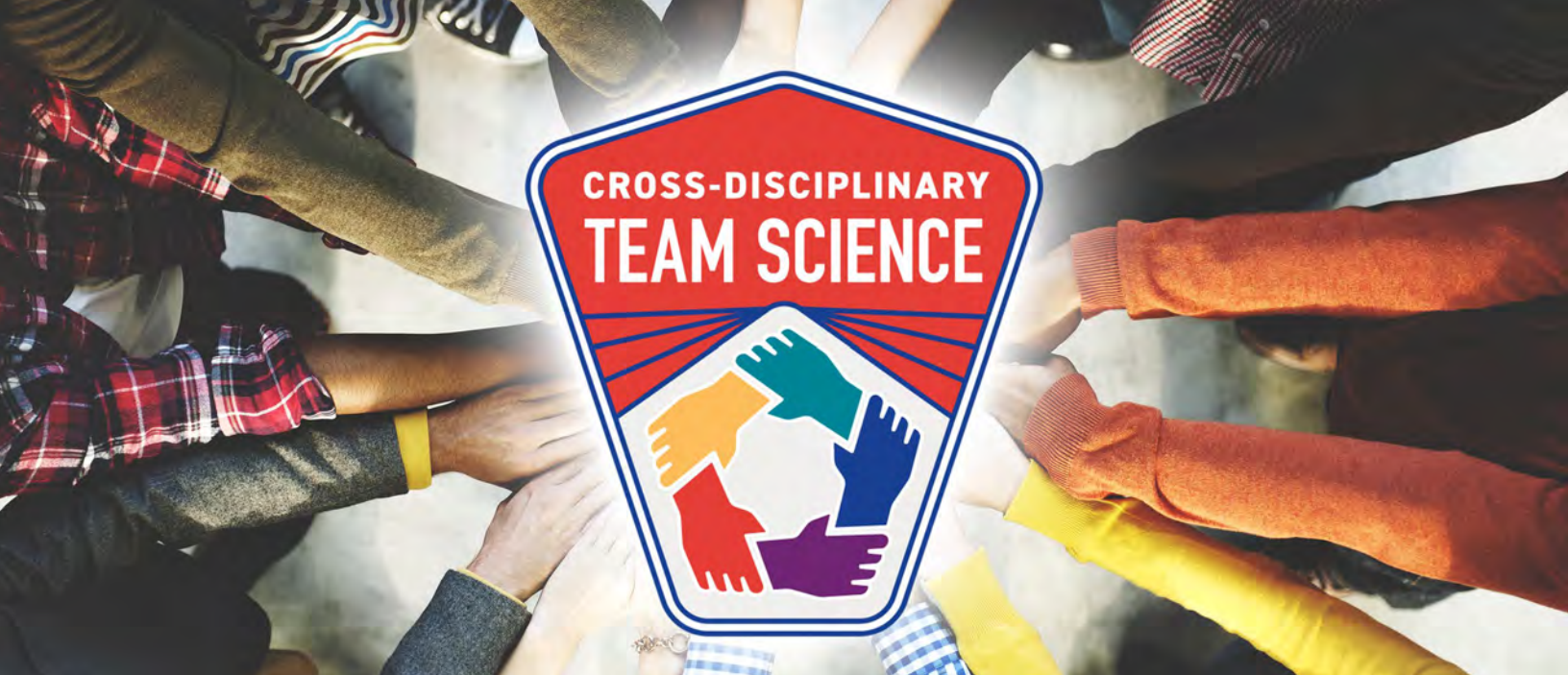## How a Multidisciplinary Team Built a Library of 10,000 Chemicals to Deliver Safer Medicines

People are exposed to thousands of environmental and chemical agents, and testing their toxicity can be costly. The methods scientists use typically test only one chemical compound at a time over months or years. To speed up this process, NCATS scientists and federal partners with expertise in toxicology, informatics, chemistry and biology created a vast chemical library that scientists can use to probe the possible toxic effects of compounds quickly and efficiently.

The library is part of the Toxicology in the 21st Century (Tox21) program, a research collaboration among NCATS, the National Toxicology Program (NTP) at NIH's National Institute of Environmental Health Sciences, the U.S. Environmental Protection Agency (EPA) and the U.S. Food and Drug Administration (FDA). Tox21 aims to develop new ways to determine whether substances can be harmful to human health.

The Tox21 chemical library combines libraries from the different federal agencies into a set of approximately 10,000 compounds spanning environmental chemicals and FDA-approved drugs. Public release of all research data is a hallmark of the program.
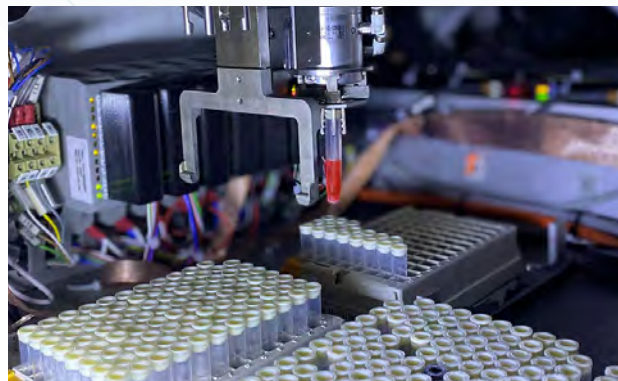
The Tox21 compound collection samples can be reformatted by NCATS Compound Management staff for testing in a variety of ways, from single test tubes to 96 well plates. (Credit: Katlin Recabo, Glenn Gomba and Paul Shinn, NCATS)

Because the Tox21 chemical library includes the NCATS Pharmaceutical Collection — a group of compounds representing more than 90% of all FDA-approved drugs and some drugs still in clinical trials — Tox21 investigators can test directly for toxic side effects of drugs approved by the FDA or by European Union, Japanese, Australian, or Canadian authorities.

> **We want to streamline the testing process for a chemical, yet still tell how it may be dangerous to people.**

During the COVID-19 pandemic, scientists used the Tox21 compound library to rapidly test thousands of potential therapies to assess how they worked and if they were toxic to cells. Researchers also used Tox21 to identify more than 100 compounds that interfere with acetylcholine, a neurotransmitter vital to the brain's nerve cells and to muscle movement. Reduced acetylcholine activity is linked with such conditions as Alzheimer's disease and myasthenia gravis. In addition, scientists from the Tox21 group have tested about 500 topically applied compounds to assess their risk of sensitizing and irritating skin. The study is a key initial step toward replacing animal tests with bioengineered skin models.

The Tox21 program has also shaped federal regulatory processes. Tox21 researchers created tests assessing chemicals' effects on the body's response to the hormone estrogen. Those tests are now part of regulatory agencies' recommended tests to evaluate how chemicals affect estrogen receptors.

"With Tox21, we want to streamline the testing process for a chemical, yet still tell how it may be dangerous to people or say with some degree of confidence that it will be safe," said NCATS Scientific Director Anton Simeonov, Ph.D.

Learn more about how Tox21 unites expertise across scientific disciplines to streamline the chemical testing process and speed new therapies to those who need them.

More Team Science Stories

Tissue Model Approach Provides Clues to SARS-CoV-2 Brain Infections
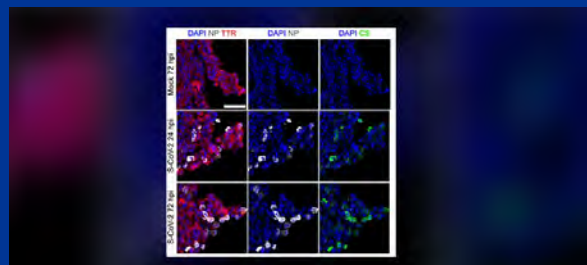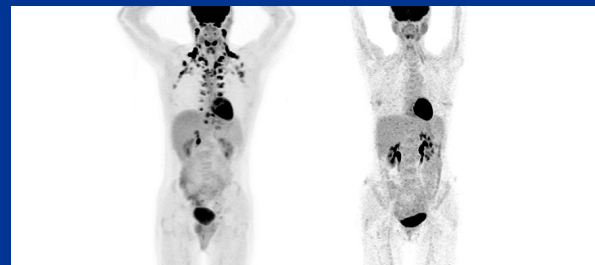
https://ncats.nih.gov/pubs/features/tissue-model-approach-provides-clues-to-sars-cov2-brain-infections

CTSA Program-Supported Researchers May Turn Brown Fat into an Ally Against Obesity

https://ncats.nih.gov/pubs/features/ctsa-program-supported-researchers-may-turn-brown-fat-into-an-ally-against-obesity

EFFICIENCY AND SPEED

NCATS uses evidence-informed practices and scientific and operational innovations to accelerate translational research.

Building a More Efficient Clinical Trial to Accelerate Therapeutic Answers

Speed. It's not a word that typically describes the traditional one-drug-at-a-time approach to clinical trials. But in a pandemic, speed is a word that means everything to people who need treatments that work.

Speed has been central to the mission of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public–private partnership. ACTIV coordinated and accelerated development of the most promising COVID-19 treatments and vaccines.

NCATS and our partners led two ACTIV phase 3 clinical trials of potential COVID-19 treatments: ACTIV-1 and ACTIV-6. The ACTIV-1 Immune Modulators clinical trial evaluated the safety and efficacy of three immune modulator drugs in more than 1,900 hospitalized adults with COVID-19. ACTIV-6 is testing six repurposed prescription and over-the-counter medications in up to 13,500 people. Participants administer the drugs themselves to treat mild to moderate symptoms of COVID-19.

Phase 3 clinical trials can last for up to 48 months. ACTIV-1 and ACTIV-6 delivered evidence-based treatment answers in less than half that time. In both trials, we put translational science tools to work to find evidence-based answers faster than traditional clinical trial approaches.
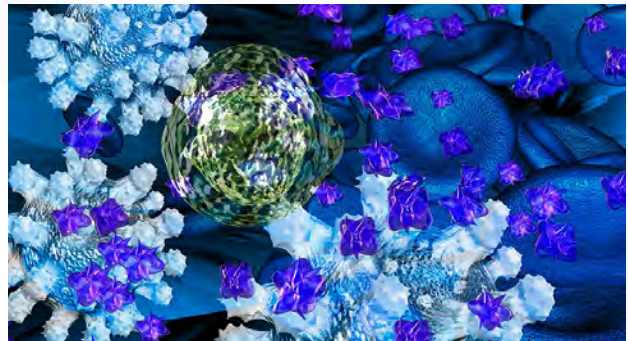
Illustration of a cytokine storm response to infection with the new coronavirus SARS-CoV-2. A cytokine storm is a severe immune reaction that results in greatly elevated levels of inflammatory immune proteins (cytokines, purple) in the body. (Credit: Fernando Da Cunha/Science Photo Library)

To accelerate ACTIV-1 and ACTIV-6, we used master protocols. Master protocols let researchers evaluate multiple drugs at the same time within the same clinical trial structure. ACTIV6's adaptive platform trial design allowed investigators to use data from ongoing treatment arms to revise the trial in real time, rather than waiting until the end. As a result, researchers could swiftly eliminate drugs that didn't show effectiveness, quickly identify those that do work, and rapidly bring other potential treatments into the clinical trial. And thanks to a national decentralized

> **These collaborative and efficient trial designs streamlined our ability to urgently and robustly test promising therapies.**

recruitment approach that let people join from anywhere in the country, ACTIV-6 met its enrollment goals quickly. Both ACTIV-1 and ACTIV-6 also used electronic participant consent methods developed by the NCATS Trial Innovation Network to speed the enrollment process.

"These collaborative and efficient trial designs streamlined our ability to urgently and robustly test promising therapies for treating people with COVID-19," said Joni L. Rutter, Ph.D., director of NCATS.

How urgently?

Within 19 months of its start date, ACTIV-1 released topline results showing two of the drugs tested did not significantly shorten time to recovery but did substantially improve clinical status and reduce deaths. The ACTIV-6 trial's results from five of its study arms — all showing no benefit — were publicly available in preprint within 8–14 months of those arms' starts.

Learn more about how NCATS accelerates biomedical research through clinical trial innovation.

More Efficiency, Speed Stories
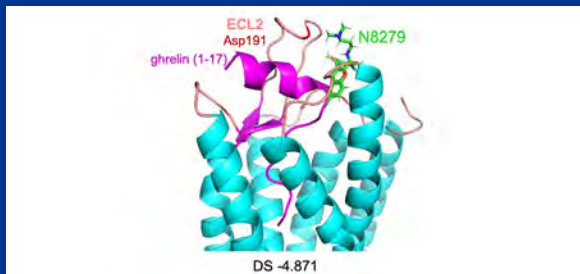
NCATS, Duke Scientists Show Compound's Novel Effects on Key Brain Chemical in Drug Addiction

https://ncats.nih.gov/news/releases/2022/ncats-duke-scientists-show-compounds-novel-effects-on-key-brain-chemical-in-drug-addiction

Drug Testing Approach Uncovers Effective Combination for Treating Small Cell Lung Cancer

https://ncats.nih.gov/news/releases/2021/drug-testing-approach-uncovers-effective-combination-for-treating-small-cell-lung-cancer

BOUNDARY-CROSSING PARTNERSHIPS
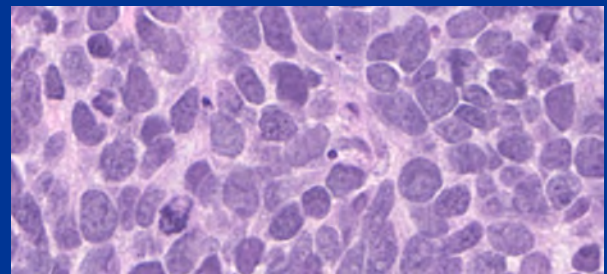
NCATS leverages collaborations across agencies, sectors and communities to speed research advances.

Building Bridges to Overcome Treatment Gaps

Ten thousand. And two.

An enormous biomedical challenge separates those two numbers. An extraordinary collaborative response could bring them closer together.

Ten thousand is the estimated number of known rare diseases. But by 2021, two was the number of rare diseases that had U.S. Food and Drug Administration (FDA)–approved gene therapies. Closing that therapeutic gap demands scientific expertise from every corner of biomedical research.

Most rare inherited diseases stem from a specific gene mutation that is already known, making gene therapy a promising therapeutic approach. To bring more gene therapies more quickly to those with rare diseases, NCATS teamed with a diverse group of partners across the public and private sectors to launch the Bespoke Gene Therapy Consortium (BGTC). Working as one, NIH, the FDA, pharmaceutical companies and nonprofit organizations partnered to accelerate the development of gene therapies for the 30 million people in the United States who suffer from a rare disease.

Gene therapy development for rare diseases is highly complex, time consuming and expensive. The development

3-D rendering of genetic medicine with DNA isolated. (Credit: xsense/Shutterstock)

process is held up by limited access to tools and technologies, lack of standards across the field, and a one-disease-at-a-time approach. A standardized therapeutic development model that includes a common gene delivery technology (i.e., a vector) could offer a more efficient approach to specific gene therapies, saving time and money.

The BGTC will improve and simplify the gene therapy development process to help fill the unmet medical needs of people with rare diseases — particularly those diseases that are too rare to be of commercial interest.

"The BGTC aims to make it easier, faster and less expensive to pursue bespoke gene therapies to encourage more companies to invest in this space and bring more treatments to people," said Joni L. Rutter, Ph.D., director of NCATS.

One of the BGTC's primary goals is to deepen our understanding of a common gene delivery vector known as the adeno-associated virus (AAV). BGTC researchers will study AAV vector production, vector delivery of genes into human cells, and activation of therapeutic genes in target cells. These results will simplify vector manufacturing and enhance the overall therapeutic benefit of AAV gene therapy. The BGTC selected eight rare diseases for its clinical trials portfolio.

> **The BGTC aims to make it easier, faster and less expensive to pursue bespoke gene therapies.**

NCATS' wide-ranging collaborations also advance gene therapy solutions, such as the Platform Vector Gene Therapy (PaVe-GT) program, and support small businesses developing and commercializing new translational technologies. Learn more about how NCATS builds partnerships across sectors to close the therapeutic gap between 10,000 and two.

More Partnership Stories

Scientists Identify Characteristics to Better Define Long COVID
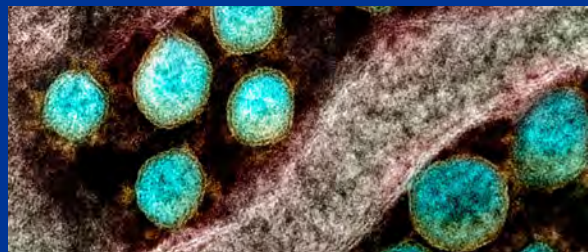
https://ncats.nih.gov/news/releases/2022/scientists-identify-characteristics-to-better-define-long-COVID

National EHR Data Resource Reveals COVID-19's Stark Mortality Risk in People with COPD

https://ncats.nih.gov/pubs/features/national-ehr-data-resource-reveals-covid-19-stark-mortality-risk-in-people-with-copd

NCATS addresses ambitious research questions with rigorous and robust methods that generate reproducible findings and advance translation.
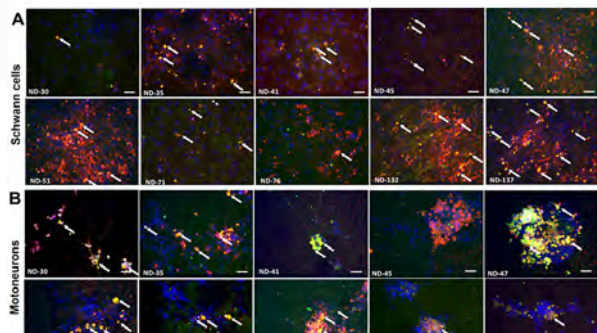
3-D Model for Rare Neuromuscular Disorders Speeds Clinical Trial

For people with rare diseases, the road to effective treatments can seem endless. But a tiny device that recreates how human tissues and organs work could help those with two rare, devastating neuromuscular diseases find a shorter route to new therapies.

Chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy cause the immune system to attack nerve cells and disrupt messages from the brain to the muscles. Current treatments can help but often are inconsistent.

Traditional drug development tools, such as two-dimensional cell cultures and animal models, don't accurately predict how people will respond to an experimental therapy. As a result, about 90% of promising therapies fail when they reach clinical trials in people.

A scientific team supported by NCATS took a bold approach to boost the odds for a promising drug that targets these two neuromuscular diseases. The researchers created a tiny, bioengineered three-dimensional model that uses human tissue to better mimic how the two neuromuscular diseases take their toll in humans. Such organ-on-a-chip models, or "tissue chips," allow researchers to rigorously test a new drug and more

Scientists have created a 3-D bioengineered model that mimics the biology of two rare neuromuscular diseases. In both disorders, the brain's messages to muscles are disrupted by the body's immune system. The model consists of motoneurons, which are cells that transmit messages from the brain to muscles, and Schwann cells, which help the signals move more quickly. In section A, arrows point to immune system antibodies (red and green) that bind to Schwann cells, interfering with their activity. In section B, the arrows show antibodies binding to motoneurons. (Credit: Reproduced with permission. Copyright 2022, The Authors, published by Wiley-VCH)

accurately predict how it will work when it reaches clinical trials in people.

To simulate the diseases, the research team created a tissue chip model with motoneurons, which transmit messages from the brain to muscles, and Schwann cells,

which help the signals move faster. The scientists then exposed the cells to blood serum from people with the two rare diseases. That exposure caused a shower of immune system antibodies against the cells, slowing down the motoneuron signals.

The scientists treated their tissue chip model with a drug that blocks the faulty immune system reaction. With the drug, the cells and the message speed returned to normal.

This tissue chip study provided key preclinical data for a company developing the drug to receive U.S. Food and Drug Administration (FDA) authorization to test the drug in a clinical trial. This work marks one of the first examples of scientists using primarily tissue chip data for an FDA Investigational New Drug application to test the efficacy of a candidate drug in people with rare diseases.

"Tissue chip technologies have tremendous implications for drug discovery and the development of more effective medicines to treat rare and common diseases," said Danilo Tagle, Ph.D., director of the Office of Special Initiatives at NCATS. "This system is already demonstrating its utility in modeling rare diseases and as an alternative to animal models in determining the effectiveness of therapeutics."

Learn more about how NCATS uses bold and rigorous approaches with technology like tissue chips to study diseases and test therapies quickly to better predict which ones will move from the laboratory to successful clinical trials in people.

More Approaches Stories

Building Lung Tissue Models to Speed Virus Drug Testing
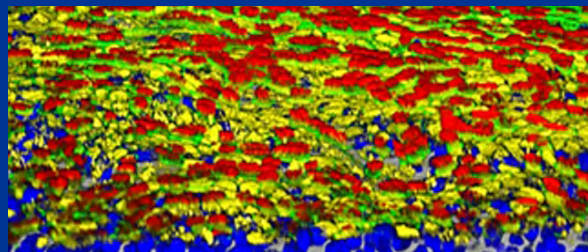
https://ncats.nih.gov/pubs/features/building-lung-tissue-models-to-speed-virus-drug-testing

New 3-D Model Offers Insights into the Role of Glucose in a Deadly Kidney Disease
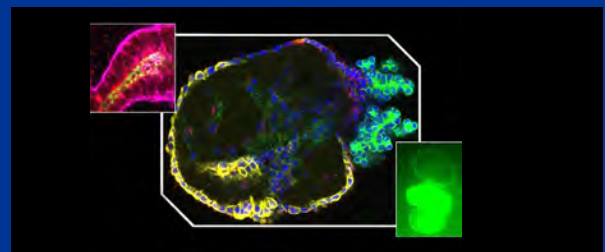
https://ncats.nih.gov/news/releases/2023/New-3-D-Model-Offers-Insights-into-the-Role-of-Glucose-in-a-Deadly-Kidney-Disease

NCATS leverages diversity, equity, inclusion and accessibility to produce research outcomes that are relevant to the full diversity of the population.

Using Health Record Data to Reveal Disparities in Diagnosing Long COVID

For millions of Americans, the COVID-19 pandemic has left a lingering condition known as long COVID. Long COVID encompasses complex symptoms and challenging health problems that last for weeks, months, or years after a COVID-19 infection.

Researchers in NIH's Researching COVID to Enhance Recovery (RECOVER) Initiative assessed what a new long COVID diagnostic code reveals about who's developing the condition — and whose diagnoses may be missed. Central to their study was the National COVID Cohort Collaborative (N3C) Data Enclave, a nationwide database developed by NCATS and its partners that reflects the diversity of the country.

The researchers looked at N3C data from the electronic health records of 33,782 adults and children who received a long COVID diagnosis between October 2021 and May 2022. All had been given a diagnosis of "post COVID-19 condition, unspecified," the diagnostic code introduced in U.S. health care systems in October 2021.

In studying peoples' profiles and symptoms, the researchers found multiple patterns. Among the more striking findings was that most of the people were white,
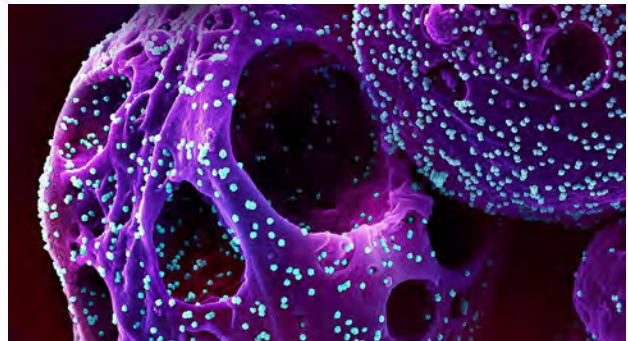
Colorized scanning electron micrograph of a cell (purple) infected with the Omicron strain of SARS-CoV-2 virus particles (teal), isolated from a patient sample. (Credit: National Institute of Allergy and Infectious Diseases)

female, non-Hispanic and likely to live in areas with low poverty and greater access to health care.

Those findings stood out, given what researchers already knew about the disproportionate impact of COVID on people of color and economically disadvantaged populations. The pattern suggested that not all patients who have long COVID are being diagnosed, said Emily Pfaff, Ph.D., a study author and assistant professor in the Division of Endocrinology and Metabolism at the University

of North Carolina, Chapel Hill. Those disparities in diagnosis lead to poor outcomes and less access to treatments.

> " Looking at COVID-19 outcomes from EHR data that are representative of the U.S. population … has been a key priority of N3C.

The reasons for underdiagnosis vary. In addition to long-documented health disparities based on race and other factors, Pfaff explained, women are more likely than men to seek health care in general. People with the time and resources to access health care also tend to be disproportionally represented in clinical data.

"You can see all the different ways these diagnostic codes can provide insight, but they can also skew the whole story," Pfaff said.

Still, she added, the insights help. She and her team found, for example, that most of the people with long COVID had mild to moderate symptoms of acute infection. They also discovered that long-term symptoms could be grouped into common clusters — cardiopulmonary, neurological, gastrointestinal and coexisting conditions — as well as by age.

"Looking at COVID-19 outcomes from EHR data that are representative of the U.S. population, including the communities hardest hit, has been a key priority of the N3C," explained NCATS Director Joni L. Rutter, Ph.D. "By linking clinical data with demographic information, the N3C has helped us learn more about how risks for COVID-19 vary across ages, races, chronic conditions, and treatment regimens."

From machine-learning models that better identify who has long COVID to initiatives such as N3C Public Health Answers to Speed Tractable Results (PHASTR) that speed answers to COVID-19 health outcomes, NCATS has developed research tools to sharpen understanding of long COVID, overcome treatment disparities and deliver solutions to everyone who needs them.

More DEIA Stories

N3C Data Reveal More Severe COVID-19 Outcomes in Rural Communities

https://ncats.nih.gov/pubs/features/n3c-data-reveal-more-severe-covid-19-outcomes-in-rural-communities

Low Vitamin D Levels May Boost COVID-19 Risk in Black People

https://ncats.nih.gov/pubs/features/low-vitamin-d-levels-may-boost-covid-19-risk-in-black-people

Appendix

Appendix: Statutory Language on Biennial Report

Public Health Service Act

Section 479 NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

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

    (1) the molecules being studied;

    (2) clinical trial activities being conducted;

    (3) the methods and tools in development;

    (4) ongoing partnerships, including—

        (A) the rationale for each partnership;

        (B) the status of each partnership;

        (C) the funding provided by the Center to other entities pursuant to each partnership, and

        (D) the activities which have been transferred to industry pursuant to each partnership;

    (5) known research activity of other entities that is or will expand upon research activity of the Center;

    (6) the methods and tools, if any, that have been developed since the last biennial report was prepared; and

    (7) the methods and tools, if any, that have been developed and are being utilized by the Food and Drug Administration to support medical product reviews.

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

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

Responses to Required Information

(1) the molecules being studied	The NCATS Pharmaceutical Collection (NPC) is a comprehensive collection of approved and investigational drugs for high-throughput screening that provides a valuable resource for both validating new models of disease and better understanding the molecular basis of disease pathology and intervention. The NPC consists of a physical collection of drugs and an information browser and database. Access to the collection is provided through both the TRND program and Tox21 initiative and instructions are available at https://tripod.nih.gov/npc. Sources for the current collection include traditional chemical suppliers, specialty collections, pharmacies and custom synthesis.
	All data generated through this effort are deposited in PubChem (within the NIH's National Library of Medicine). PubChem consists of three dynamically growing databases:
	1. PubChem Compound: Contains pure and characterized chemical compounds. 2. PubChem Substance: Contains mixtures, extracts, complexes and uncharacterized substances. 3. PubChem BioAssay: Contains database results from high-throughput screening programs with several million values.
	For a list of NCATS-utilized compounds, go to https://www.ncbi.nlm.nih.gov/pccompound/?term=NCGC%5Bsourcename%5D.
(2) clinical trial activities being conducted	ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. Studies for which NCATS is a sponsor/collaborator are available at https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=&titles=&outc=&spons=NCATS&lead=&id=&cntry=&state=&city=&dist=&locn=&fund=0&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort=.
	For a list of clinical research studies being supported by NCATS Rare Diseases Clinical Research Network (RDCRN), go to https://www.rarediseasesnetwork.org/research-groups.
(3) the methods and tools in development	This biennial report highlights many of the ongoing efforts of NCATS to develop methods and tools that will improve the translational research process. For a complete list of all of the active projects funded by NCATS, go to https://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=15E8C1094A85C3D47598B8961CAA4A01A2FFCEB861BF.
4) ongoing partnerships, including— (A) the rationale for each partnership; (B) the status of each partnership; (C) the funding provided by the Center to other entities pursuant to each partnership, and (D) the activities which have been transferred to industry pursuant to each partnership;	A and B) The NCATS Division of Preclinical Innovation develops approaches that improve the efficiency and effectiveness of translation. To do so, NCATS intramural scientists leverage state-of-the-art laboratories and collaborations among government, industry, academia, and patient and rare disease communities to advance new technologies to make preclinical research more predictive and efficient.
	C) Investigators do not receive grant funds through the NCATS intramural program. Instead, selected researchers partner with NCATS experts to generate pre-clinical data and clinical-grade material through government contracts for use in Investigational New Drug (IND) applications to a regulatory authority such as the U.S. Food and Drug Administration (FDA).
	For a list of NCATS intramural projects, please visit https://intramural.nih.gov.
	D) For information on any activities which have been transferred to industry, please inquire with NCATSPartnerships@mail.nih.gov.
(5) known research activity of other entities that is or will expand upon research activity of the Center	NIH investigators frequently conduct PubMed searches on areas of research interest. However, NIH does not conduct competitive intelligence on for-profit entities.

(6) the methods and tools, if any, that have been developed since the last biennial report was prepared	Small molecule chemical compounds, which can be used to test or "probe" the effects of increasing or decreasing the activity of a biological target in cells or animals, are some of the most powerful tools for target validation, which is the process of demonstrating that engaging a target provides meaningful therapeutic benefit. Probes enable researchers to investigate protein and cell functions and biological processes. If appropriate, probes can be optimized to become potential drug candidates. Generating these chemical probes requires specialized expertise and facilities, and the NCATS Early Translation Branch (ETB) provides world-leading collaborative services to meet these needs. Collaborators work with ETB scientists to develop screens against promising drug targets and to refine these results into small molecule probes and potential therapies.
	For a list and descriptions of the assays (tests) developed through the ETB, go to https://www.ncbi.nlm.nih.gov/pcassay?term=NCGC%5Bsourcename%5D&cmd=search.
(7) the methods and tools, if any, that have been developed and are being utilized by the Food and Drug Administration to support medical product reviews	https://ncats.nih.gov/expertise/preclinical/gsrs
	Global Substance Registration System (GSRS)
	The GSRS resource is a registration system for the ingredients in medicinal products. This project, developed by NCATS scientists, makes it easier for regulators and other stakeholders to exchange information about substances in medicines, supporting scientific research on the use and safety of these products.
	While the main goal of production software is to assist agencies in registering and documenting information about substances found in medicines, a collaboration with the FDA also has enabled NCATS to publish a public data set of substance records, which is updated on a regular basis and used by collaborators in regulatory science as well as industry.
	EU-SRS is sponsored by EMA and BfArM (Germany). They will use the GSRS software and load the NCATS hosted FDA public GSRS data to EU-SRS for "production" use in order to support their substance curation processes in mid-2022.
	The link to GSRS is available at https://gsrs.ncats.nih.gov.
	CURE ID, created through a collaboration between NCATS and the FDA, enables the crowdsourcing of medical information from health to facilitate the development of new treatments using repurposed drugs for difficult-to-treat infectious diseases, including COVID-19. CURE ID is accessible through a website, smartphone or other mobile device. The CURE ID app, which was developed with NCATS' support, includes information on most clinical trials for COVID-19 drugs, biologics and vaccines.