Rare Diseases Intervention Development Resources at NCATS

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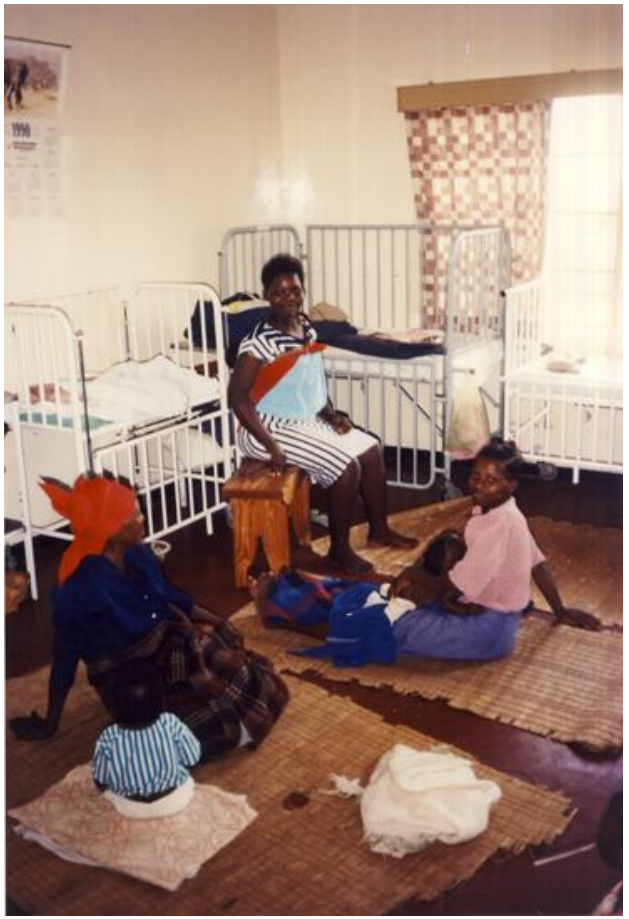
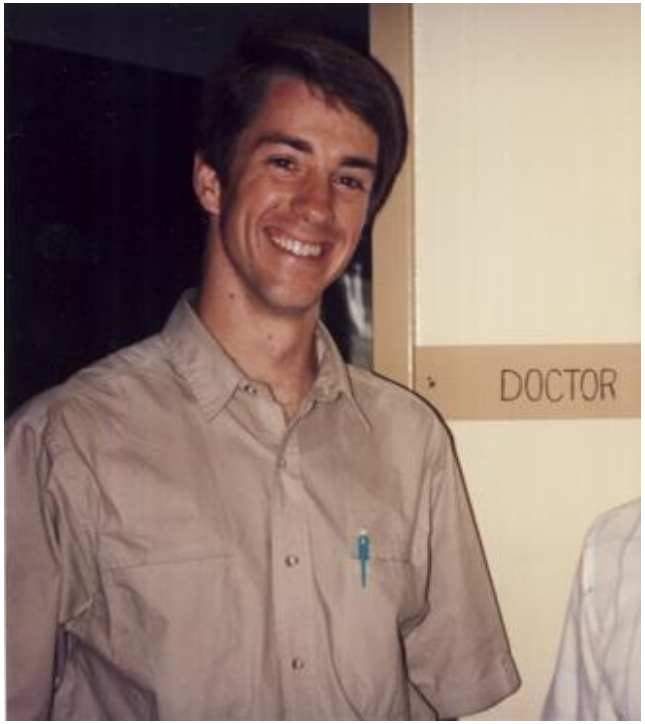
NATIONAL INSTITUTES OF HEALTH

ICORD-RareX
OCTOBER 21, 2016

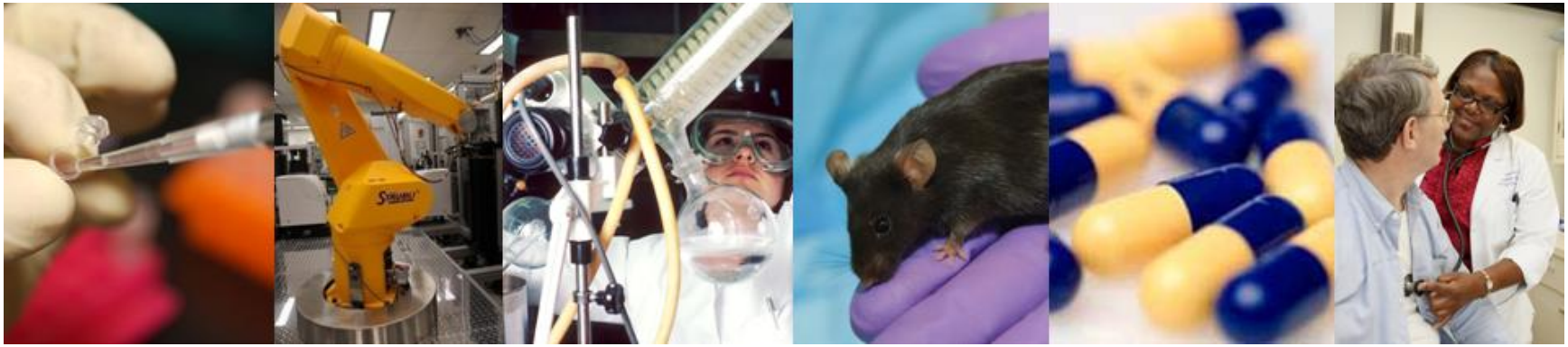
NCATS

NIH National Center for Advancing Translational Sciences





NCATS Mission



To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

What is Translation?

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.

What is Translational Science?

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

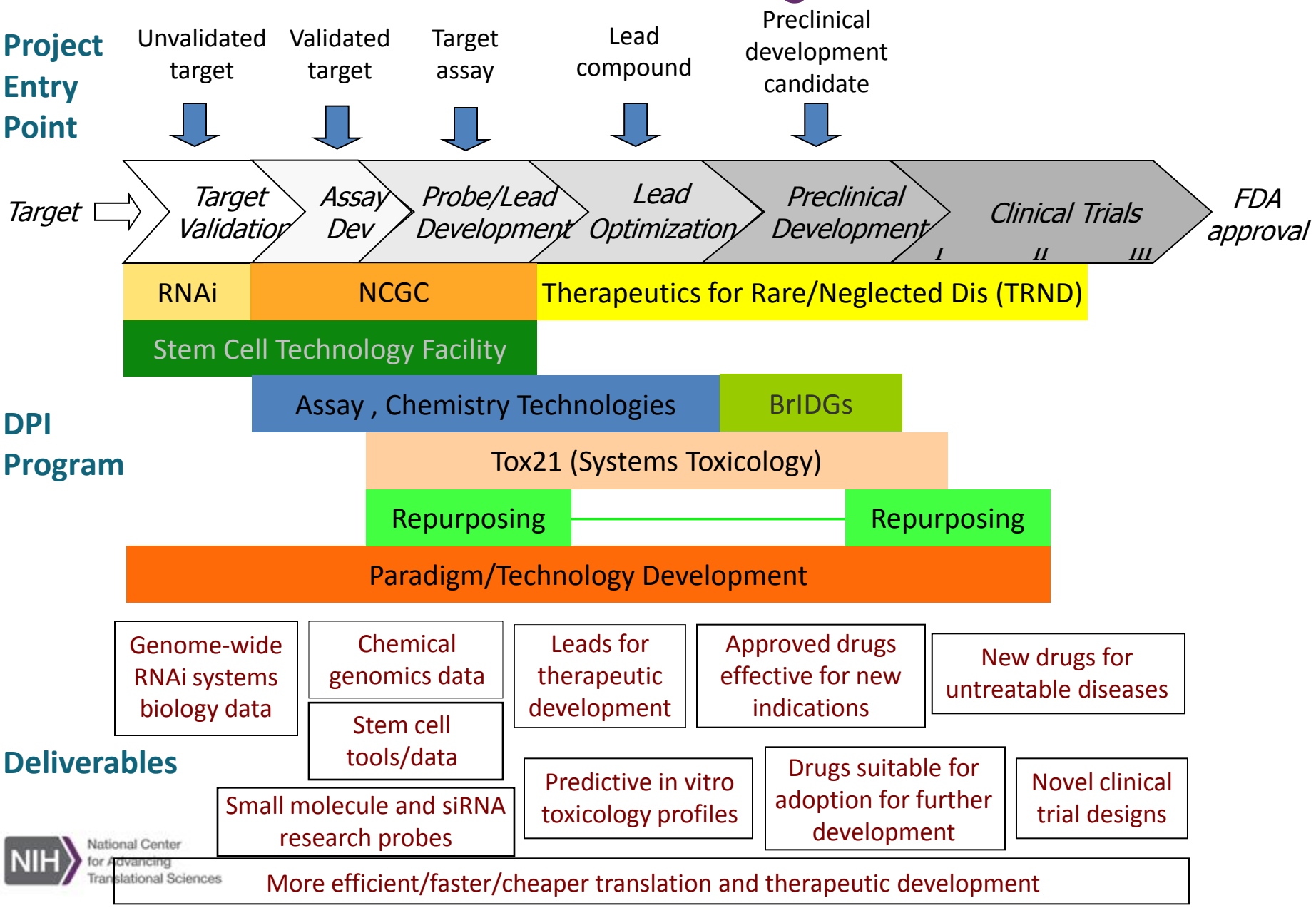
NCATS studies translation as a scientific and organizational problem.

Some of the translational problems on NCATS' to-do list

- Predictive toxicology
- Predictive efficacy
- Derisking undruggable targets/untreatable diseases
- Data interoperability
- Biomarker qualification process
- Clinical trial networks
- Patient recruitment
- Electronic Health Records for research
- Harmonized IRBs
- Clinical diagnostic criteria
- Clinical outcome criteria (e.g., PROs)
- Adaptive clinical trial designs
- Shortening time of intervention adoption
- Methods to better measure impact on health (or lack of)

NCATS Division of Preclinical Innovation

A Collaborative Engine



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Developing drugs for Galactosemia

NCATS collaboration with Kent Lai, University of Utah)

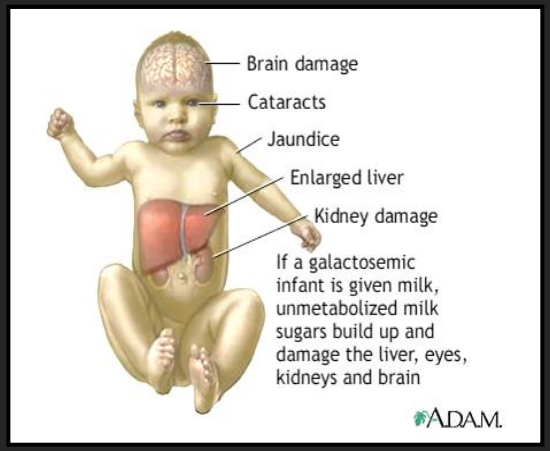
Rare autosomal recessive, metabolic disorder caused by GALT deficiency (1 in 60,000)

Currently diagnosed by testing newborns for GALT activity and galactose in blood spot test

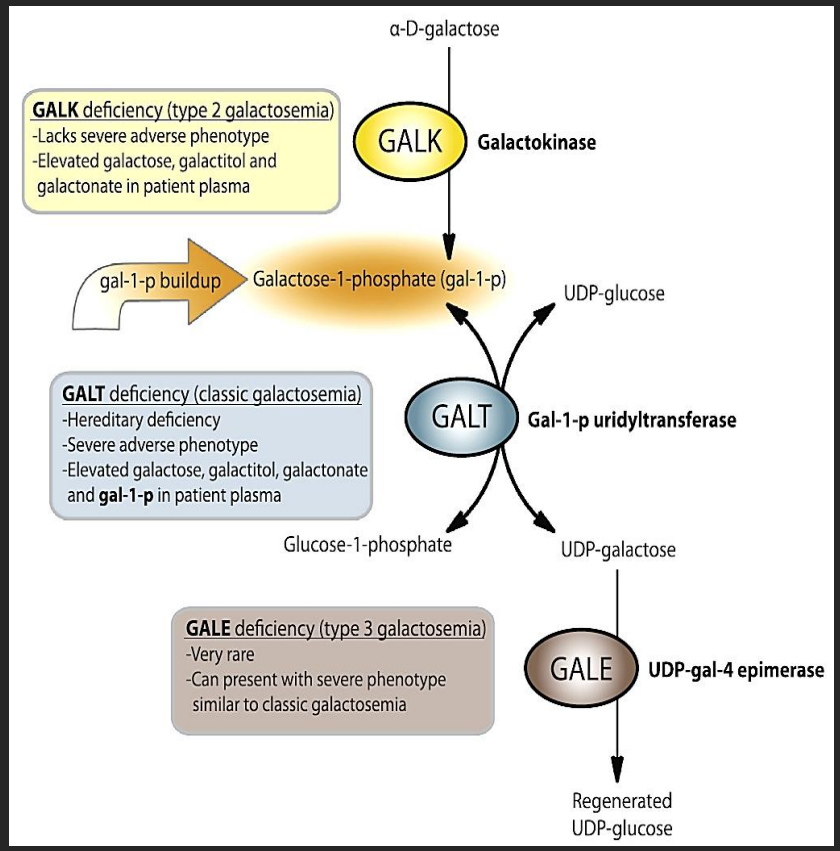
Only treatment is to restrict galactose & lactose

mortality if untreated

Chronic complications



Leloir Pathway



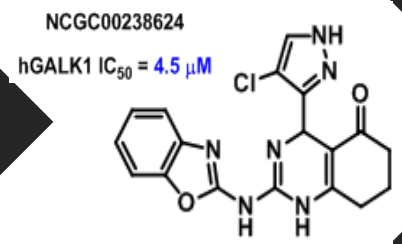
Hypothesis: inhibition of **GALK** could prevent toxic buildup of gal-1-p and improve patient outcomes

DEVELOPMENT OF GALK INHIBITORS

High-throughput screen

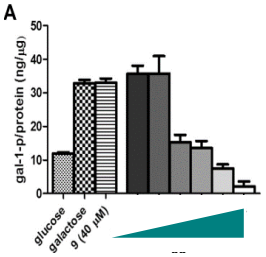
- 280,000+ compounds screened
- Single chemical series identified

Selective GALK inhibition



- Inactive against GALK2
- Clean in Kinome panel

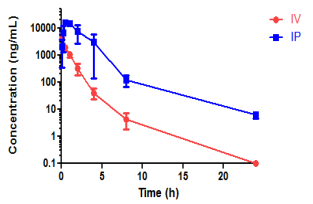
Cellular efficacy



- Decreases gal-1-p levels in patient cells
- No effect on cell viability

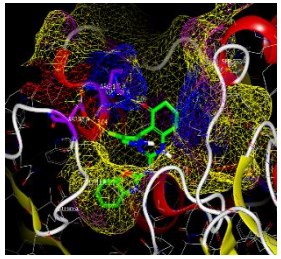
Medicinal chemistry optimization of series (GALK activity, ADME/PK properties)

Pharmacokinetic profiling



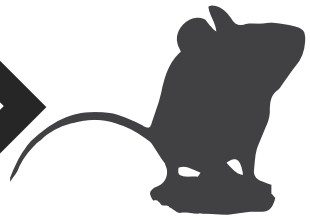
- Single chemical series identified
- Possesses acceptable PK profile

Co-crystal



- Inhibitor/GALK co-crystal structure resolved

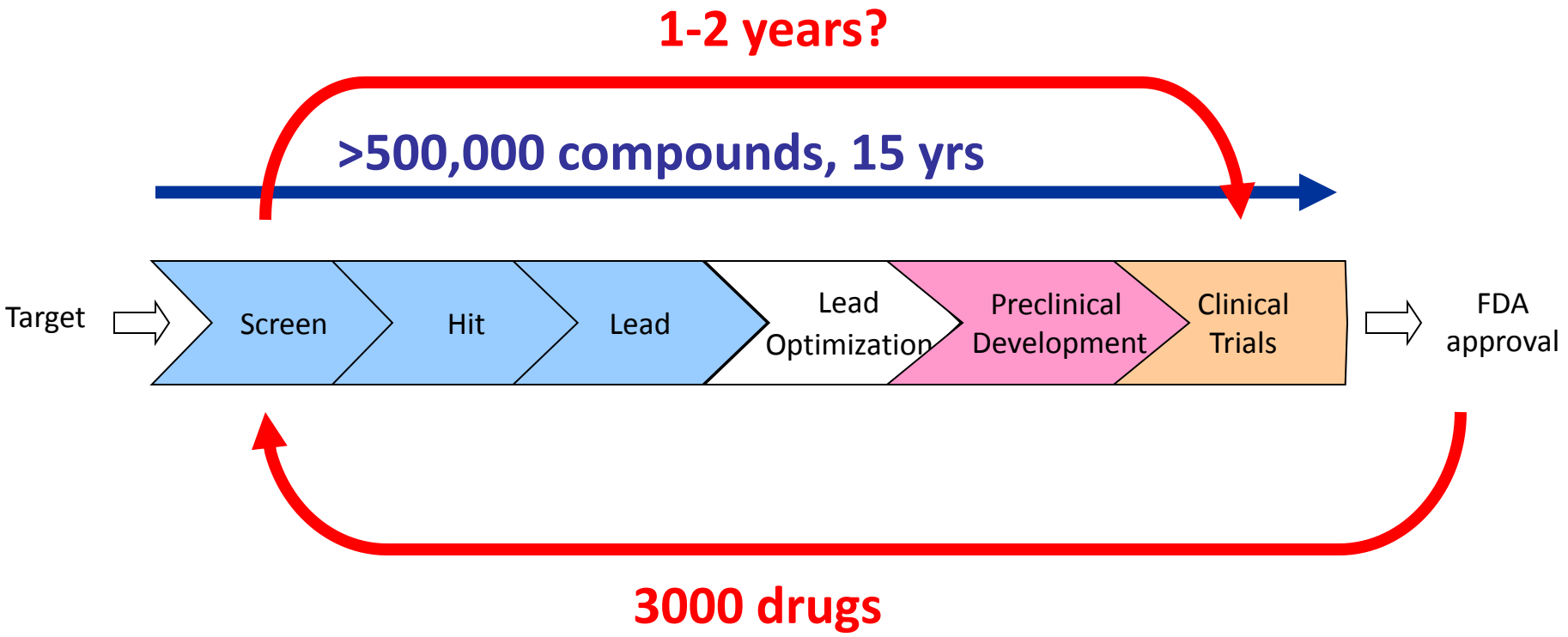
Galactosemia mouse



- Only mouse model for galactosemia that closely mimics the human phenotype
- Compounds currently being tested

GOAL: Preclinical development

Drug Repurposing



NCATS Comprehensive Repurposing Program
"Systematizing Serendipity"

The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.

Patient-Driven Science

ACS chemical biology

Articles

pubs.acs.org/acschemicalbiology

Identification of Drug Modulators Targeting Gene-Dosage Disease CMT1A

Sung-Wook Jang,[†] Camila Lopez-Anido,[§] Ryan MacArthur,[†] John Svaren,[§] and James Inglese*[,†,‡]

[†]National Center of Advancing Translational Sciences and [‡]National Human Genome Research Institute, National Institutes of Health, Bethesda,

[§]Department of Cc

Cancer Biology & Therapy 14:7, 638–647; July 2013; © 2013 Landes Bioscience

Supporting In

ABSTRACT: T
Schwann cells i
required for pro
adequate expres
myelin protein
resulting from it
been directly ass
Charcot-Marie-T
prevalent type
transcriptional
CMT1A, we de
reporter assays,
(βLac), capable
Each compound
pharmacological
independent counter-screen for cytotoxicity, the design of our orthogon
prioritization of active compounds, among which three drugs (fenretini
of endogenous Pmp22 mRNA and protein. Overall, the findings of this
for gene-dosage diseases such as CMT1A.

Identification of repurposed small molecule drugs for chordoma therapy

Menghang Xia,[1,†,*] Ruili Huang,[1,†] Srilatha Sakamuru,[1] David Alcorta,[2] Ming-Hsuang Cho,[1] Dae-Hee Lee,[3] Deric M Park,[3] Michael J Kelley,[2] Josh Sommer,[4] and Christopher P Austin[1]

[1]NIH Chemical Genomics Center; Nati
[2]Department of Medicine; Duke University;

nature COMMUNICATIONS

Keywords: chordoma, NCGC

ARTICLE

Received 4 Mar 2013 | Accepted 23 May 2013 | Published 28 Jun 2013

DOI: 10.1038/ncomms3044

Induction and reversal of myotonic dystrophy type 1 pre-mRNA splicing defects by small molecules

Jessica L. Childs-Disney[1,*], Ewa Stepniak-Konieczna[2,*], Tuan Tran[1,3,*], Ilyas Yildirim[4], HaJeung Park[1], Catherine Z. Chen[5], Jason Hoskins[6], Noel Southall[5], Juan J. Marugan[5], Samarjit Patnaik[5], Wei Zheng[5], Chris P. Austin[5], George C. Schatz[4], Krzysztof Sobczak[2], Charles A. Thornton[6] & Matthew D. Disney[1]

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Partnering with Disease Foundations to Speed Drug Discovery

When scientists who specialize in drug development have a promising idea for a new disease treatment, they often start by designing biological tests called assays. By using high-throughput (robotically assisted) screening, researchers use the assays to evaluate hundreds of thousands of compounds with the potential to become new treatments. This complex process requires teamwork to involve the right types of expertise and perspectives in the research project team.

Designing high-throughput screening assays is a science in itself. The team must have in-depth familiarity not only with assay technology but also with the target disease and its unique challenges. When the disease is rare, limited information can present additional challenges.

As director of NCATS' Assay Development and Screening Technology Laboratory, Jim Inglese, Ph.D., leads a team of experts who take on these challenges every day. To increase the likelihood of success, Inglese encourages postdoctoral researchers who are knowledgeable about specific diseases to join project teams through fellowships sponsored by patient groups and foundations.

These fellows bring strong disease expertise to NCATS, where Inglese mentors them in broad translational capabilities including assay development and early drug discovery. The overall goal is to develop new technologies and methods to build better disease models that can help advance the search for potential treatments.

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

Charcot-Marie-Tooth Association

Michael J. Fox Foundation

Hannah's Hope

Lori Sames, founder of Hannah's Hope Fund, and her daughter Hannah, who has giant axonal neuropathy, a progressive neurological condition. (Lori Sames Photo)

Hannah's Hope Fund

Alpha-1 Foundation

http://ncats.nih.gov/pubs/features/adst-fellows

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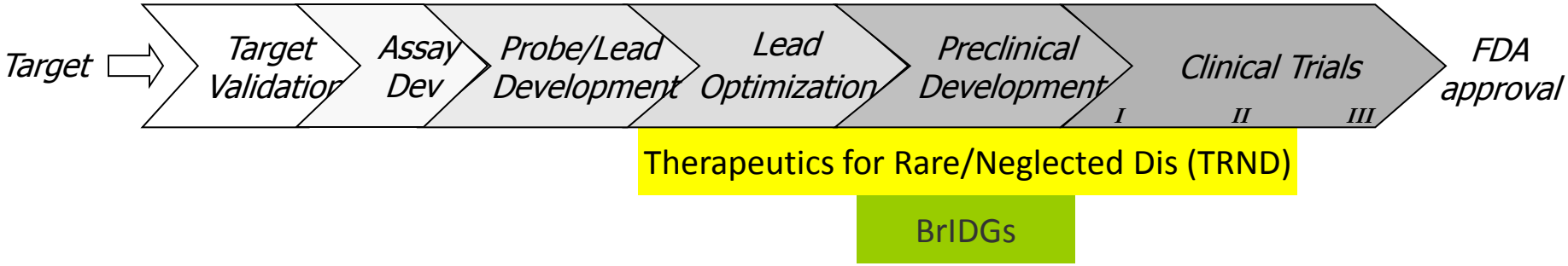
NCATS Therapeutics Development Programs

Therapeutics for Rare and Neglected Diseases (TRND)
Bridging Interventional Development Gaps (BrIDGs)



Model: Collaboration between NCATS labs with preclinical drug development expertise and external organizations with disease area/target expertise

Projects:

- Disease must meet FDA Orphan or WHO NTD criteria
- Entry from Probe to IND-enabling
- Exit by adoption by external organization for completion of clinical development
- Serve to develop new generally applicable platform technologies and paradigms

Eligible Collaborators:

- Academic, Non-Profit, Government Lab, Biotech, Pharma
- International applications accepted

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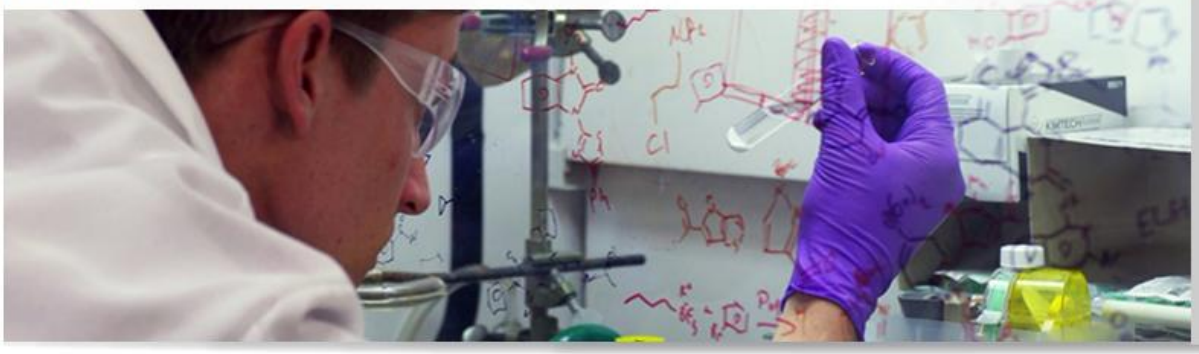
Submit a Pre-Clinical Collaboration Proposal

NCATS is accepting proposals on a rolling basis to collaborate with BrIDGs and TRND program scientists.

More...



Work with Us

The TRND program is designed to encourage and speed the development of new treatments for diseases with high unmet medical needs. Find project details, scientific capabilities, information for applicants and more.

Contact TRND

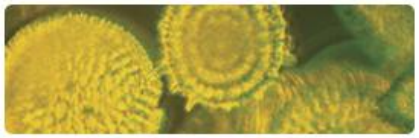
Therapeutics for Rare and Neglected Diseases (TRND)

Access NCATS Expertise & Resources

Find NCATS Programs & Initiatives

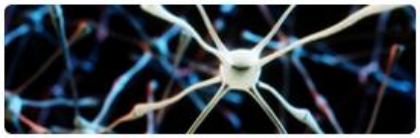
The TRND program supports pre-clinical development of therapeutic candidates intended to treat rare or neglected disorders, with the goal of enabling an Investigational New Drug (IND) application. Learn more.

About TRND



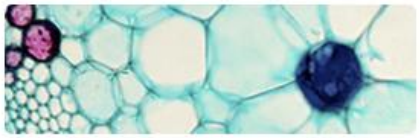
TRND supports pre-clinical development from lead optimization through IND

Scientific Capabilities



TRND offers world-class in-house experts and connections to external resources

Work with TRND

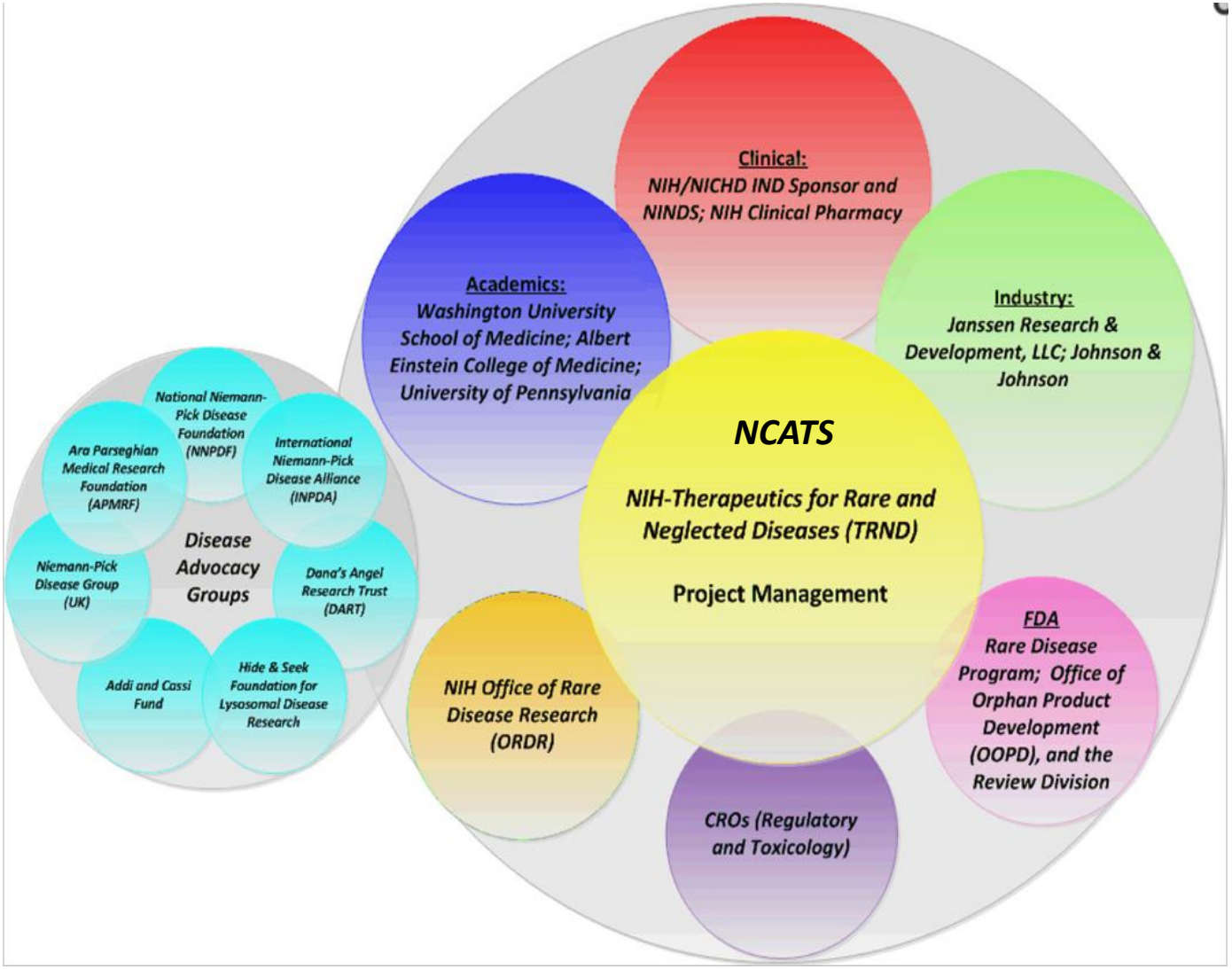


Partner with TRND to create and implement a therapeutic project plan for

TRND Projects

Explore active and completed therapeutic development projects supported by TRND

TRND Niemann-Pick C Disease Collaborative

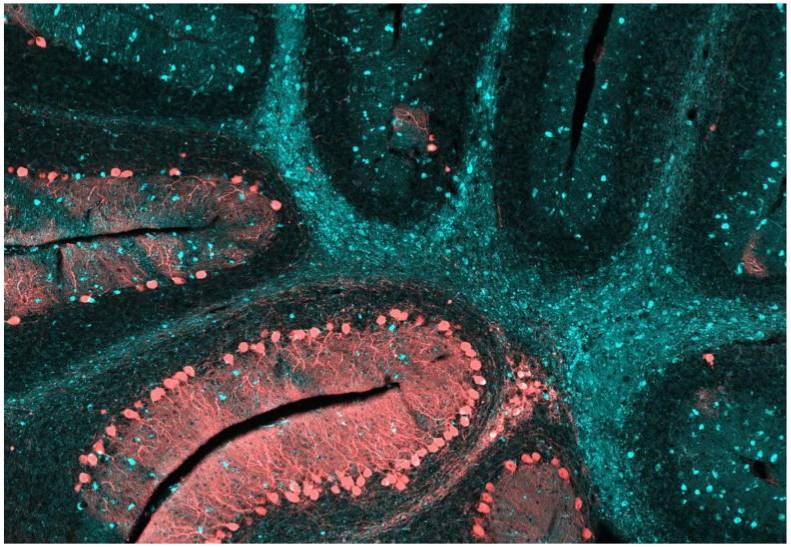


Ottinger et al., Curr Top Med Chem 2014;14(3):330

NEWS RELEASES

Wednesday, January 7, 2015

NIH teams with industry to develop treatments for Niemann-Pick Type C disease.



This image shows the cerebellum of a brain affected by NPC at the end stage of the disease. The blue staining shows the dense pockets of lipid accumulations throughout the brain. *NICHD*

Researchers from the National Institutes of Health have entered into an agreement with biotechnology company Vtesse, Inc., of Gaithersburg, Maryland, to develop treatments for Niemann-Pick disease type C (NPC) and other lysosomal storage disorders.

Lysosomal storage diseases, also known as lipid storage diseases, comprise about 50 rare inherited disorders that usually affect children. Fatty materials accumulate in the cells and tissues of the body. These diseases can result in damage to the brain, peripheral nervous system, liver, and other organs and tissues; they are often fatal.

Researchers at the National Center for Advancing Translational Sciences (NCATS) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), both parts of NIH, will conduct studies on NPC and other lysosomal storage disorders with funding provided by Vtesse.

"This is an excellent example of how launching a project to study the underlying biology of one disease can lead to advances that hold promise for an entire group of diseases — the NCATS goal of finding what is common among diseases and the translational science process," said NCATS Director Christopher P. Austin, M.D. "I am grateful to all of the NPC patients, their families and patient support groups who have been equal partners in our efforts to find therapeutic solutions to these devastating disorders."

> *"Our role is to test promising new drugs and therapies to ensure that they are safe and effective."*
>
> **—Forbes D. Porter, M.D., Ph.D.**
> NICHD Clinical Director

Institute/Center

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

National Center for Advancing Translational Sciences (NCATS)

Contact

NCATS Office of Communications
301-435-0888

NICHD Press Office
Meredith Daly
301-496-5134

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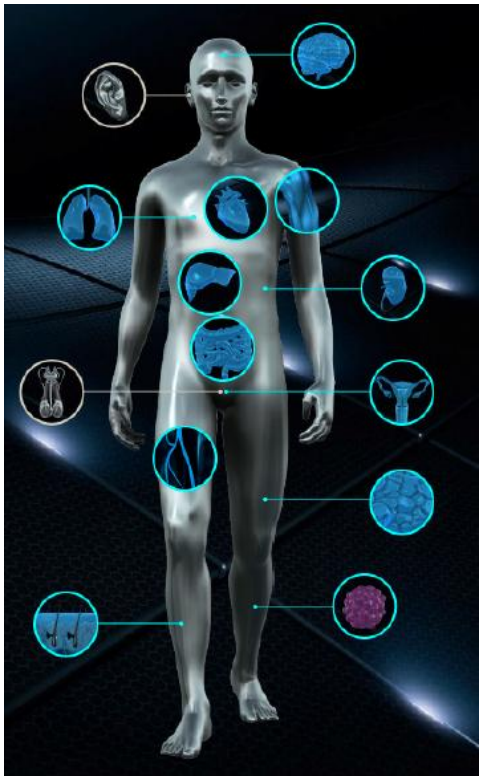
Microphysiological System (Tissue Chips) Program

GOAL: Develop an *in vitro* platform that uses human tissues to evaluate the efficacy, safety and toxicity of promising therapies.



NIH National Institutes of Health

Phase 1: Development

Phase 2: Cell incorporation & organ integration

2012-13 → 2013-14 → 2014-15 → 2015-16 → 2016-17

NIH National Institutes of Health

$75 M over 5 years – cell source, platform development, validation and integration

DARPA

$75 M over 5 years – platform dev

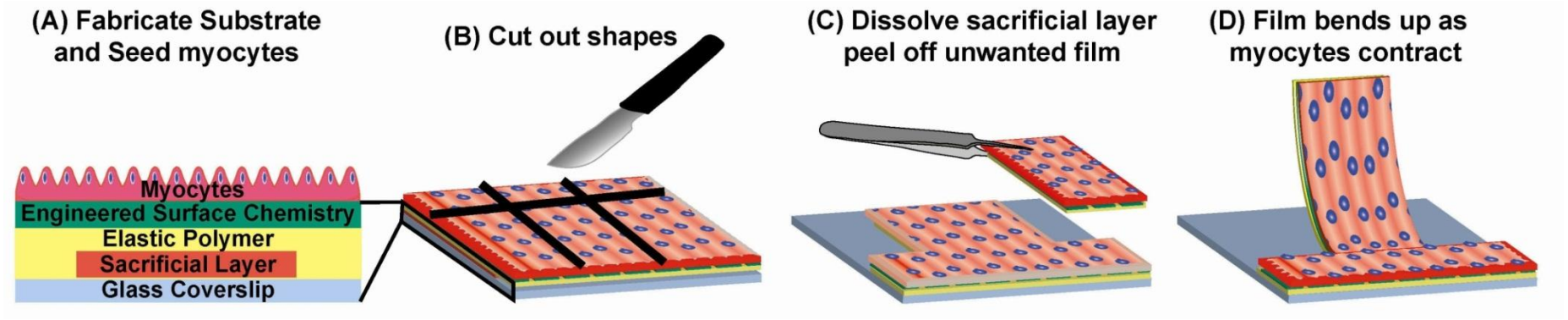
FDA

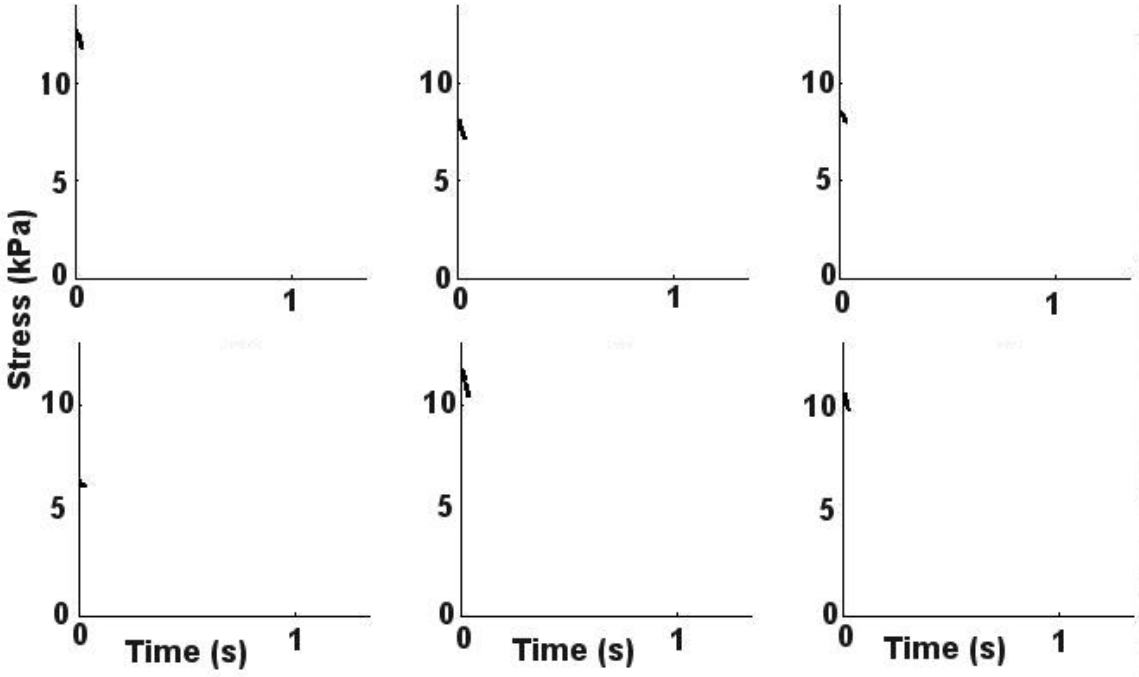
****FDA provides insight and expertise throughout the program**

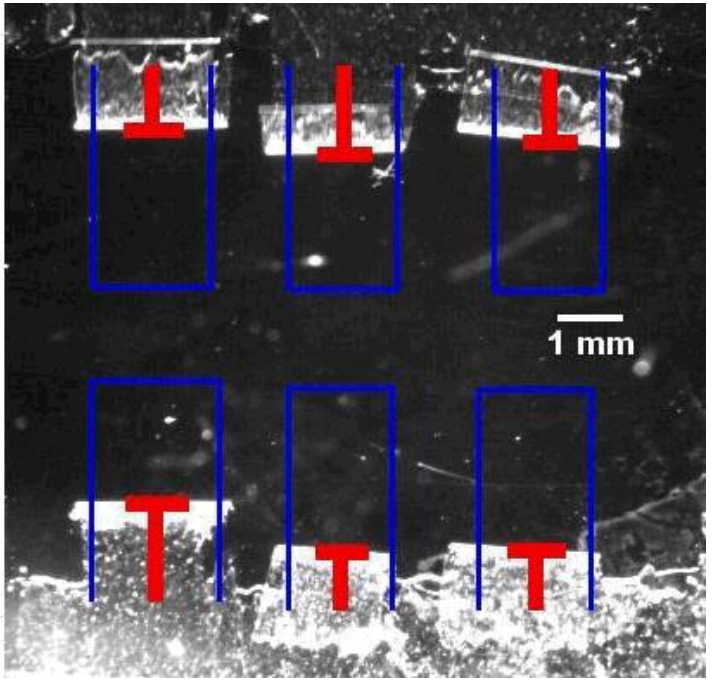
Current Goals:

- Integration
- Compound testing
- Validation
- Partnerships
- Adoptions of the tech to the community

Engineered Cardiac Muscular Thin Films







Film length
Automatic projection tracking

Data provided by Dr. Kit Parker, Wyss Institute

National Center for Advancing Translational Sciences

Science 2007;317:1366
Lab Chip 2011;11:4165

Biomaterials 2010;31:3613
J Pharm Tox Methods 2012;65:126

What is Barth Syndrome?

Barth syndrome (BTHS; OMIM #302060) is a rare, life-threatening genetic disorder primarily affecting males around the world. It is caused by a mutation in the *tafazzin* gene *(TAZ,* also called G4.5), resulting in an inborn error of lipid metabolism.

Though not always present, cardinal characteristics of this multi-system disorder often include combinations and varying degrees of:

- **Cardiomyopathy**
  (Usually dilated with variable myocardial hypertrophy, sometimes with left ventricular noncompaction and/or endocardial fibroelastosis)
- **Neutropenia**
  (Chronic, cyclic, or intermittent)
- **Underdeveloped skeletal musculature and muscle weakness**
- **Growth delay**
  (Growth pattern similar to but often more severe than constitutional growth delay)
- **Exercise intolerance**
- **Cardiolipin abnormalities**
- **3-methylglutaconic aciduria**
  (Typically a 5- to 20-fold increase)

Devin (age 9) and Henry (age 5).

Important Clinical Problems May Include (in varying severity):

- Congestive heart failure
- Life-threatening bacterial infection
- Gross motor delay
- Risk of fatal arrhythmia
- Short stature in the early years, followed by accelerated growth in mid- to late puberty
- Extreme fatigue
- Diarrhea and/or constipation
- Feeding problems (*e.g.*, difficulty sucking, swallowing, or chewing; aversion to some food textures; selective or picky eating)
- Recurrent mouth ulcers
- Risk of thrombosis
- Diminished capacity for exercise
- Hypoglycemia, including fasting hypoglycemia (especially in the newborn period)
- Chronic headache, abdominal pain, and/or body aches (especially during puberty)
- Osteoporosis
- Some mild learning disabilities

Will (age 27) and John (age 31) at BSF's 2012 Conference.

"The Barth Syndrome Foundation has saved my life due to some clinical information that was shared through the organization. Beyond the clinical impact that the BSF has had on my life, the foundation has also been a haven of understanding and social support as well as providing a built-in group of friends."
~ Will, age 27, Affected Individual

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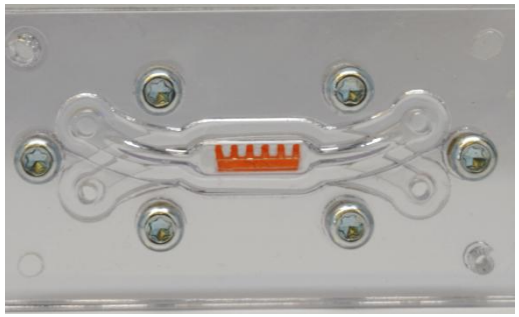
Heart on a Chip Barth Model

A



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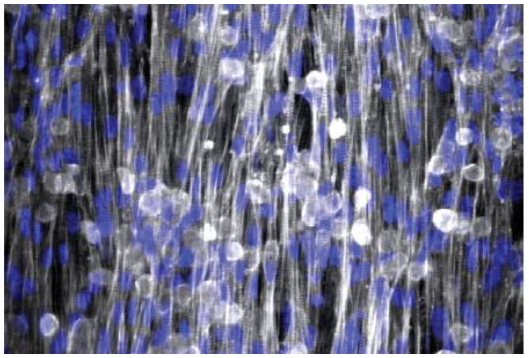

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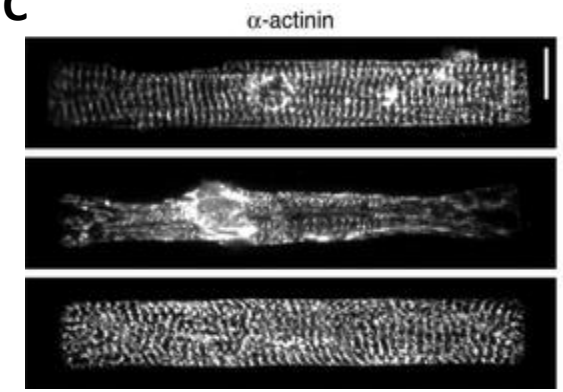

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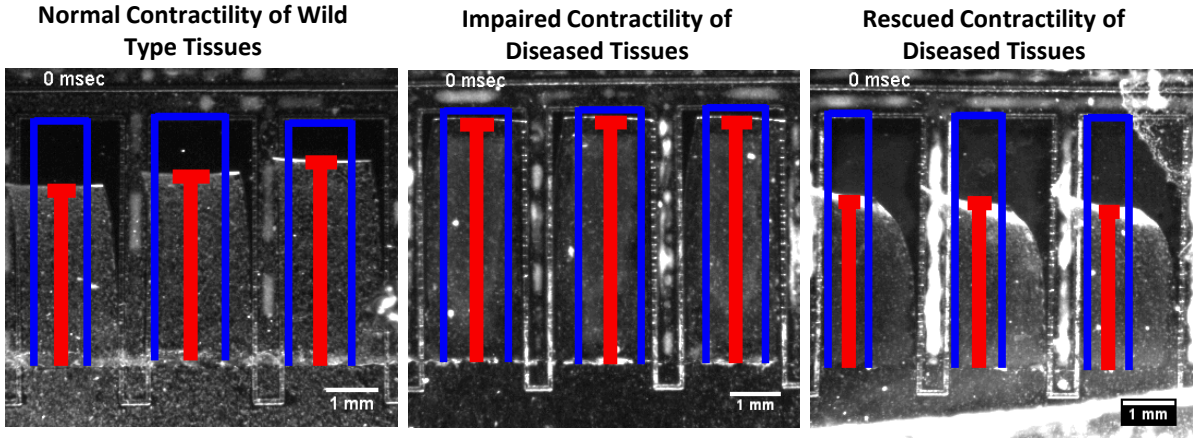

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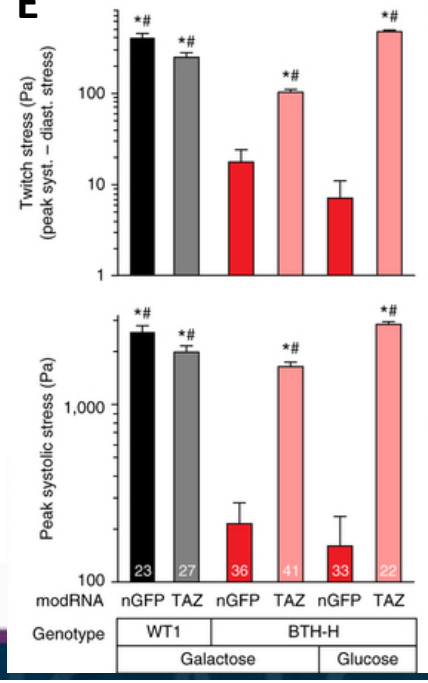

Dr. Kevin Parker, Harvard University:
http://diseasebiophysics.seas.harvard.edu

The Future: The Biomedical Data Translator

NCATS launched the Biomedical Data Translator program as a multiyear, iterative effort toward the eventual development of a comprehensive, relational, N-dimensional "data translator" that integrates multiple types of existing data sources. These sources may include objective signs and symptoms of disease, drug effects, and intervening types of biological data relevant to understanding pathophysiology. The Translator could enable a significant shift from the current symptom-based diagnosis of disease classification to one that is based on a set of molecular and cellular abnormalities that can be targeted by various preventative and therapeutic interventions.

Watch this video to hear NCATS Director Christopher P. Austin, M.D., explain the purpose and goals of the Biomedical Data Translator program.

https://ncats.nih.gov/translator/about

NCATS Funds Feasibility Assessment for Biomedical Data Translator

The goal is to identify and design innovative tools to integrate and leverage vast amounts of medical research data.

More...

Work with Us

Learn more about how you can access funding and collaborate with NCATS through the Biomedical Data Translator program.

Contact Translator staff

Biomedical Data Translator Program

Access NCATS Expertise & Resources

Find NCATS Programs & Initiatives

NCATS launched the Biomedical Data Translator (Translator) program to accelerate biomedical translation for the research community. Through this program, NCATS will integrate existing biomedical data to help reveal new relationships within those data and also identify novel opportunities for research. Learn more.

About Biomedical Data Translator

Learn more about the Biomedical Data Translator program and its objectives.

Funding Information

Find out how to apply for Biomedical Data Translator funding.

Translator Projects

Access details about ongoing Biomedical Data Translator projects.

Learn More About NCATS

Website: www.ncats.nih.gov

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