The National Center for Advancing Translational Sciences

Catalyzing Translational Innovation

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

STANFORD DRUG DISCOVERY CONFERENCE
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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
Sickle Cell Anemia, a Molecular Disease

Linus Pauling, Harvey A. Itano, S. J. Singer, and Ibert C. Wells

Gates and Crellin Laboratories of Chemistry,
California Institute of Technology, Pasadena, California

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 lower, these cells change their form from the normal biconcave disk to crescent, biconvex, and other forms. This process is known as sickling. About 8 percent of African Negroes possess this characteristic, usually they exhibit no pathological consequences whatsoever to it. These people are said to have sickle-cell, or sickle-cell trait. However, about 1 in 40 (0.25) 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 these conditions.

The main observable differences between the erythrocytes of sickle cell trait and sickle cell anemia have 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. Tests in vivo have demonstrated that between 20 and 40 percent of sickled erythrocytes in the venous circulation of sickle cell anemia individuals, but less than 1 percent of those in the venous circulation of sickle cell trait 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 that 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 erythrocytes. Sickle cell erythrocytes, in which the hemoglobin is combined with oxygen, or in deoxygenated sickle cell anemia, have the biconcave disk contour and are indistinguishable in

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*Institutional Head of the Division of Medical Sciences of the National Research Council.
**Chief, Radiology Div. No. 303.
Moore’s Law

The graph illustrates the exponential growth in the number of transistors on a microchip, with the curve showing that the transistor count doubles every two years. The data points represent the introduction dates of various computer processors over the years, starting from the early 1970s to the late 2000s.

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.

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
NCATS Division of Preclinical Innovation

**Project Entry Point**
- Unvalidated target
- Validated target
- Target assay
- Lead compound
- Preclinical development candidate

**Target**
- RNAi
- Stem Cell Technology Facility
- NCGC
- Therapeutics for Rare/Neglected Dis (TRND)

**DPI Program**
- Tox21 (Systems Toxicology)
- Repurposing
- Paradigm/Technology Development

**Deliverables**
- Genome-wide RNAi systems biology data
- Chemical genomics data
- Leads for therapeutic development
- Approved drugs effective for new indications
- New drugs for untreatable diseases
- Small molecule and siRNA research probes
- Predictive in vitro toxicology profiles
- Drugs suitable for adoption for further development
- Novel clinical trial designs

More efficient/faster/cheaper translation and therapeutic development
NCATS – Catalyzed Drug Development for Niemann-Pick C Disease

Academics:
- Washington University School of Medicine; Albert Einstein College of Medicine; University of Pennsylvania

Clinical:
- NIH/NICHD IND Sponsor and NINDS; NIH Clinical Pharmacy

Industry:
- Janssen Research & Development, LLC; Johnson & Johnson

NIH-Therapeutics for Rare and Neglected Diseases (TRND)
- Project Management

NIH Office of Rare Disease Research (ORDR)

CROs (Regulatory and Toxicology)

FDA Rare Disease Program; Office of Orphan Product Development (OOPD), and the Review Division

Disease Advocacy Groups
- Ara Parseghian Medical Research Foundation (NNPDF)
- International Niemann-Pick Disease Alliance (INPDA)
- Niemann-Pick Disease Group (UK)
- Addi and Cassi Fund
- Hida & Seek Foundation for Lysosomal Disease Research
- Dana's Angel Research Trust (DART)

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δ-Tocopherol Reduces Lipid Accumulation in Niemann-Pick Type C1 and Wolman Cholesterol Storage Disorders*5

From the 3National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, Maryland 20892, the 4Program in Developmental Endocrinology and Genetics, Eunice Kennedy Shriver NICHD, National Institutes of Health, Bethesda, Maryland 20892, the 5Diabetic Cardiovascular Disease Center, Washington University School of Medicine, St. Louis, Missouri 63110, the 6Genetic Disease Research Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, the 7Sidney Weisner Laboratory of Genetic Neurological Disease, Rose F. Kennedy Center, Albert Einstein College of Medicine, Bronx, New York 10461, the 8Laboratory of Lipoprotein Metabolism, NHLBI, National Institutes of Health, Bethesda, Maryland 20892, the 9Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, China, and the 10Electron Microscopy Laboratory, NCI, National Institutes of Health, Bethesda, Maryland 20892

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

Daozhan Yu1,*, Manju Swaroop2,*, Mengqiao Wang2,*, Ulrich Baxa3, Rongze Yang1, Yiping Yan4, Turhan Coksaygan5, Louis DeTolla4, Juan J. Marugan2, Christopher P. Austin2, John C. McKew2, Da-Wei Gong1,6, and Wei Zheng2

HPBCD in combination with δ-Tocopherol

Filipin: red; nuclei: green

Lysotracker

Nuclei: blue

iPSC-derived neurons

Tuj1

Control

50µM HBPCD

50µM HBPCD+δ-T

500µM HBPCD

WT

NPC1

NPC1 + 40µM δ-T

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

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.”

—Perker D. Porter, M.D., Ph.D.
NCIOD Clinical Director
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.

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 iPSCs into retinal pigment epithelium (RPE)

Authentication of iPSC-derived RPE cells

![Schematic](image)

Marc Ferrer, NCATS NCGC
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
Tissue Chip Program

NIH

Phase 1: Development

Phase 2: Cell incorporation & organ integration

Year 1 Year 2 Year 3 Year 4 Year 5

DARPA base periods: Organ integration

FDA provides insight and expertise throughout the program

Pharma partnerships

NCATS
NIH - FDA - DARPA
- Share expertise, materials
- Hold joint semi-annual meetings
- Provide a common set of validation compounds
- Facilitate collaborations

Biotech/Industry Partnerships
- Heart-Vasc-tumor
  - WashU
- Heart-Lung
  - Wyss
- Liver
  - Pittsburg/MGH
- Muscle/TEBV
  - Duke
- Brain
  - U Wisconsin
- Heart-liver-WAT
  - UC-Berkley
- Kidney
  - U Washington
- Female Repro
  - Northwestern
- Gut innervation
  - Cincinnati-Children’s
  - Johns Hopkins
- Heart-Liver-Vascular
  - Columbia
- Neurovascular
  - Vanderbilt/Cleveland Clinic
- Gut Disease
  - Johns Hopkins
- Human Organs on a Chip
  - Wyss
- Skin
  - Columbia
- Liver-Metastasis
  - MIT
- BIO-MIMETICS
  - MIT/Draper Labs

Tissue Chip Consortium
Engineered Cardiac Muscular Thin Films

(A) Fabricate Substrate and Seed myocytes
(B) Cut out shapes
(C) Dissolve sacrificial layer peel off unwanted film
(D) Film bends up as myocytes contract

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Science 2007;317:1366
Biomaterials 2010;31:3613
Lab Chip 2011;11:4165
J Pharm Tox Methods 2012;65:126

Film length
Automatic projection tracking
Kit Parker, Wyss Institute
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 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)

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

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

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
Heart on a Chip Barth Model

A

B

C

D

E

Dr. Kevin Parker, Harvard University: http://diseasebiophysics.seas.harvard.edu
Tissue Chip Resources on NCATS.nih.gov

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

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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