DRUG DISCOVERY & DEVELOPMENT IN NICHD POPULATIONS

Overview

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

NATIONAL ADVISORY CHILD HEALTH AND HUMAN DEVELOPMENT COUNCIL
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Human Conditions with Known Molecular Basis

Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome
SO....
Steps in the drug development process

1. Identify target
2. Create testing system (aka, “assay”)
3. Test >100,000 chemicals for activity on target
4. Make modifications to active chemicals to make suitable for human use
5. Test in animals for safety, effectiveness
6. Test in humans for safety, effectiveness

Assay Development
- Basic research
- Discovery
- Preclinical and early clinical
- Late clinical

HTS
- Medicinal Chemistry
- Preclinical Development
- Clinical Development

(Per project cost)
- $50-100K
- $500K-1M
- $5-10M
- $50-100M
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.

Costs and probabilities in drug development

Paul SM et al., Nature Reviews Drug Discovery 9:203, 2010
Drug Discovery
BIG RISKS, BIG REWARDS
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 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.
NCATS Division of Preclinical Innovation

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

Target Validation Dev Probe/Lead Development Lead Optimization Preclinical Development Clinical Trials
- FDA approval
- RNAi
- NCGC
- Therapeutics for Rare/Neglected Dis (TRND)
- Stem Cell Technology
- Assay, Chemistry Technologies
- BrIDGs
- Tox21 (Systems Toxicology)
- Repurposing
- Paradigm/Technology Development

DPI Program
- Genome-wide RNAi systems biology data
- Chemical genomics data
- Leads for therapeutic development
- Approved drugs effective for new indications
- New drugs for untreatable diseases
- Stem cell tools/data
- Predictive in vitro toxicology profiles
- Drugs suitable for adoption for further development
- Novel clinical trial designs

Deliverables
- Small molecule and siRNA research probes
- More efficient/faster/cheaper translation and therapeutic development
Video of NCATS Preclinical Innovation Laboratories
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

75% mortality if untreated

Chronic complications

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

Leloir Pathway

GALK deficiency (type 2 galactosemia)
- Lacks severe adverse phenotype
- Elevated galactose, galactitol and galactonate in patient plasma

GALK deficiency (classic galactosemia)
- Hereditary deficiency
- Severe adverse phenotype
- Elevated galactose, galactitol, galactonate and gal-1-p in patient plasma

GALE deficiency (type 3 galactosemia)
- Very rare
- Can present with severe phenotype similar to classic galactosemia
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 1p 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 models
- Only mouse model for galactosemia that closely mimics the human phenotype
- Compounds currently being tested

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

Identification of repurposed small molecule drugs for chordoma therapy

Menghang Xia,1,2*, Ruili Huang,1† Srilatha Sakamuru,1 David Alcorta,2 Ming-Hsuan Cho,1 Dae-Hee Lee,2 Deric M Park,3 Michael J Kelley,2 Josh Sommer,1 and Christopher P Austin1

1NIH Chemical Genomics Center; National Institute of Biomedical Imaging and Bioengineering; National Institutes of Health; National Human Genome Research Institute; National Institute of Diabetes and Digestive and Kidney Diseases; 2National Institute of General Medical Sciences; National Institutes of Health; Department of Medicine; 3Duke University; Department of Medicine; 4Department of Physiology; Duke University; 5Department of Pathology; Duke University; Department of Medicine

Keywords: chordoma, NCGC, ChEMBL

ARTICLE

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

Jessica L. Childs-Disney1,*, Ewa Stepniak-Koniczewska2,*, Tuan Tran1,3,*, Ilyas Yildirim4, HaJeung Park1, Catherine Z. Chen5, Jason Hoskins6, Noel Southall5, Juan J. Marugan6, Samarjit Patnaik5, Wei Zheng5, Chris P. Austin5, George C. Schatz6, Krzysztof Sobczak2, Charles A. Thornton5 & Matthew D. Disney1
Why Repurposing?

>500,000 compounds, 15 yrs

1-2 years?

Target ➔ Screen ➔ Hit ➔ Lead ➔ Lead Optimization ➔ Preclinical Development ➔ Clinical Trials ➔ FDA approval

3000 drugs
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.
Therapeutics for Rare and Neglected Diseases (TRND) Program

- **Model:** Collaboration between NIH intramural labs with preclinical drug development expertise and extramural labs with disease-area / target expertise

- **Projects:**
  - May enter at various stages of development
  - Taken to stage needed to attract external organization to adopt for final clinical development
  - Serve to develop new generally applicable platform technologies and paradigms

- **Eligible Applicants:**
  - Academic, Non-Profit, Government Lab, Small Business, or Large Biotech / Pharma
  - Ex-U.S. applicants accepted

- **Intellectual Property:**
  - Partnerships are creative
  - TRND may generate intellectual property
## TRND Portfolio

<table>
<thead>
<tr>
<th>Therapeutic Area/Disease</th>
<th>Organization Name(s)</th>
<th>Partner Type(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune pulmonary alveolar proteinosis</td>
<td>Cincinnati Children’s Hospital</td>
<td>Academic</td>
</tr>
<tr>
<td>Creatine Transporter Defect</td>
<td>Lumos Pharma, Inc.</td>
<td>Biotech</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>Leukemia &amp; Lymphoma Society, University of Kansas Cancer Center</td>
<td>Disease foundation, academic</td>
</tr>
<tr>
<td>Core binding factor leukemia</td>
<td>NHGRI</td>
<td>NIH intramural labs</td>
</tr>
<tr>
<td>Fibrodysplasia ossificans progressiva</td>
<td>Massachusetts General Hospital</td>
<td>Academic</td>
</tr>
<tr>
<td>GNE Myopathy (Hereditary Inclusion Body Myopathy NIBM)</td>
<td>New Zealand Pharmaceuticals, NHGRI</td>
<td>Biotech and NIH intramural clinical labs</td>
</tr>
<tr>
<td>Hemoglobinopathies</td>
<td>Phoenicia Biosciences, Inc.</td>
<td>Biotech</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Eli Lilly &amp; Co.</td>
<td>Pharmaceutical</td>
</tr>
<tr>
<td>LEOPARD syndrome</td>
<td>Beth Israel Deaconess Medical Center</td>
<td>Academic</td>
</tr>
<tr>
<td>Malaria</td>
<td>Loyola University Chicago</td>
<td>Academic</td>
</tr>
<tr>
<td>Niemann-Pick disease type C</td>
<td>Ara Parseghian Medical Research Foundation, Niemann-Pick Type C Support of Accelerated Research (NPC-SOAR), Einstein College of Medicine, University of Pennsylvania, Washington University, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and National Human Genome Research Institute (NHGRI)</td>
<td>Disease foundation, academic, NIH intramural labs</td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td>University of California, Irvine</td>
<td>Academic</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>CoNCERT Pharmaceuticals</td>
<td>Biotech</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Aes-Rx, National Heart, Lung and Blood Institute</td>
<td>Biotech, NIH intramural labs</td>
</tr>
</tbody>
</table>
TRND
Niemann Pick Type C Collaboration

• Drug: Cyclodextrin (HPBCD)

• Collaborators
  ➢ NICHD
    ▪ Denny Porter - Clinical
  ➢ Washington University
    ▪ Dan Ory - Biochemistry, Biomarkers
  ➢ Albert Einstein and UPenn
    ▪ Steve Walkley and Charles Vite - Animal models
  ➢ Johnson & Johnson Pharmaceuticals

• NPC disease foundations involved and facilitating

• Milestones
  ➢ February 2011: 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) selected by TRND as pre-clinical candidate
  ➢ December 2012: IND filed
  ➢ February 2013: Phase I initiated and 1st patient dosed
  ➢ January 2015: Agreement signed with Vtesse to complete clinical development of HPBCD for NPC and investigate use in other LSDs
  ➢ September 2015: Phase I completed
  ➢ October 2015: Phase II start planned
Agreement with Vtesse January 7, 2015
Advancing treatments for Lysosomal Storage Disorders

• CRADA: NCATS - NICHD - Vtesse (Gaithersburg, MD)

For Immediate Release: Wednesday, January 7, 2015

NIH teams with industry to develop treatments for Niemann-Pick 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 and other lysosomal storage disorders.

Lysosomal storage diseases, also known as lipid storage diseases, comprise about 50 rare inherited disorders that usually affect those with fatty materials accumulating in the cells and tissues of their organs and tissues; they are often fatal.

Researchers at the National Center for Advancing Translational Sciences, within the National Institute of Child Health and Human Development, are working with Vtesse and other lysosomal storage disorder companies to advance treatments.

3. Pfizer, NEA orphan drug project launches its first biotech on PhII/III threshold

Less than two years after New Enterprise Associates and Pfizer Ventures got together to launch Cydan, an incubator for new orphan disease drug developers, the group is spawning its first new biotech with a $25 million round and a program for Niemann-Pick disease type C ready to go straight into a Phase II/III study.

The venture backing provides enough money to get the pivotal data needed to know whether or not they have a product, says Chris Adams, who runs Cydan out of Cambridge, MA, and is on the board of the newly created Vtesse. The same syndicate that set up Cydan--NEA, Pfizer (SPFE), Lundbeckfond Ventures, Bay City Capital and Alexandria Venture Investments--is also backing the startup, he adds, which is being run by the experienced drug developer Ben Machielse and his small but knowledgeable team.

It’s a virtual operation, notes Machielse, but there’s also a wide group of investors at the NIH and elsewhere who have pitched in to get VTS-270—a formulation of 2-hydroxypropyl-beta-cyclodextrin—to the threshold of a pivotal study.

“I actually got approached by Dave (Mott, NEA partner and former MedImmune CEO) in May to actually see if I could help out with this particular opportunity,” says Machielse, a MedImmune veteran and former CEO of Onthera, which was acquired by AstraZeneca (AZ). Vtesse licensed the program but will continue to work with public investigators to take it the final step in the clinic.

“This public/private model is pretty cool,” says Machielse, adding that this particular biotech business model should be something that can be replicated in other developers. Machielse is keeping the biotech close to home--and the NIH--in Gaithersburg, MD.

Their lead drug, VTS-270, is designed to clear away the cholesterol that builds up inside the cells of Niemann-Pick patients. But there are also plans to add to the pipeline. Vtesse is starting up with a Cooperative Research and Development Agreement, or CRADA, with the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Center for Advancing Translational Sciences at NIH. Vtesse and NCATS forged a licensing agreement for the current rights held by NIH for the worldwide use of cyclodextrin, delta-tocopherol, and derivatives of tocopherol for lysosomal storage diseases, including NPC.
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.
Microphysiological Systems from Common Building Blocks

Computational Design
- systems integration
- multi-scale modeling
- simulation
- feedback

Functional Readout
- real-time, label-free, non-destructive sensing
- imaging

Scaffold
- purified ECM
- synthetic polymers
- composites

Cells
- stem/progenitor
- differentiated
- mixed cell types

Structure
- porosity
- topography
- stiffness

Spatial/Temporal Patterning
- cytokine gradients
- controlled release

Perfusion
- embedded channels
- vascularization

Bioreactors
- optimized culture conditions
- biomechanical properties
- blood mimetics

Host Response
- generalized inflammation
- specific immunity

Innervation
- signal propagation
- coordinated response
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

Data provided by Dr. 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

Film length

Automatic projection tracking

1 mm
**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)

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**Important Clinical Problems May Include (in varying severity):**

- Congestive heart failure
- Life-threatening bacterial infection
- Gross motor delay
- Risk of thrombosis
- 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
- 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

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

*Will (age 27) and John (age 31) at BSF3 2011 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

Normal Contractility of Wild Type Tissues

Impaired Contractility of Diseased Tissues

Rescued Contractility of Diseased Tissues

E

Twitch area (Pa) (peak systolic stress)

Peak systolic stress (Pa)

Genotype

modRNA nGFP TAZ nGFP TAZ nGFP TAZ

WT1 BTH-H

Galactose Glucose

Dr. Kevin Parker, Harvard University: http://diseasebiophysics.seas.harvard.edu
Modeling the mitochondrial cardiomyopathy of Barth syndrome with induced pluripotent stem cell and heart-on-chip technologies

Gang Wang¹,¹⁴, Megan L McCain²,¹⁴, Luhan Yang²,³, Aibin He¹, Francesco Silvio Pasqualini², Ashutosh Agarwal², Hongyan Yuan², Dawei Jiang¹, Donghui Zhang¹, Lior Zangi¹, Judith Geva¹, Amy E Roberts¹,⁴, Qing Ma¹, Jian Ding¹, Jinghai Chen¹, Da-Zhi Wang¹, Kai Li¹, Jiwu Wang⁵,⁶, Ronald J A Wanders⁷, Wim Kulik⁷, Frédéric M Vaz⁷, Michael A LaFlamme⁸, Charles E Murry⁸–¹⁰, Kenneth R Chien¹¹, Richard I Kelley¹², George M Church²,³, Kevin Kit Parker²,¹³ & William T Pu¹,¹³

VOLUME 20 | NUMBER 6 | JUNE 2014  NATURE MEDICINE
Modeling the Female Reproductive Tract in 3-D: The Birth of EVATAR™

Science fiction and gaming enthusiasts are familiar with the concept of an avatar, the digital character a user creates to navigate a virtual world. Now, NIH-funded researchers are turning science fiction into scientific reality by building one. EVATAR™ is a miniaturized 3-D representation of the female reproductive tract and liver on a handheld, interconnected platform. The team of scientists from Northwestern University, Charles Stark Draper Laboratory, and the University of Illinois at Chicago (UIC) is designing the model for use in drug testing and to study the basic biology of female reproduction.

Too often, laboratory and animal tests used by scientists in the early phases of research fail to predict a therapy’s effectiveness or potential side effects in humans. Use of inaccurate models can result in many years and millions of dollars being wasted while patients wait for effective treatments. Researchers need scientifically valid alternatives for predicting treatment effectiveness and safety.

Another issue is consideration of sex as a biological variable. Although women now comprise roughly half the participants in NIH-funded clinical trials, the same is not true for pre-clinical research. More often than not, pre-clinical research conducted to date has involved mostly male-derived cells and male animals. These practices have resulted in a lack of information about female physiology and women’s health.

To address these and other drug development challenges, NCATS, along with the Defense Advanced Research Projects Agency® and the Food and Drug Administration®, developed the Tissue Chip for Drug Screening program. Program funding is used to support scientists developing 3-D platforms with living human tissues and cells, called tissue chips or organs-on-chips. These devices are designed as accurate models of the structure and function of human organs and systems, such as the lung, liver, heart and, in this case, female reproductive tract.

A Team Effort

The EVATAR™ team at Northwestern University. (Northwestern University Photo)
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