The National Center for Advancing Translational Sciences

Catalyzing Translational Innovation

CHRISTOPHER P. AUSTIN, M.D.
DIRECTOR, NCATS

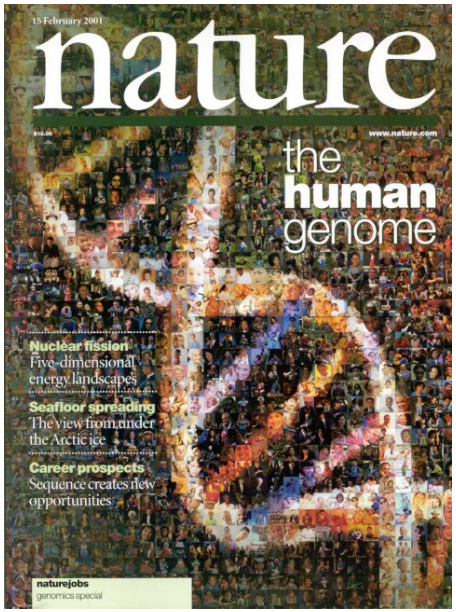
STANFORD DRUG DISCOVERY CONFERENCE
MARCH 29, 2016

NCATS

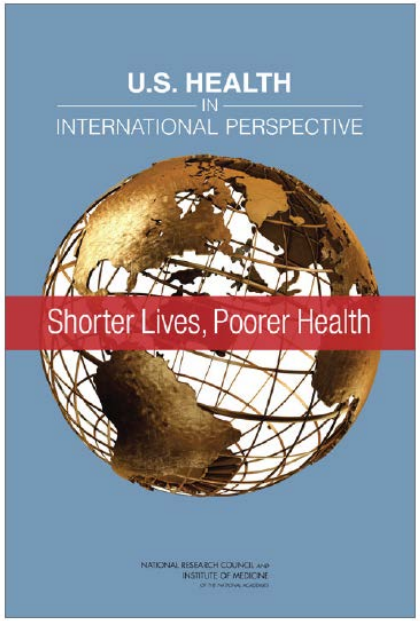
NIH National Center for Advancing Translational Sciences

The Best of Times, the Worst of Times

Fundamental science unprecedentedly advanced, but:



- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Drug/device/diagnostic development expensive and failure-prone
- Clinical trials system inefficient
- Poor adoption of demonstrably useful interventions



People unhealthier and funders of biomedical research enterprise (public and private) impatient

Human Conditions with Known Molecular Basis

Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome

SO....

Reprinted from SCIENCE, November 25, 1949, Vol. 110, No. 2865, pages 543–548.

Sickle Cell Anemia, a Molecular Disease[1]

Linus Pauling, Harvey A. Itano,[2] S. J. Singer,[2] and Ibert C. Wells[3]

Gates and Crellin Laboratories of Chemistry,
California Institute of Technology, Pasadena, California[4]

THE ERYTHROCYTES of certain individuals possess the capacity to undergo reversible changes in shape in response to changes in the partial pressure of oxygen. When the oxygen pressure is lowered, these cells change their forms from the normal biconcave disk to crescent, holly wreath, and other forms. This process is known as sickling. About 8 percent of American Negroes possess this characteristic; usually they exhibit no pathological consequences ascribable to it. These people are said to have sicklemia, or sickle cell trait. However, about 1 in 40 (*4*) of these individuals whose cells are capable of sickling suffer from a severe chronic anemia resulting from excessive destruction of their erythrocytes; the term sickle cell anemia is applied to their condition.

The main observable difference between the erythrocytes of sickle cell trait and sickle cell anemia has been that a considerably greater reduction in the partial pressure of oxygen is required for a major fraction of the trait cells to sickle than for the anemia cells (*11*). Tests *in vivo* have demonstrated that between 30 and 60 percent of the erythrocytes in the venous circulation of sickle cell anemic individuals, but less than 1 percent of those in the venous circulation of sicklemic individuals, are normally sickled. Experiments *in vitro* indicate that under sufficiently low oxygen pressure, however, all the cells of both types assume the sickled form.

The evidence available at the time that our investigation was begun indicated that the process of sickling might be intimately associated with the state and the nature of the hemoglobin within the erythrocyte. Sickle cell erythrocytes in which the hemoglobin is combined with oxygen or carbon monoxide have the biconcave disk contour and are indistinguishable in that form from normal erythrocytes. In this condition they are termed promenisocytes. The hemoglobin appears to be uniformly distributed and randomly oriented within normal cells and promenisocytes, and no birefringence is observed. Both types of cells are very flexible. If the oxygen or carbon monoxide is removed, however, transforming the hemoglobin to the uncombined state, the promenisocytes undergo sickling. The hemoglobin within the sickled cells appears to aggregate into one or more foci, and the cell membranes collapse. The cells become birefringent (*11*) and quite rigid. The addition of oxygen or carbon monoxide to these cells reverses these phenomena. Thus the physical effects just described depend on the state of combination of the hemoglobin, and only secondarily, if at all, on the cell membrane. This conclusion is supported by the observation that sickled cells when lysed with water produce discoidal, rather than sickle-shaped, ghosts (*10*).

It was decided, therefore, to examine the physical and chemical properties of the hemoglobins of individuals with sicklemia and sickle cell anemia, and to compare them with the hemoglobin of normal individuals to determine whether any significant differences might be observed.

EXPERIMENTAL METHODS

The experimental work reported in this paper deals largely with an electrophoretic study of these hemoglobins. In the first phase of the investigation, which concerned the comparison of normal and sickle cell anemia hemoglobins, three types of experiments were performed: 1) with carbonmonoxyhemoglobins; 2) with uncombined ferrohemoglobins in the presence of dithionite ion, to prevent oxidation to methemoglobins; and 3) with carbonmonoxyhemoglobins in the presence of dithionite ion. The experiments of type 3 were performed and compared with those of type 1 in order to ascertain whether the dithionite ion itself causes any specific electrophoretic effect.

Samples of blood were obtained from sickle cell anemic individuals who had not been transfused within three months prior to the time of sampling. Stroma-free concentrated solutions of human adult hemoglobin were prepared by the method used by Drabkin (*3*). These solutions were diluted just before use with the

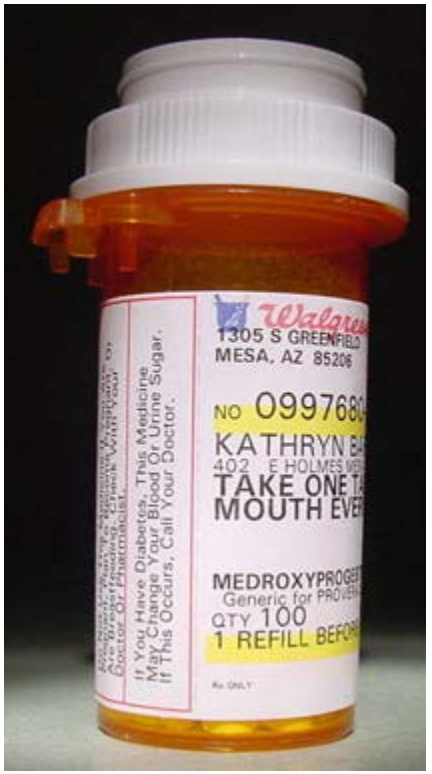
[1] This research was carried out with the aid of a grant from the United States Public Health Service. The authors are grateful to Professor Ray D. Owen, of the Biology Division of this Institute, for his helpful suggestions. We are indebted to Dr. Edward R. Evans, of Pasadena, Dr. Travis Winsor, of Los Angeles, and Dr. G. E. Burch, of the Tulane University School of Medicine, New Orleans, for their aid in obtaining the blood used in these experiments.

[2] U. S. Public Health Service postdoctoral fellow of the National Institutes of Health.

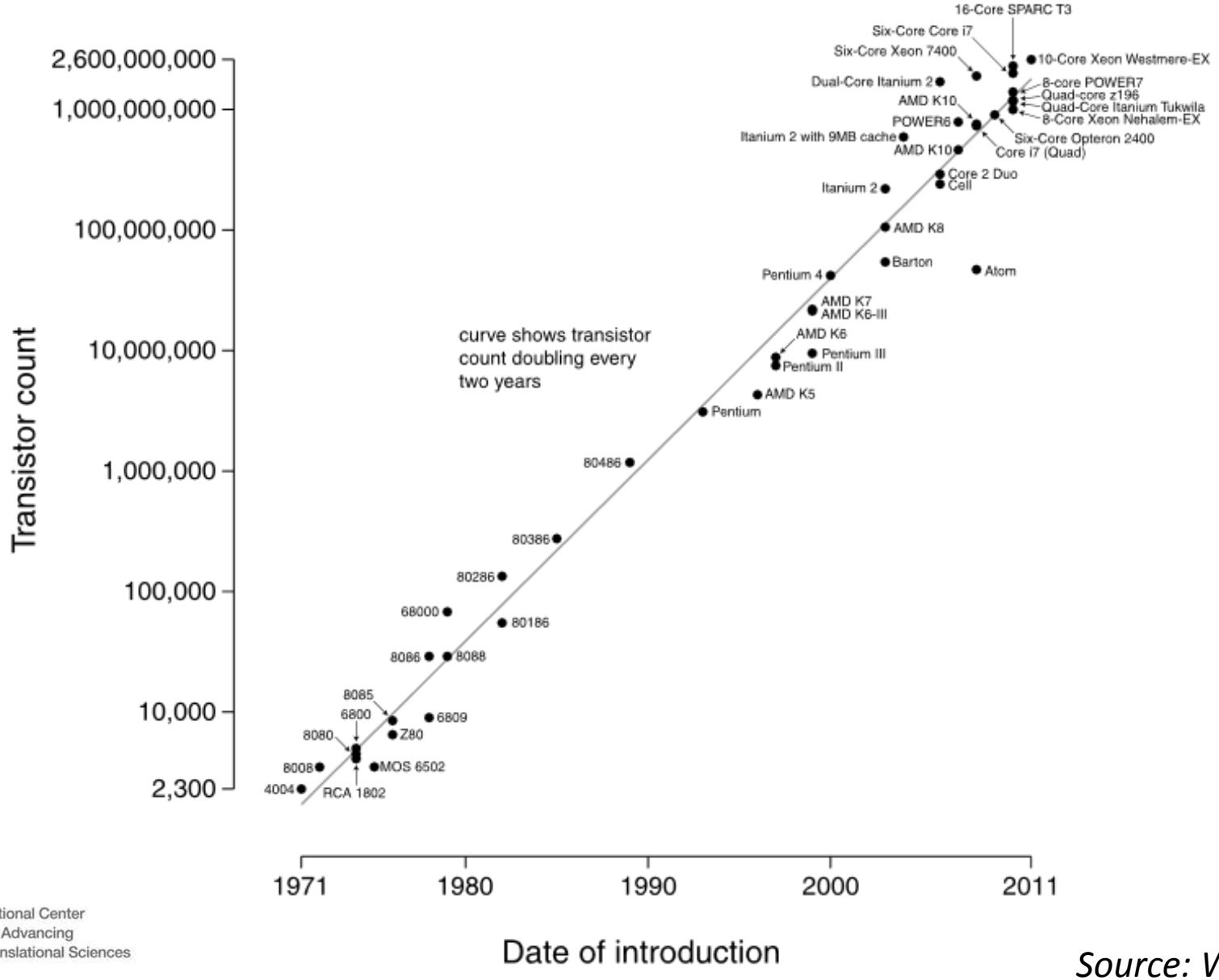
[3] Postdoctoral fellow of the Division of Medical Sciences of the National Research Council.

[4] Contribution No. 1333.

≠



Moore's Law



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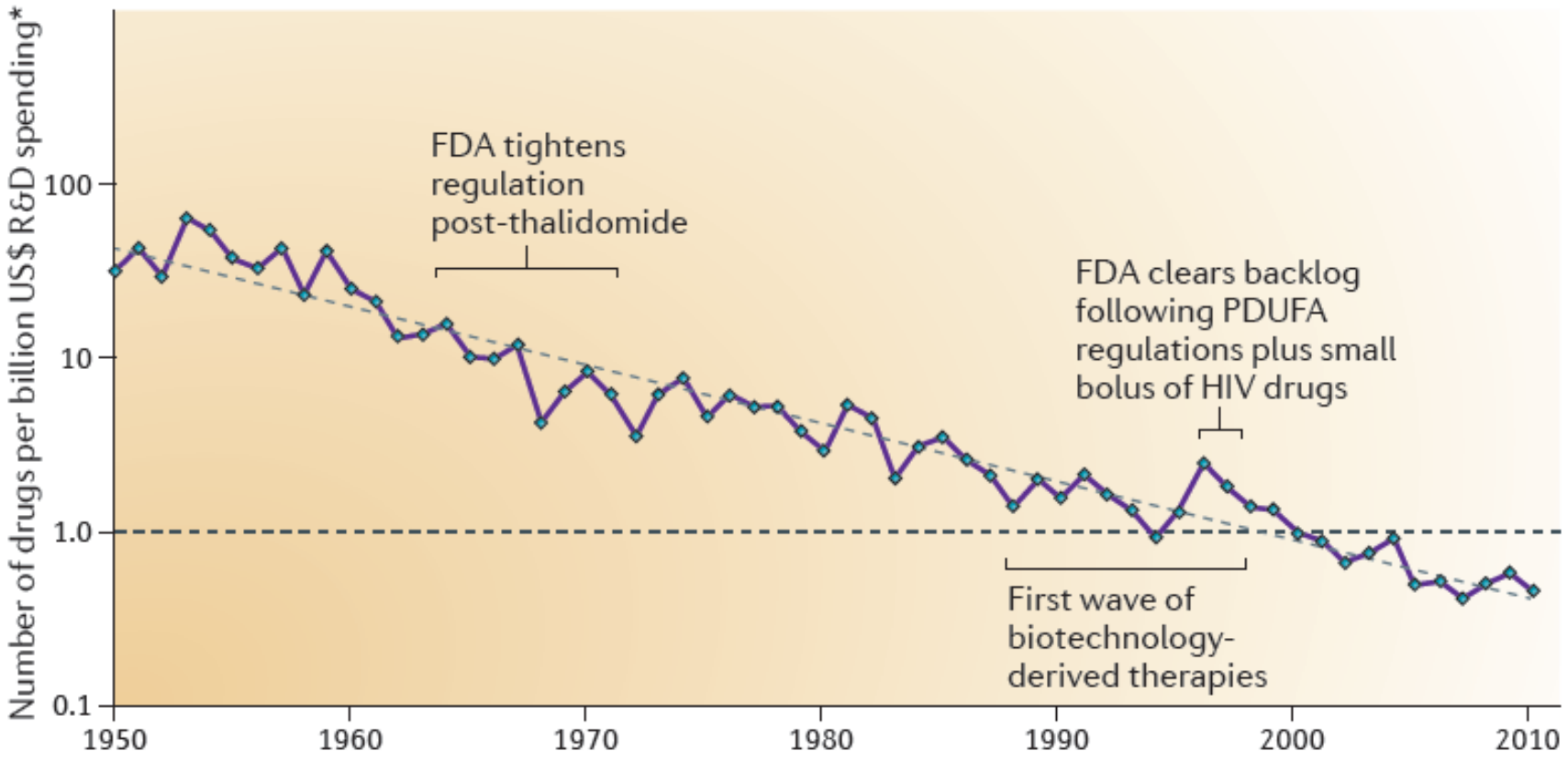
Source: Wikipedia

Eroom's Law



The number of new drugs approved by the FDA per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years since 1950.

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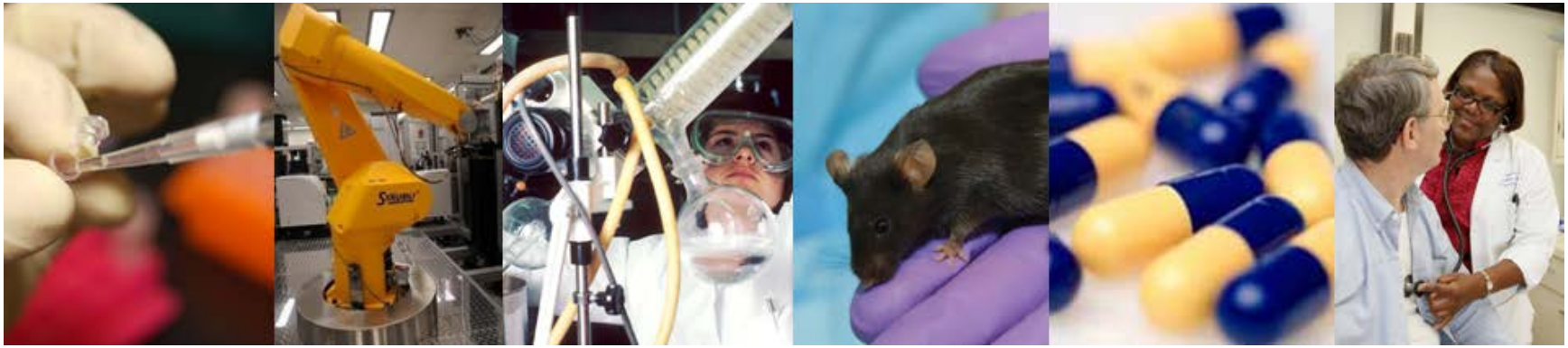
Scannell et al., *Nature Reviews Drug Discovery* 11:191, 2012

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.

NCATS Scientific Initiatives

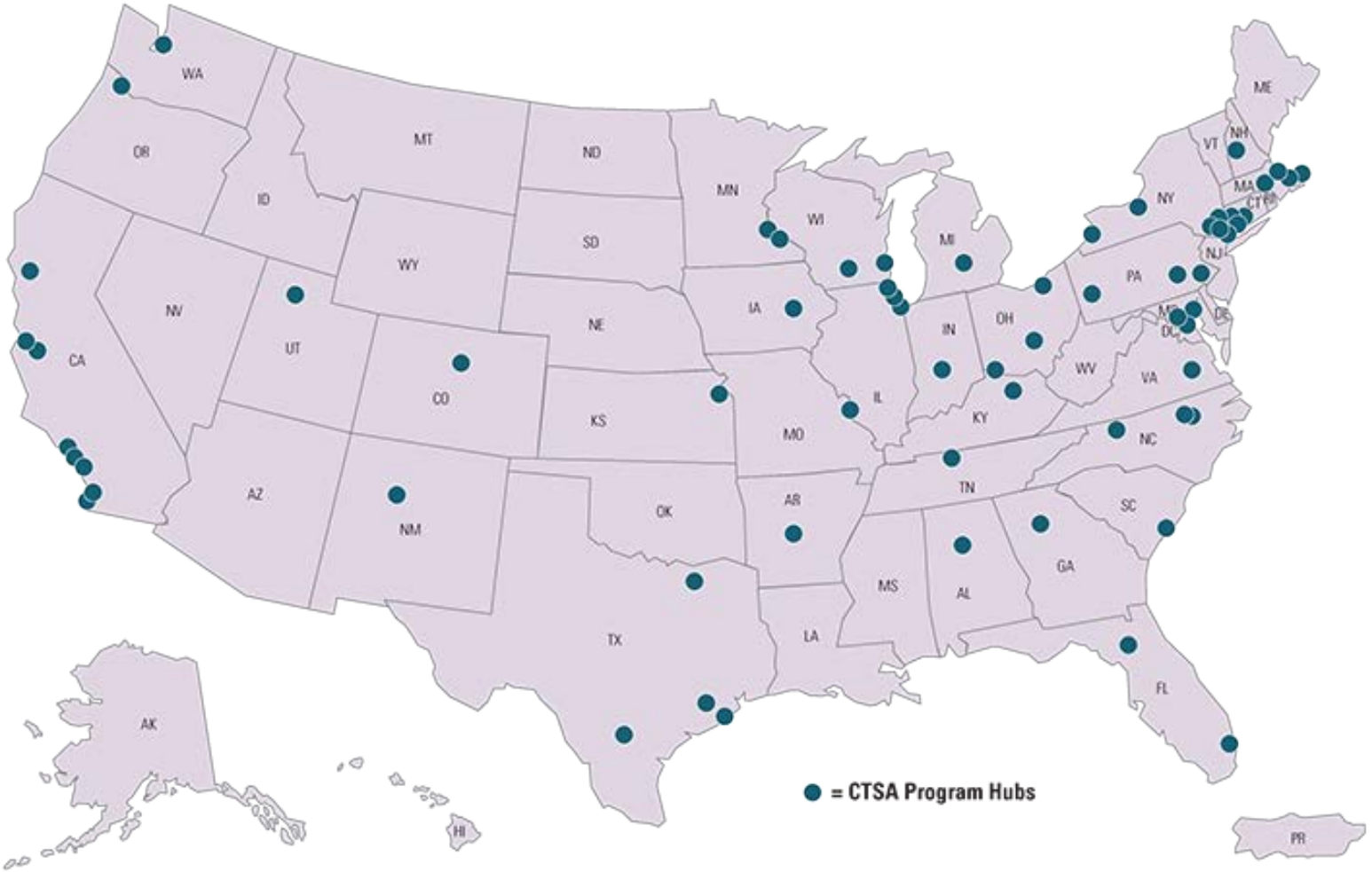
- **Clinical Translational Science**
  - » Clinical and Translational Science Awards
  - » Rare Disease Clinical Research Network
  - » New Therapeutic Uses program
- **Preclinical Translational Science**
  - » NCATS Chemical Genomics Center
  - » Therapeutics for Rare and Neglected Diseases program
  - » Bridging Interventional Development Gaps program
- **Re-engineering Translational Sciences**
  - » Toxicology in the 21st Century
  - » Microphysiological Systems (Tissue Chip) program
  - » Office of Rare Diseases Research

Division of Clinical Innovation

Clinical and Translational Science Awards (CTSA) Program

- A national consortium of medical research institutions
- Improves the way clinical and translational research is conducted nationwide
- Accelerates the research translation process
- Provides innovative training for clinical and translational researchers

The NCATS
Clinical and Translational Science Awards Program
CTSA Hubs



Streamlining Clinical Study Startup

- Major causes of delayed startup
  - Duplicative IRB reviews among sites
  - Subcontracting harmonization
  - Duplicative investigator/site qualification
- Solutions
  - Centralized IRB review (reliance agreements, IT solutions)
  - Streamlined contracting (pre-negotiated master agreements)
  - GCP training across CTSA Program sites
- Progress
  - Nationwide IRB reliance agreement established
  - Contracting agreements established
  - Pan-CTSA Program Good Clinical Practice (GCP) training in progress
  - CTSA Trial Innovation Centers (TICs) anticipated start 2016

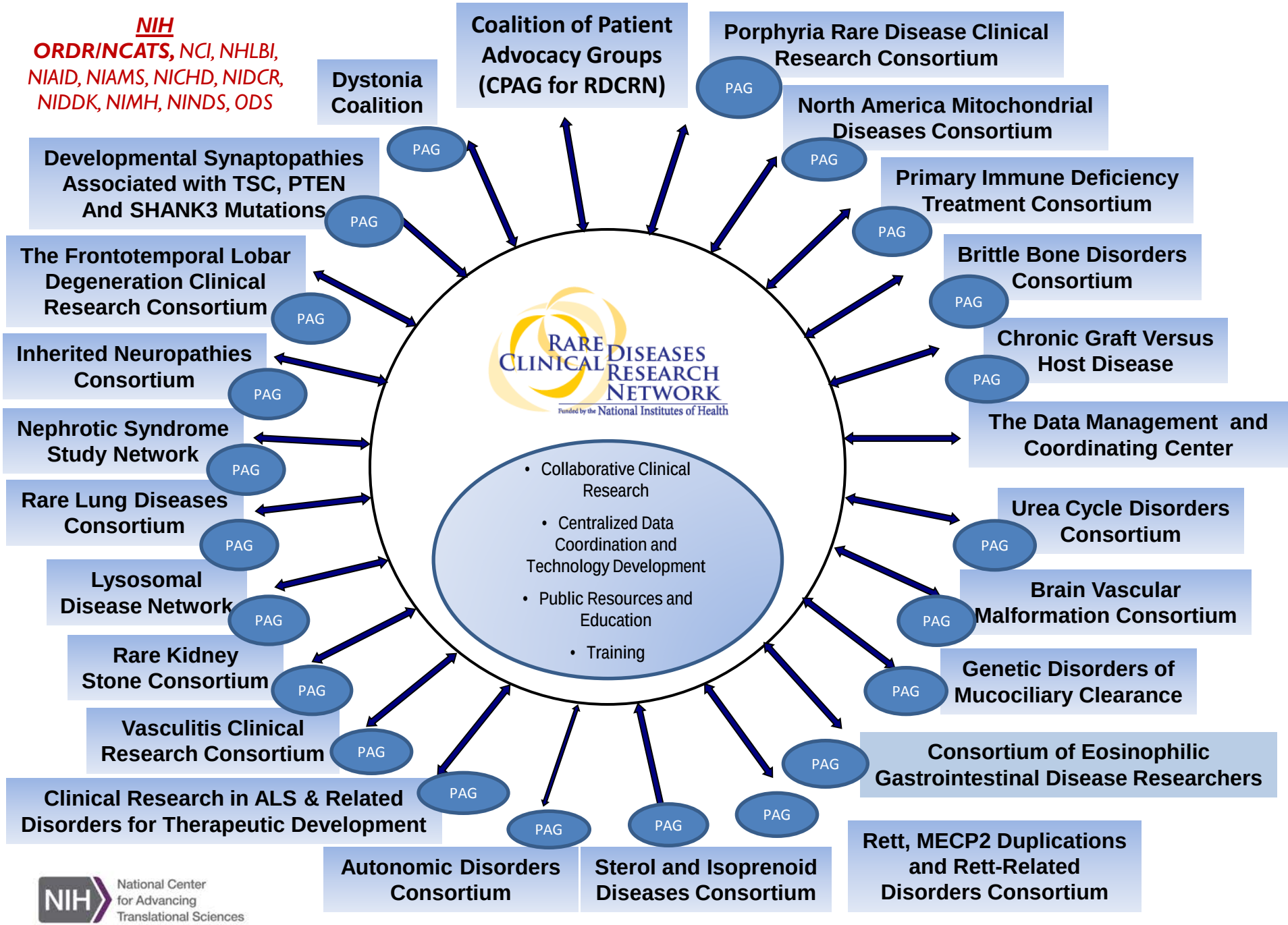
Improving Clinical Study Recruitment

- Problem: slow or failed recruitment leads to delays, inefficiency, increased costs
  - Informatics component: investigators can't find participants and vice-versa
  - Strategic component: lack of participant understanding and effective outreach strategies, particularly to underrepresented groups
- Solutions
  - National recruitment capacity across CTSA Program network using data from Electronic Health Record (EHR) to identify potential trial participants who meet entry criteria
  - Innovation in outreach and engagement
- Progress
  - Pilots to jump-start the initiative began mid-2014
  - CTSA Program Recruitment Innovation Centers (RICs) anticipated start 2016

https://www.act-network.org

Training the Translational Research Workforce

- Provide innovative, tailored curricula, including
  - Non-traditional areas such as regulatory science or entrepreneurship
  - Externships in industry, foundations, FDA, etc to enrich the training experience
  - Shared online courses/resources across CTSA network
- Foster multidisciplinary team science
- Create an environment in which translational research is a viable (and attractive!) career path


NIH
ORDR/NCATS, NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIDDK, NIMH, NINDS, ODS
Coalition of Patient Advocacy Groups (CPAG for RDCRN)
Porphyria Rare Disease Clinical Research Consortium
Dystonia Coalition
North America Mitochondrial Diseases Consortium
Developmental Synaptopathies Associated with TSC, PTEN And SHANK3 Mutations
Primary Immune Deficiency Treatment Consortium
The Frontotemporal Lobar Degeneration Clinical Research Consortium
Brittle Bone Disorders Consortium
Inherited Neuropathies Consortium
Chronic Graft Versus Host Disease
Nephrotic Syndrome Study Network
The Data Management and Coordinating Center
Rare Lung Diseases Consortium
Urea Cycle Disorders Consortium
Lysosomal Disease Network
Brain Vascular Malformation Consortium
Rare Kidney Stone Consortium
Genetic Disorders of Mucociliary Clearance
Vasculitis Clinical Research Consortium
Consortium of Eosinophilic Gastrointestinal Disease Researchers
Clinical Research in ALS & Related Disorders for Therapeutic Development
Autonomic Disorders Consortium
Sterol and Isoprenoid Diseases Consortium
Rett, MECP2 Duplications and Rett-Related Disorders Consortium
PAG
RARE CLINICAL DISEASES RESEARCH NETWORK
Funded by the National Institutes of Health
• Collaborative Clinical Research
• Centralized Data Coordination and Technology Development
• Public Resources and Education
• Training
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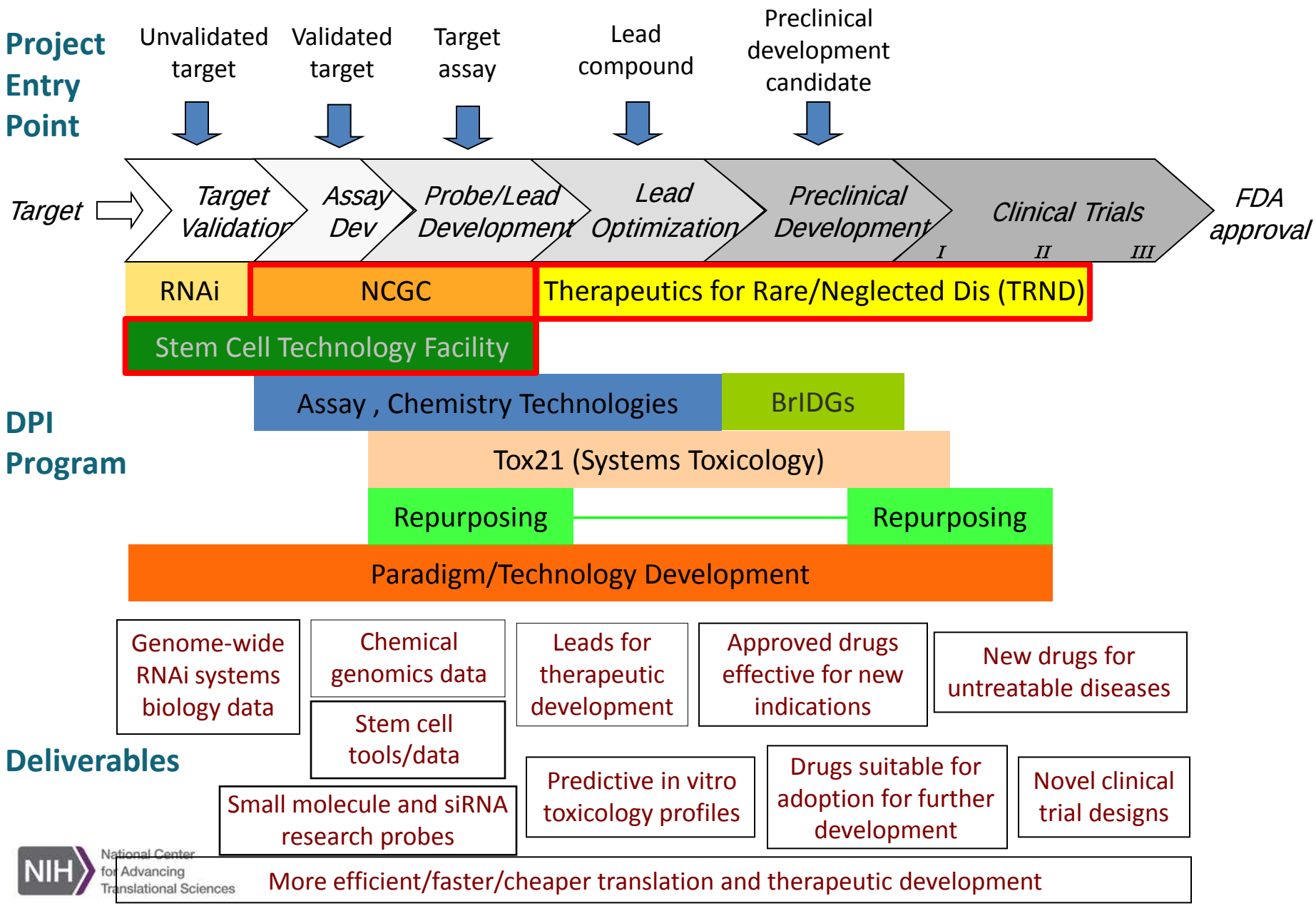
NCATS Division of Preclinical Innovation



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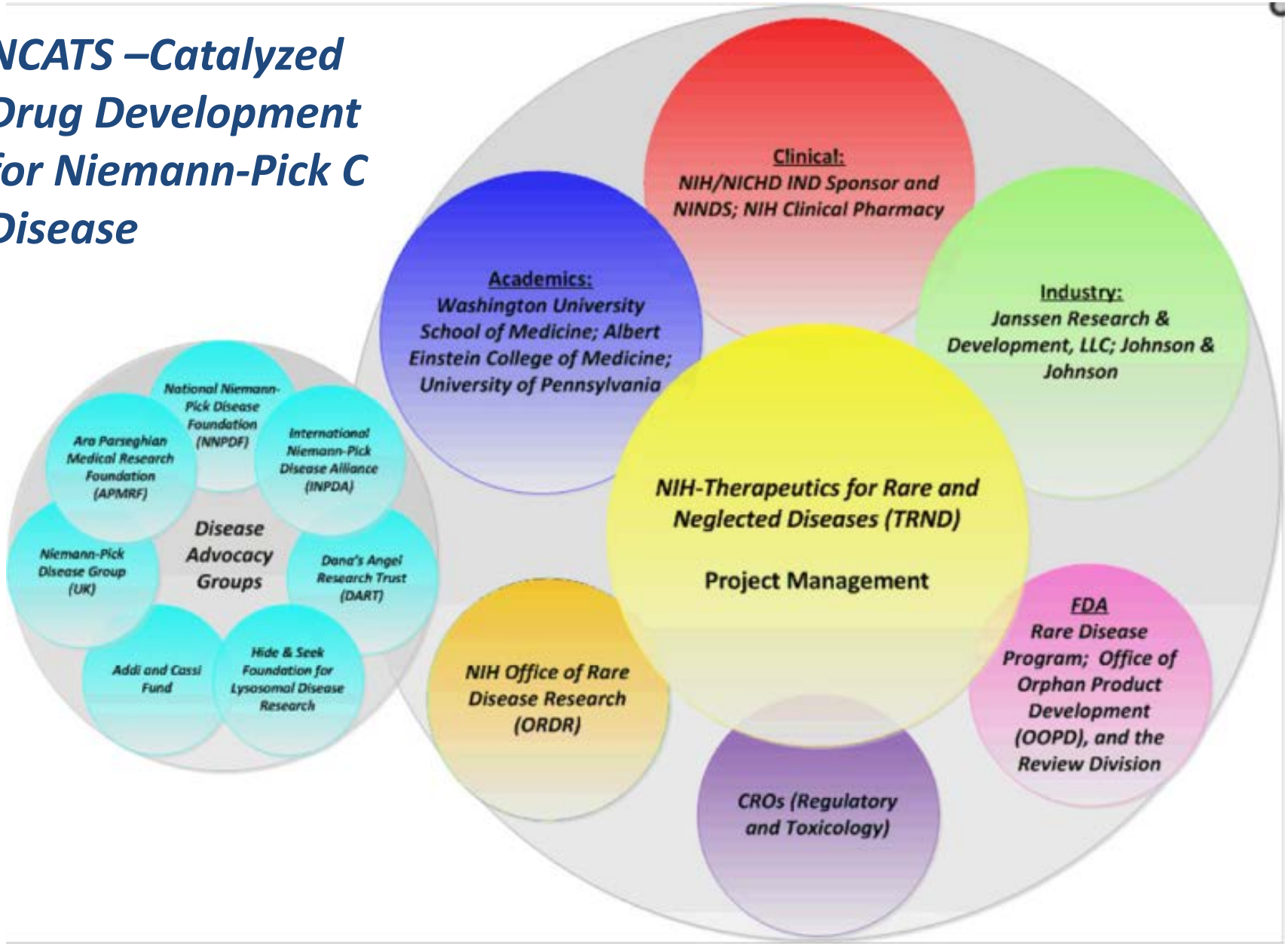
NCATS DPI Staff

NCATS –Catalyzed Drug Development for Niemann-Pick C Disease



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THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 287, NO. 47, pp. 39349–39360, November 16, 2012
Published in the U.S.A.

δ-Tocopherol Reduces Lipid Accumulation in Niemann-Pick Type C1 and Wolman Cholesterol Storage Disorders*

Received for publication, February 29, 2012, and in revised form, September 28, 2012 Published, JBC Papers in Press, October 3, 2012, DOI 10.1074/jbc.M112.357707

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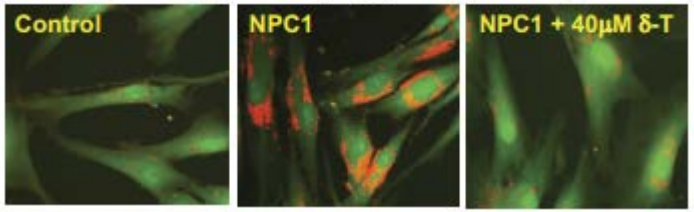
A. Filipin staining (red: filipin; green: CellMask)



Niemann–Pick Disease Type C: Induced Pluripotent Stem Cell–Derived Neuronal Cells for Modeling Neural Disease and Evaluating Drug Efficacy

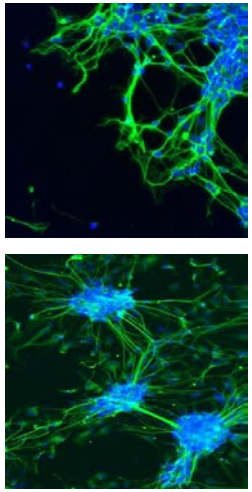
Journal of Biomolecular Screening
2014, Vol. 19(8) 1164–1173

DOI: 10.1177/1087057114537378
jbx.sagepub.com
SAGE

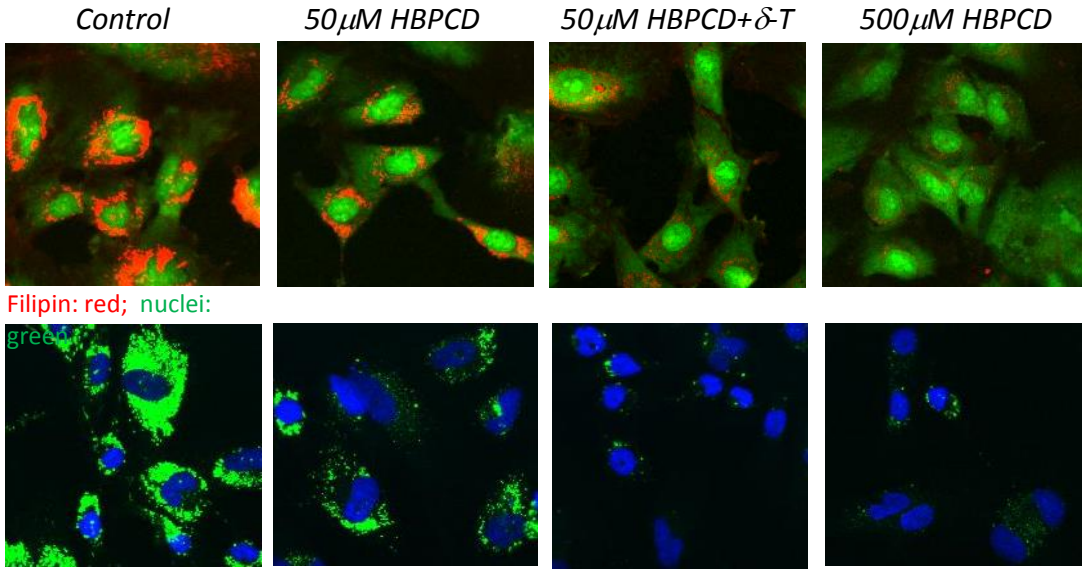
Daozhan Yu[1,*], Manju Swaroop[2,*], Mengqiao Wang[2,*], Ulrich Baxa[3], Rongze Yang[1], Yiping Yan[4], Turhan Coksaygan[5], Louis DeTolla[4], Juan J. Marugan[2], Christopher P. Austin[2], John C. McKew[2], Da-Wei Gong[1,6], and Wei Zheng[2]

iPSC-derived neurons

Tuj1



HPBCD in combination with δ-Tocopherol

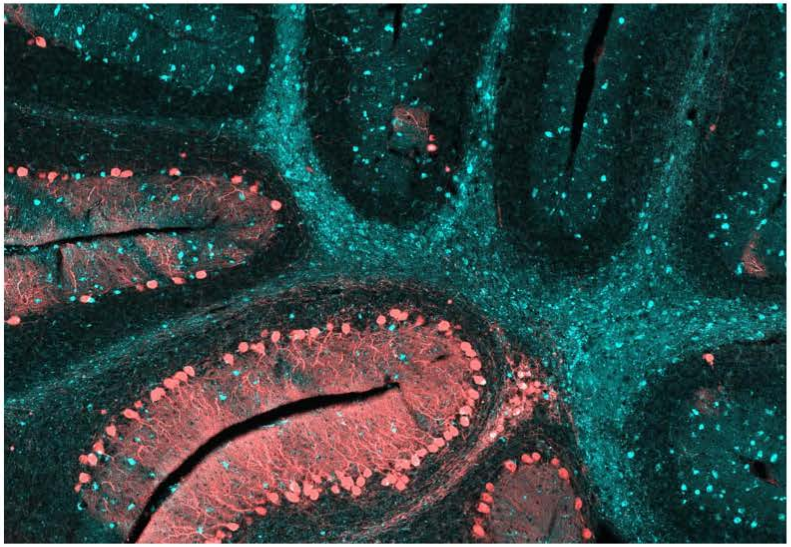


NIH National Center for Advancing Translational Sciences

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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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†

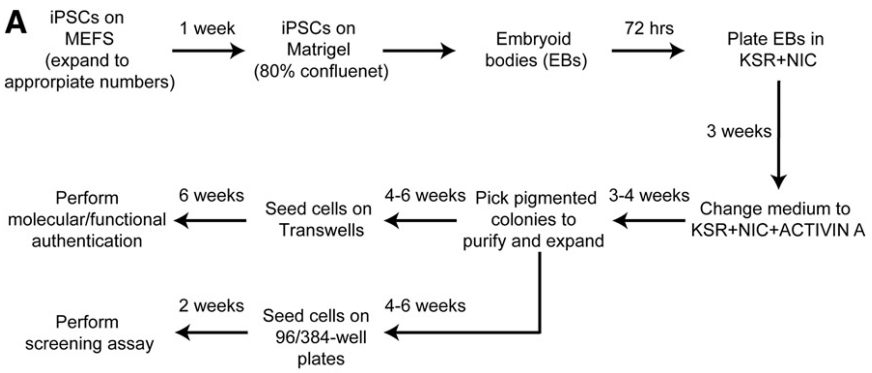
Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across 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.

www.ScienceTranslationalMedicine.org 27 April 2011 Vol 3 Issue 80 80ps16

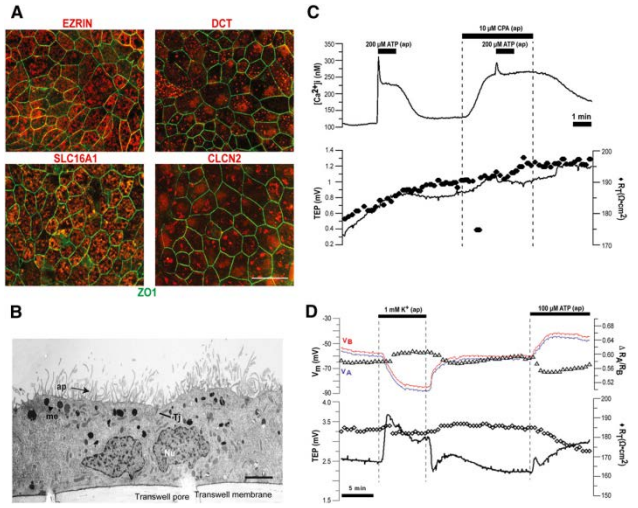
A drug-screening platform for Age-related Macular Degeneration using iPSC-derived Retinal Pigmented Epithelium cells

- **Collaborators:** Kapil Bharti and Sheldon Miller (NEI intramural)
- **Objective:** Accelerate drug discovery to treat Age-related Macular Degeneration by developing "disease-in-a-dish" models using iPSC derived retinal pigmented epithelium (RPE) cells
- **Scope:** Screen the NCGC Pharmaceutical Collection (NPC) of clinically approved compounds for small molecules that enhance differentiation of iPSC into fully mature RPE using:
  - RPE lineage GFP reporter assay
  - Multiplexed gene expression assay (panel of genes reporter on stem cell genes and RPE genes)

Schematic of the step-wise protocol for differentiation of iPS cells into retinal pigment epithelium (RPE)



Authentication of iPSC-derived RPE cells



Marc Ferrer, NCATS NCGC

NIH National Center for Advancing Translational Sciences

NCATS Stem Cell Translation Laboratory:
Established September 2015 as part of NIH Common Fund Regenerative Medicine Program

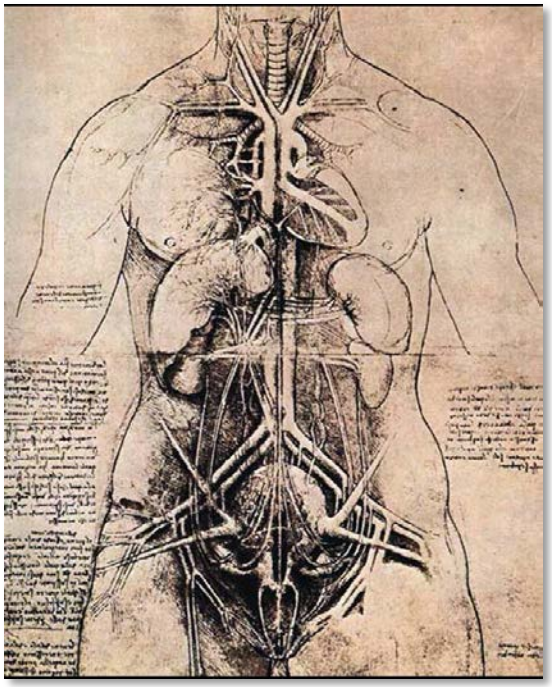
- **Establish QC standards to define pluripotency and differentiated cell types**
- **Develop methods to assess heterogeneity in iPSC-derived cells**
- **Develop standardized methods to produce mature cells**
- **Discover, validate, and disseminate small molecule reagents to replace expensive recombinant proteins, xenogenic material, undefined media components in cell differentiation protocols**

NCATS Intramural Trainee to join Stanford Stem Cell Biology and Regenerative Medicine PhD Program, Fall 2016

Francis Aguisanda

Tissue Chip Program

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



- All ten human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Integumentary
  - Musculoskeletal
  - Nervous
  - Reproductive
  - Respiratory
  - Urinary
- Physiologically relevant, genetically diverse, and pathologically meaningful
- Modular, reconfigurable platform
- Tissue viability for at least 4 weeks
- Community-wide access

Dan Tagle, NCATS OD

Tissue Chip Program

NIH National Institutes of Health

Phase 1: Development

Phase 2: Cell incorporation & organ integration

Year 1 | Year 2 | Year 3 | Year 4 | Year 5

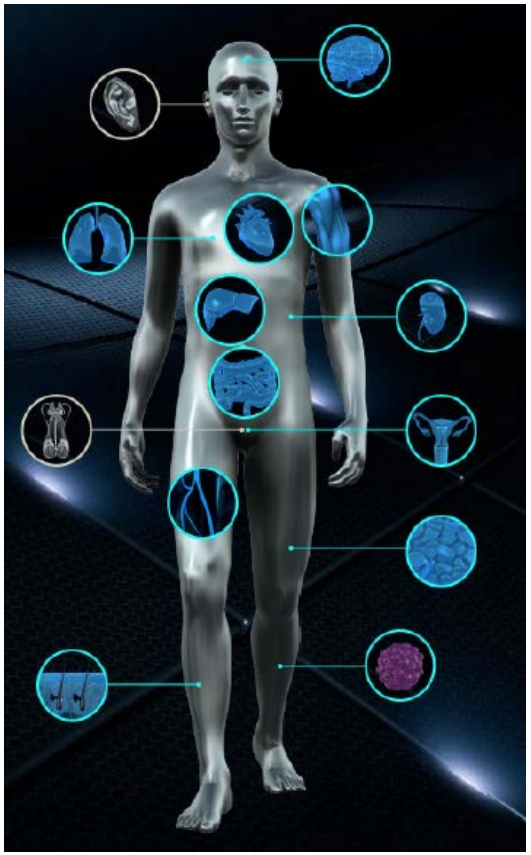
DARPA

DARPA base periods: Organ integration

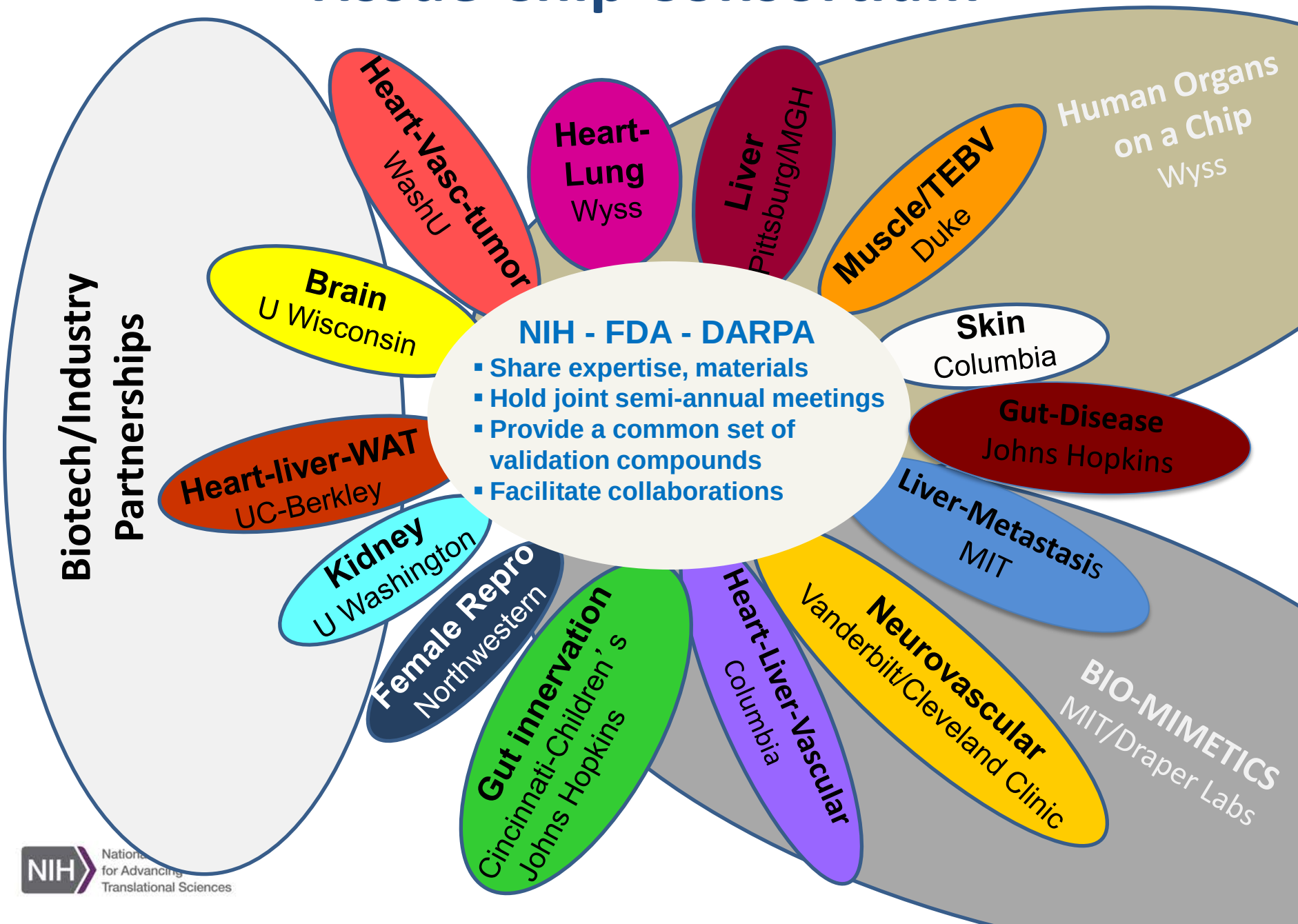
FDA

FDA provides insight and expertise throughout the program

Pharma partnerships

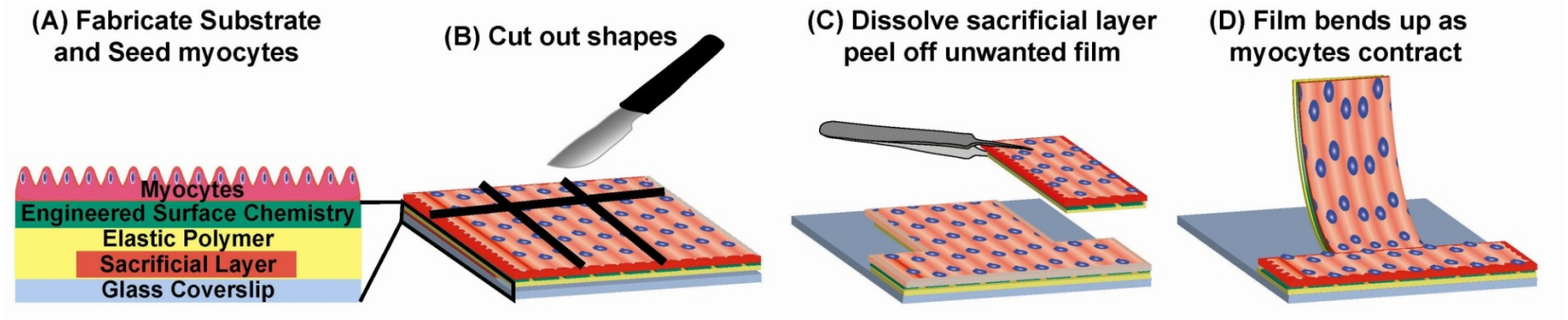


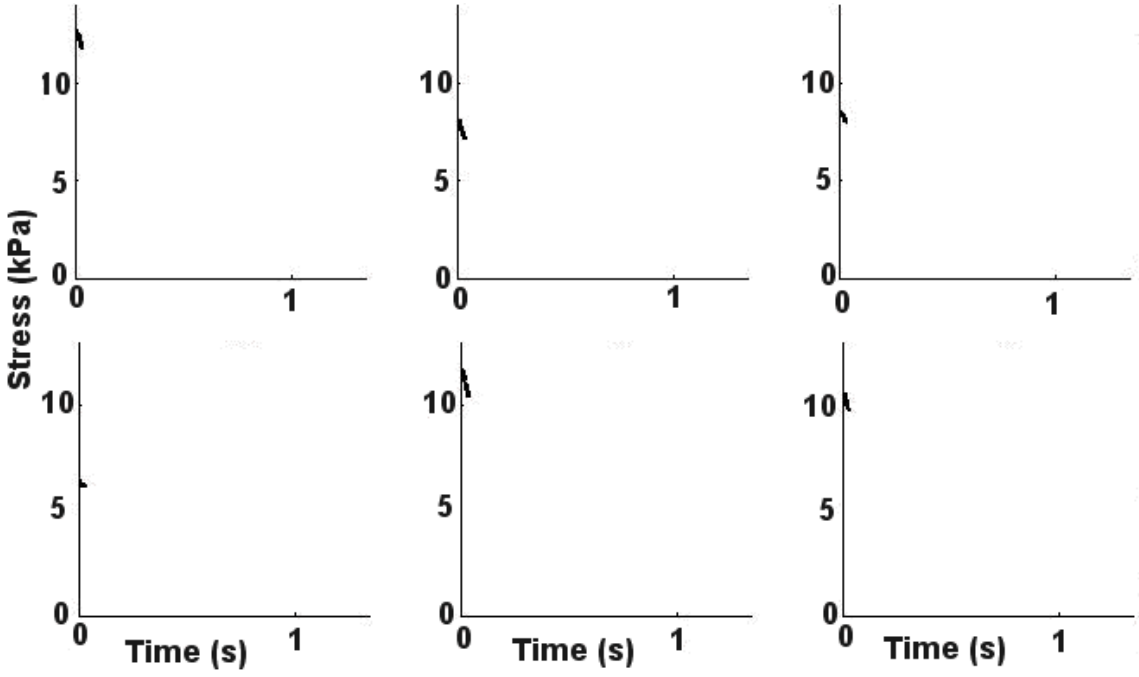
Tissue Chip Consortium

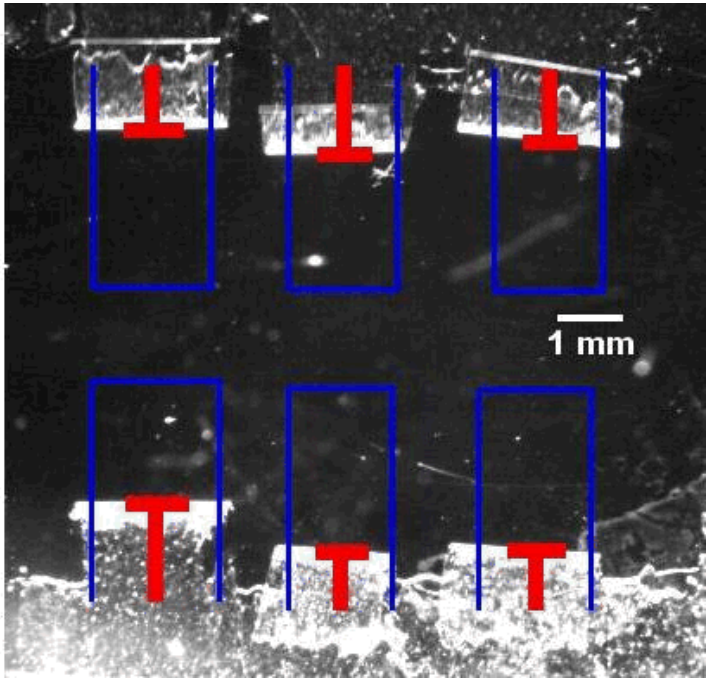


NIH National Institutes for Advancing Translational Sciences

Engineered Cardiac Muscular Thin Films







Film length
Automatic projection tracking

Kit Parker, Wyss Institute

NIH National Center for Advancing Translational Sciences

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

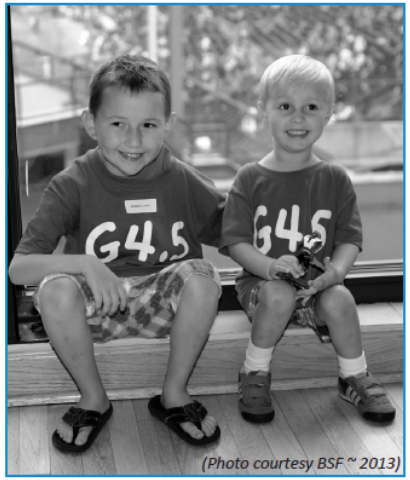
Biomaterials 2010;31:3613
J Pharm Tox Methods 2012;65:126

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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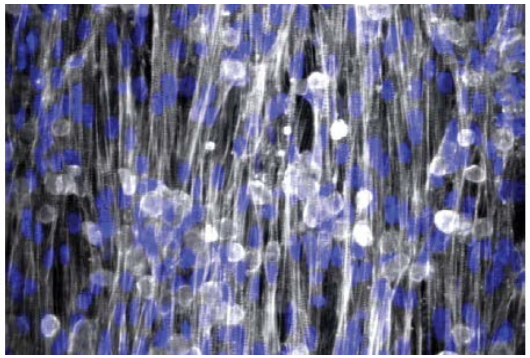
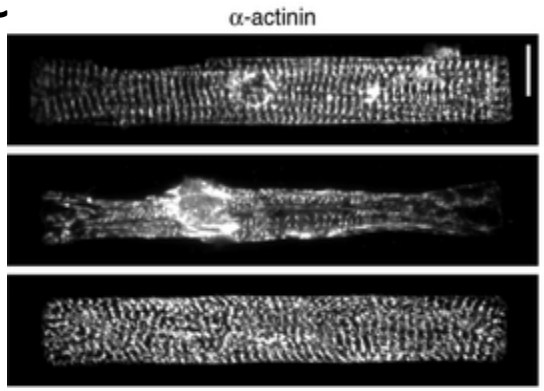
Heart on a Chip Barth Model

A

B



C



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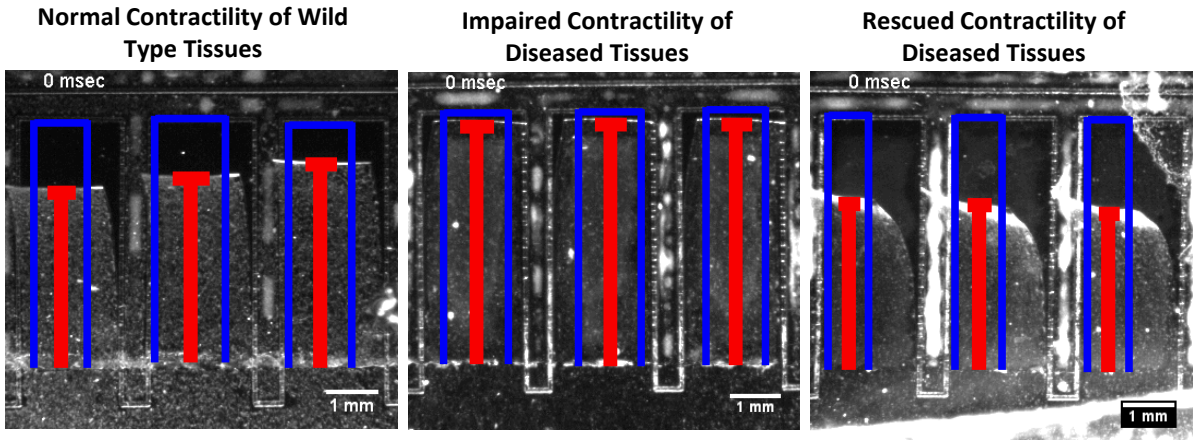

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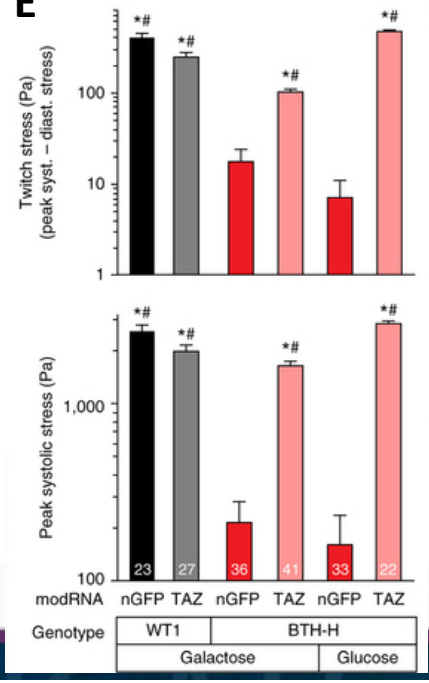

Dr. Kevin Parker, Harvard University:
http://diseasebiophysics.seas.harvard.edu

Tissue Chip Resources on NCATS.nih.gov

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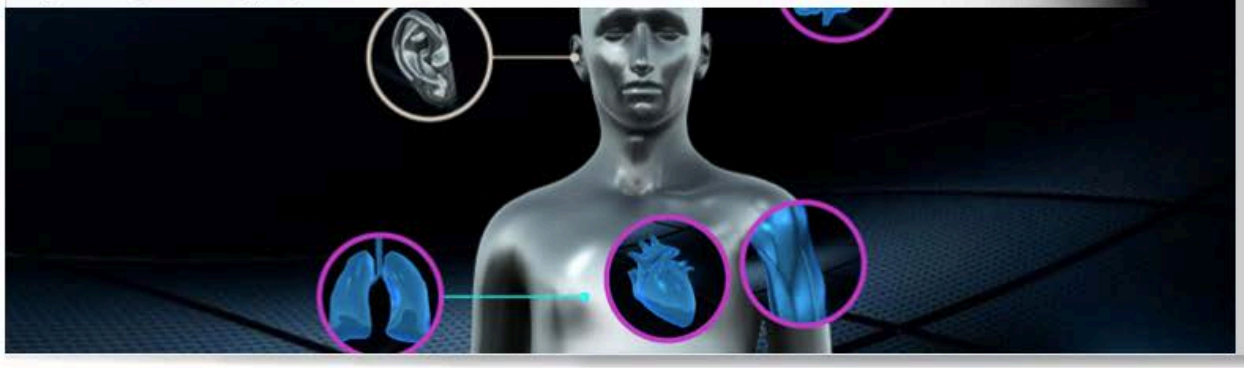
Meet Chip

Explore this interactive model of the innovative developments from the NCATS-supported Tissue Chip for Drug Screening program.

More...



Work with Us

The tissue chip program is designed to improve the way new drugs are developed and tested. Learn more about how you can join this effort.

Contact Danilo Tagle, Ph.D.

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Tissue Chip for Drug Screening

The Tissue Chip for Drug Screening program aims to develop bioengineered devices to improve the process of predicting whether drugs will be safe or toxic in humans. Learn more.

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