NCATS Improving Health Through Smarter Science

The National Center for Advancing Translational Sciences: Catalyzing Translational Innovation in Rare Disease Research

Christopher P. Austin, M.D.

Director, NCATS/NIH

National Organization for Rare Disorders Special Member Webinar

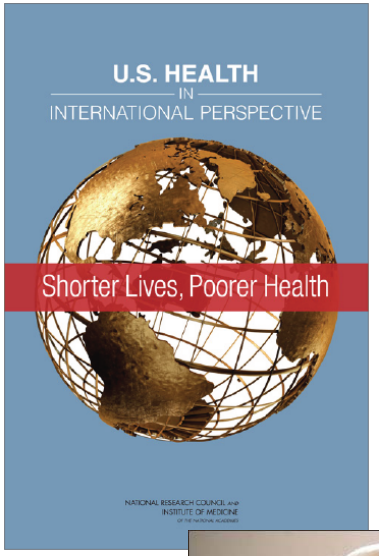
August 23, 2017

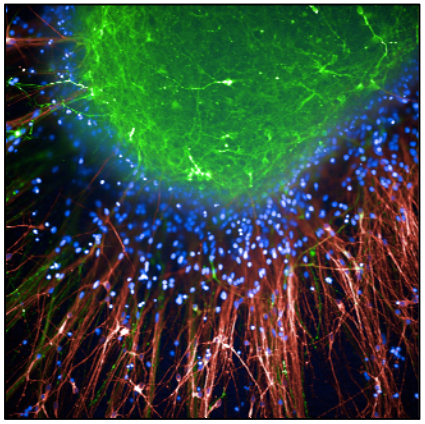
NIH National Center for Advancing Translational Sciences

The Best of Times, the Worst of Times

Fundamental science unprecedentedly advanced, but:

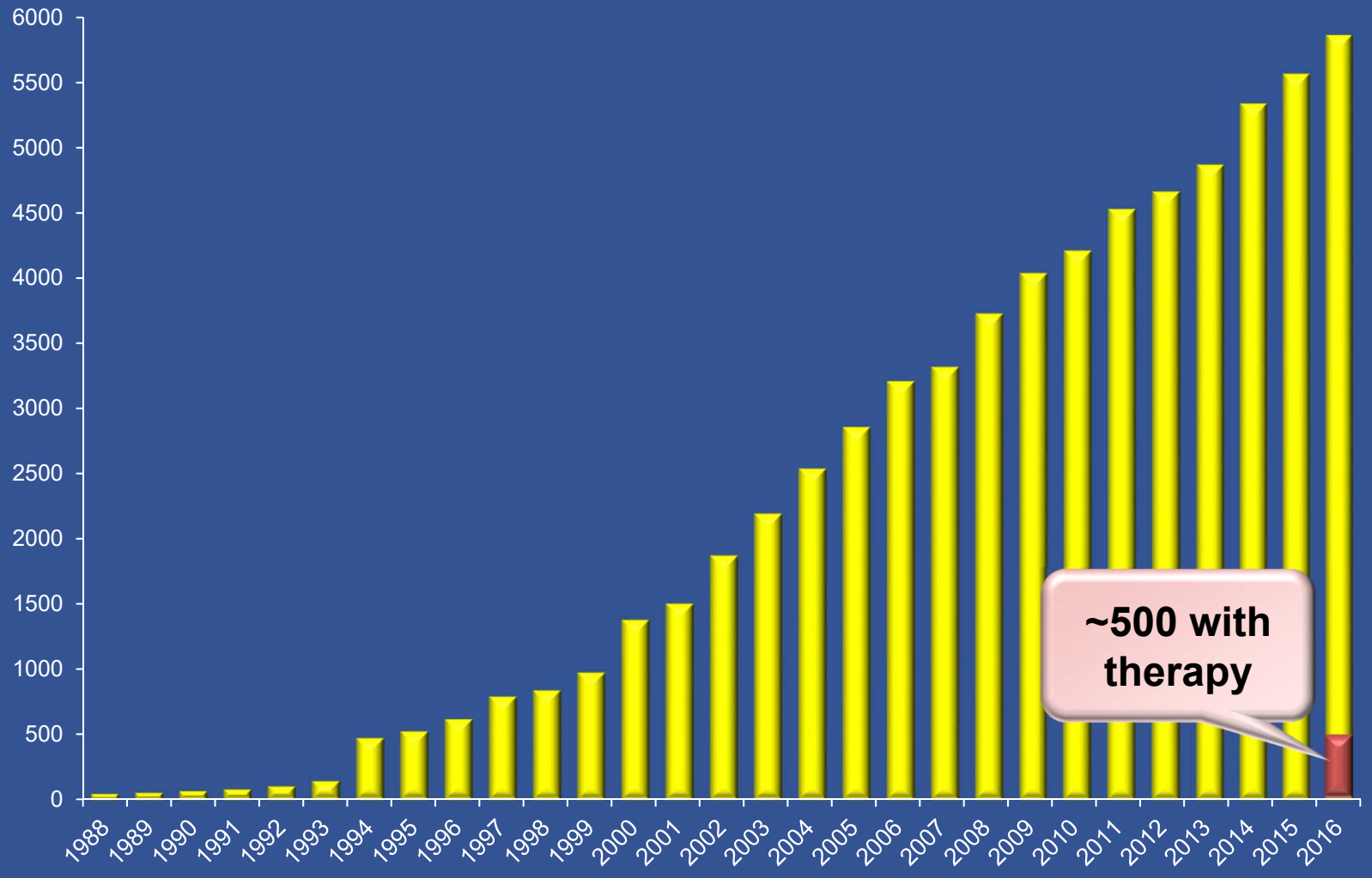
- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Intervention development failure-prone and expensive
- Poor adoption of demonstrably useful interventions





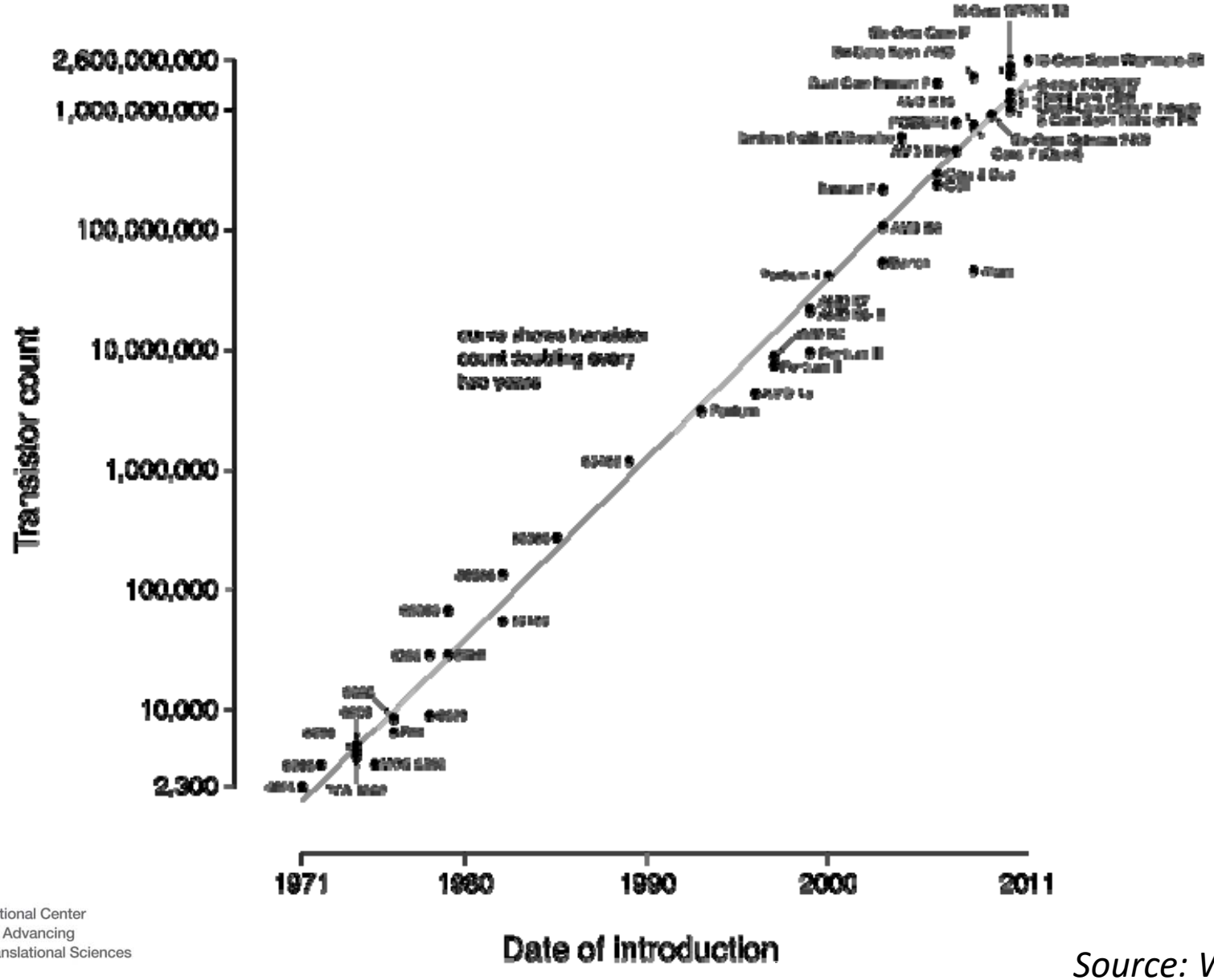
Enormous opportunity/need to deliver on promise of science for patients

Human Conditions with Known Molecular Basis



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

Moore's Law



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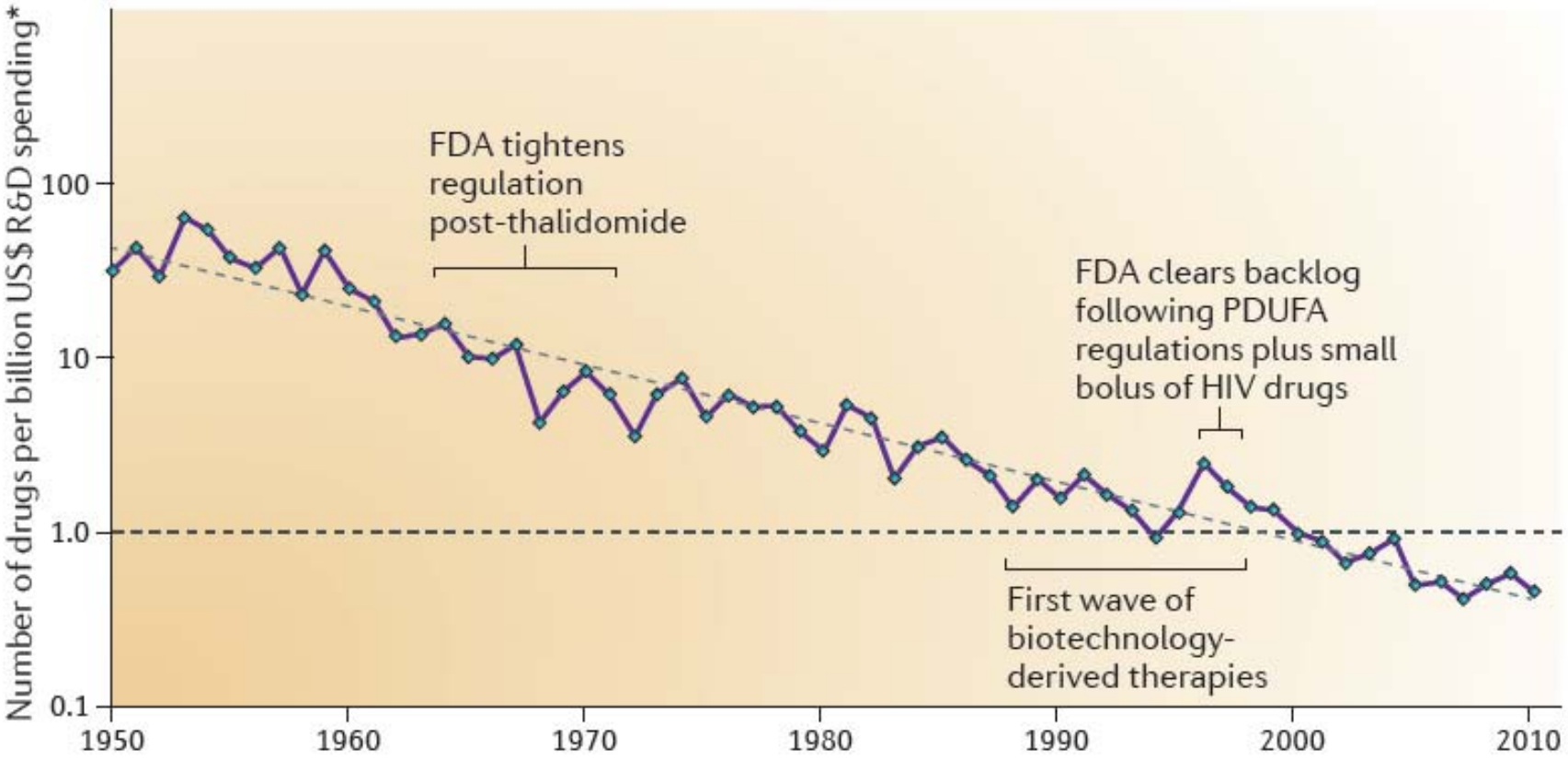
Source: Wikipedia

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.

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

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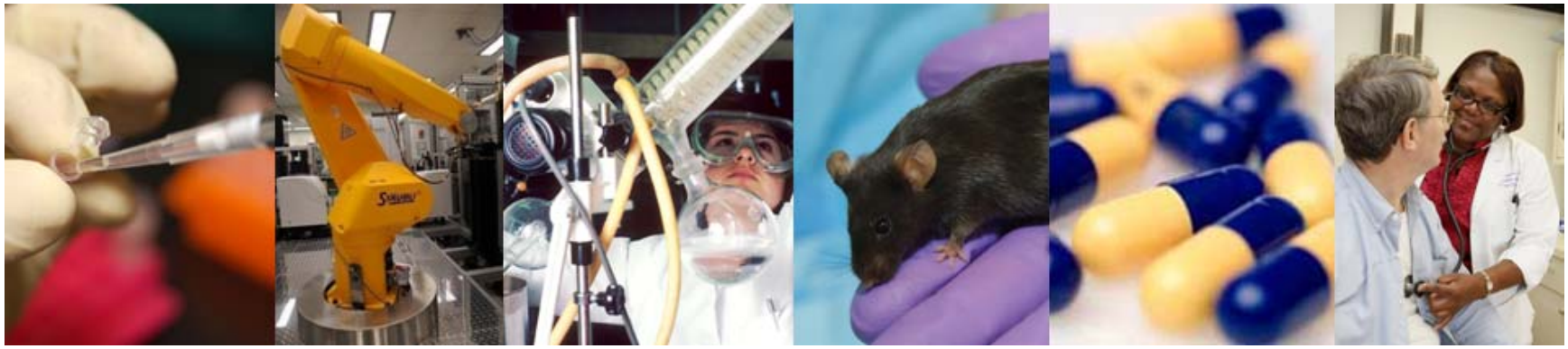
NCATS Mission



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 scientific 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 thereof)

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Some of the organizational/cultural translational problems on NCATS' to-do list…

- Data transparency/release
- IP management
- Integration of project management
- Incentives/credit for team science
- Incentives/credit for health improvements
- Education/Training (scientific and cultural)
- Collaborative structures
  - Public-private partnership models

The Scope of Rare Diseases

- ~ 7000 diseases
  - ~80% mendelian genetic
  - ~50% onset in childhood
  - ~250 new rare diseases identified each year
- Population prevalence ~8% (US ~25M; EU ~30M, World 350M)
- Definition of “rare disease” varies by country
  - Absolute prevalence: USA<200,000; Japan<50,000; S Korea <20,000…
  - Percentage prevalence: EU<5 in 10,000; Australia<1 in 2000…
- <5% of rare diseases have a regulatorily approved treatment
  - USA ~300 diseases
  - At current rate 3-5 newly treatable diseases/yr… >1000 yrs to all

NCATS Office of Rare Diseases Research

- ***ORDR Mission:*** *Accelerate the translation of rare disease science to benefit patients*
- ***Major Programs and Initiatives:***

Petra Kaufmann
Director

Anne Pariser
Deputy Director

Rare Diseases Clinical Research Network (RDCRN) Program

Genetics And Rare Diseases (GARD) Information Center

Global Rare Diseases Patient Registry Data Repository (GRDR)

NCATS Scientific Conferences Program

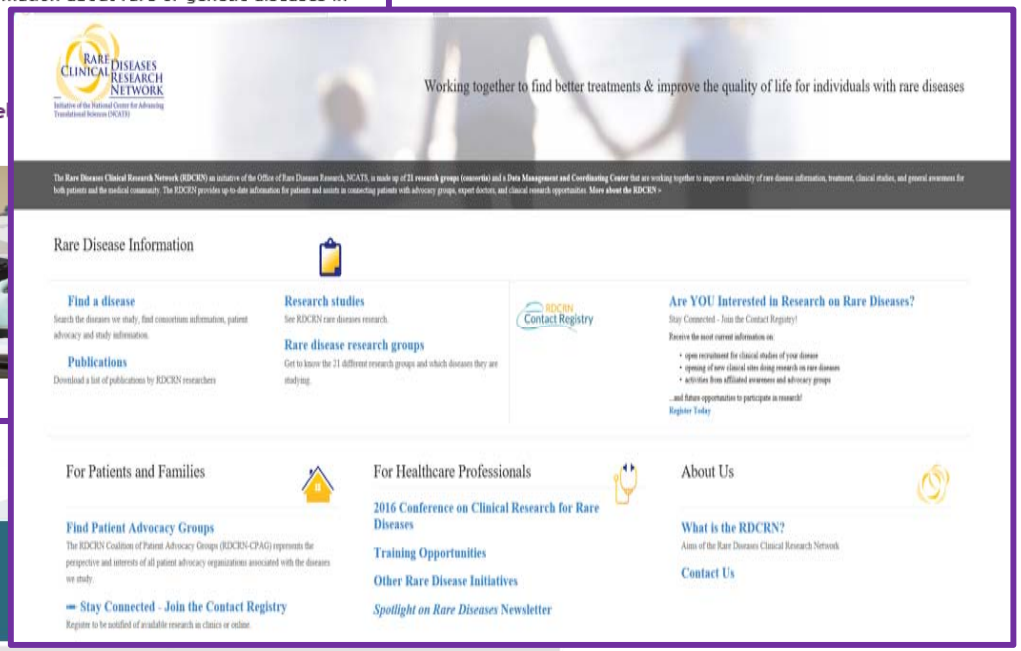
Bench to Bedside Awards

NCATS Toolkit Project

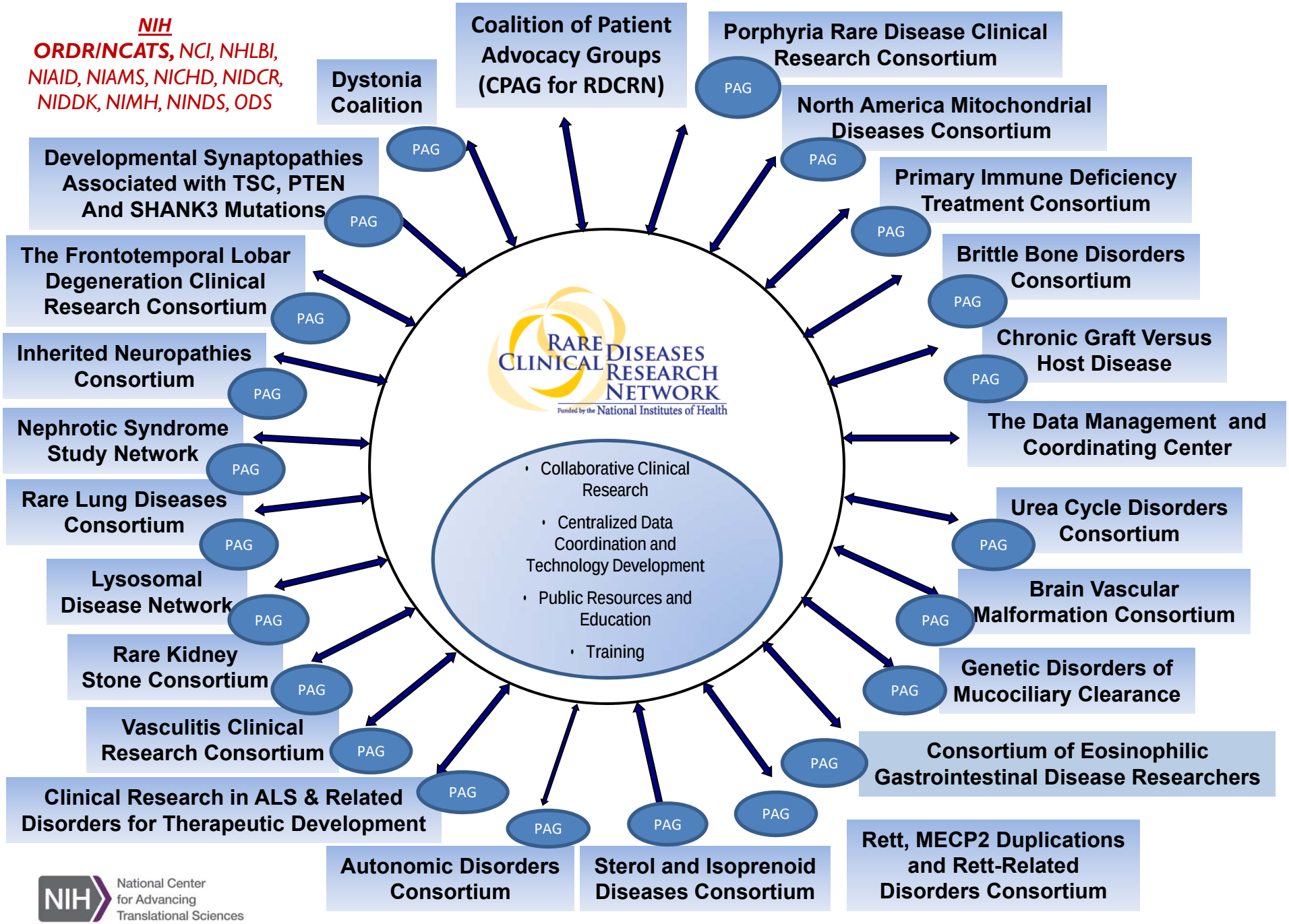
Office of Rare Diseases Research

GARD

https://rarediseases.info.nih.gov/

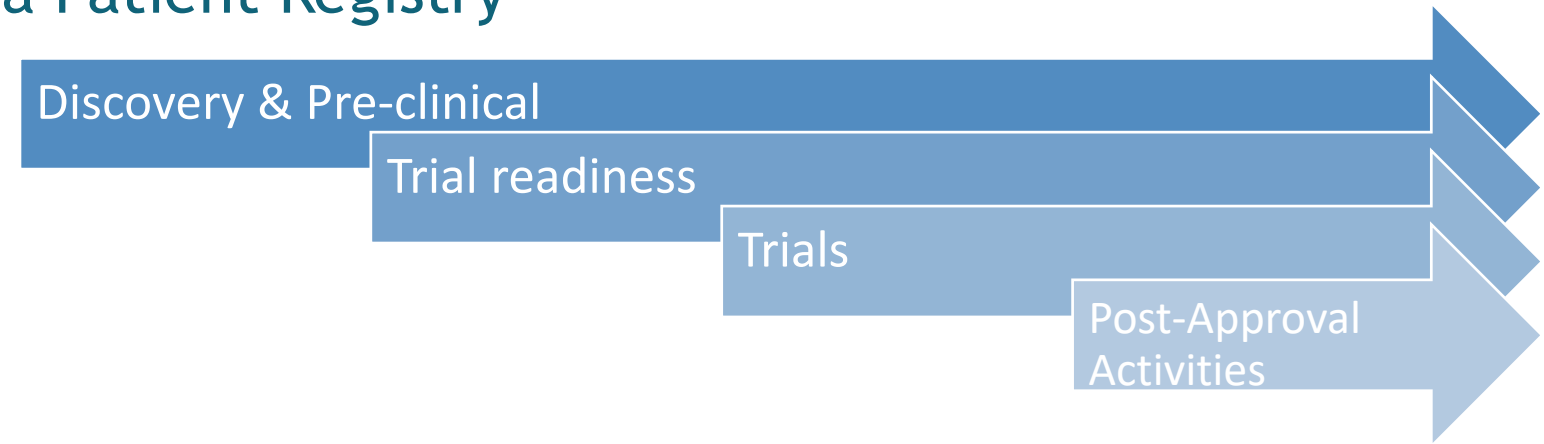


[2]https://www.rarediseasesnetwork.org/


NIH
ORDR/NCATS, NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIDDK, NIMH, NINDS, ODS
Coalition of Patient Advocacy Groups (CPAG for RDCRN)
Dystonia Coalition
Porphyria Rare Disease Clinical Research Consortium
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
NIH National Center for Advancing Translational Sciences

re Disease Patient Toolkit Project

- Provide centralized web portal to online tools and resources that patient groups can readily access to accelerate their work
- Focus on tools/resources across the drug development process
- "How-to" perspective, e.g. "How To Establish and Utilize a Patient Registry"



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National Center for Advancing Translational Sciences

Save the Date of Sept. 8, 2017!

Join us for the NCATS Toolkit for Patient-Focused Therapy Development: Demonstration and Dissemination Meeting

On Sept. 8, 2017, NCATS will launch a new, centralized online resource portal that will enable patient groups to make progress along the entire translational science spectrum, no matter where they might be in that process. The NCATS Toolkit for Patient-Focused Therapy Development: Demonstration and Dissemination Meeting will take place from 9 a.m. to 4 p.m. ET on the NIH campus in Bethesda, Maryland. The event will enable the rare diseases and other patient communities to learn more about the toolkit, including how it can streamline their therapeutic development activities. Participants also will have the opportunity to provide input into how the toolkit can be refined, expanded and made even more useful.

Developed in collaboration with patients and rare disease advocates, the toolkit is a centralized online portal for resources and tools that will cover the broad therapy development landscape, including:

- How to establish a patient registry;
- How to drive patient-focused discovery and pre-clinical research and development;
- How to work with NIH and the Food and Drug Administration; and
- How to conduct post-market surveillance.

Register now and learn more >
https://events-support.com/events/NCATS_Toolkit_Meeting

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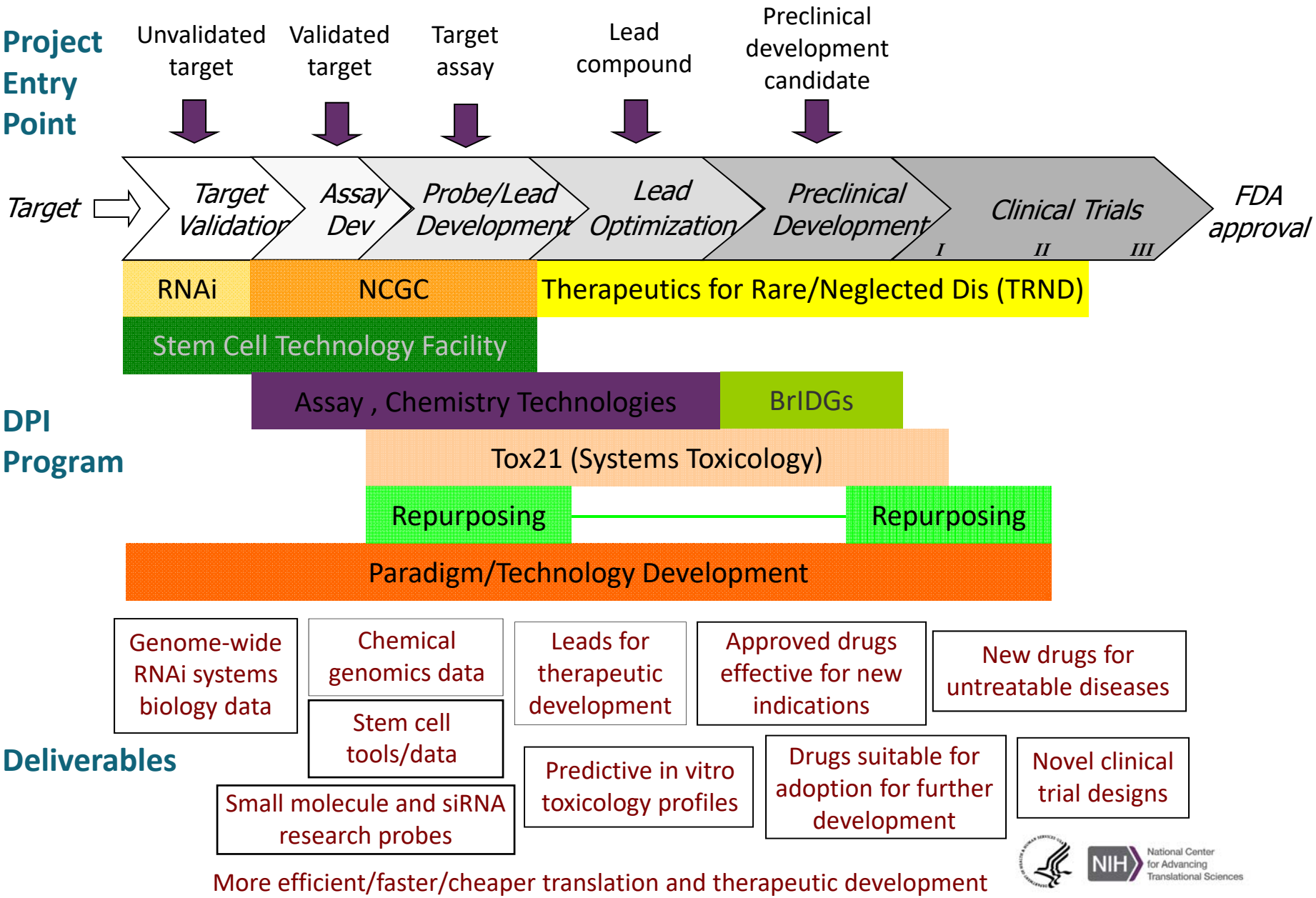
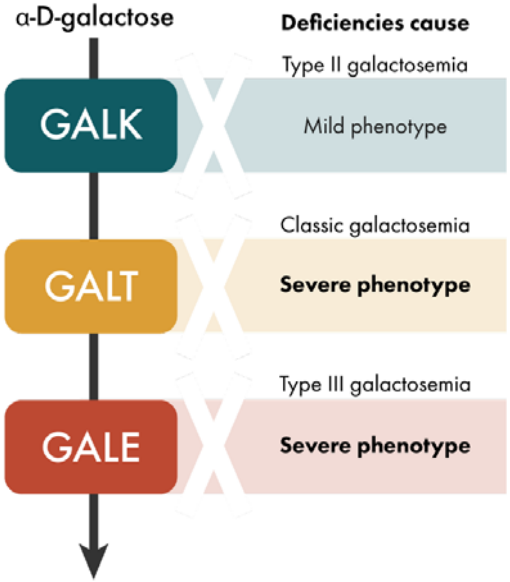
NCATS Division of Preclinical Innovation

A Collaborative Engine



First-in-class GALK Inhibitors for Classic Galactosemia

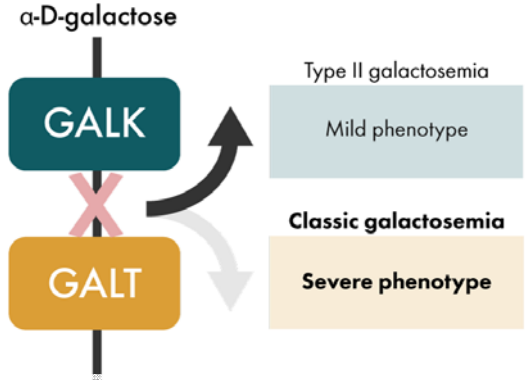
1 Galactosemias: Rare autosomal recessive disorders in which the body cannot properly metabolize galactose



Classic Galactosemia - most common & severe of the galactosemias (~1 in 30,000-60,000 births)

- Results from GALT deficiency
- Lethal without dietary galactose restriction
- Leads to mental deficits, ovarian dysfunction
- No current therapy

2 GALK as a drug target



Type II galactosemics (GALK deficient) do not suffer from same clinical manifestations and long term problems associated with Classic Galactosemia

Hypothesis: GALK inhibition will phenocopy Type II Galactosemia in Classic Galactosemics, leading to milder, more easily manageable disease

3 GALK high-throughput inhibitor screen

Screened 350,000+ compounds for human GALK inhibition → Performed med chem on top active scaffolds → Further refinement to improve ADME/PK

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Hit

GALK IC_{50}: **7.6 uM**
Solubility: **<1 ug/mL**

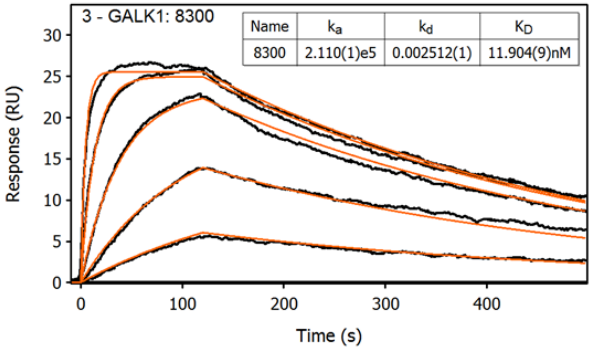
Lead

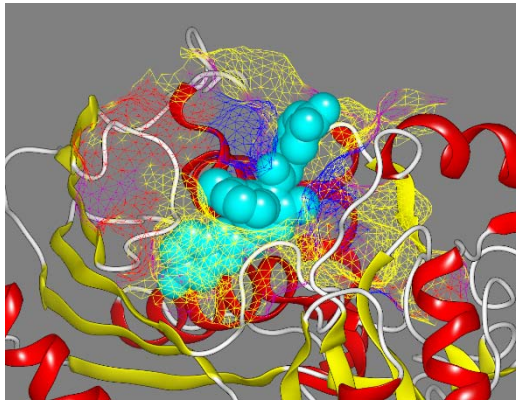
GALK IC_{50}: **330 nM**
Solubility: **64 ug/mL**

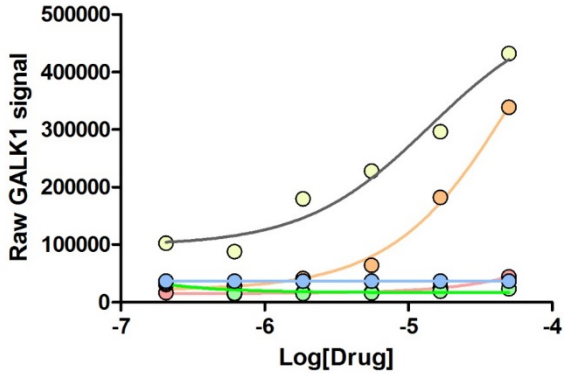
ADME:
Kin. Sol: 64 ug/mL
RLMS $t_{1/2}$: >30 min
MLMS: 93% rem @ 15 min

In vivo PK:
47 mg/kg, IP
$t_{1/2}$: 1.73 hr
Cmax: 226 uM
AUC_{inf} 28,358 h* ng/mL

4 Lead characterization & cellular activity





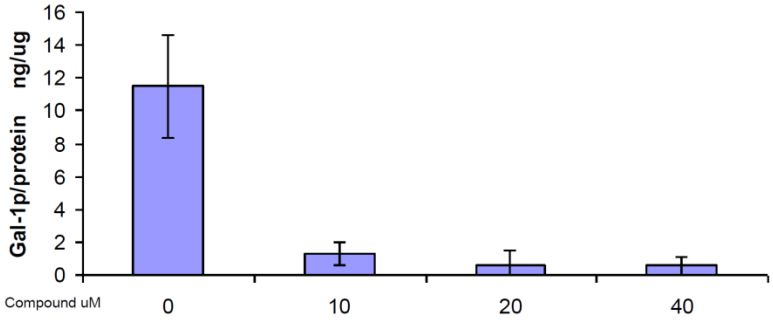


SPR demonstrating high affinity GALK binding of lead

Human GALK co-crystal w/ lead

CETSA demonstrating on-target binding of GALK in cells

5 Patient cell activity and upcoming *in vivo* models



Primary Patient Cell Data

Compounds very effectively lower gal-1-p levels in Classic Galactosemia primary patient fibroblasts with no galactose challenge (clinically relevant

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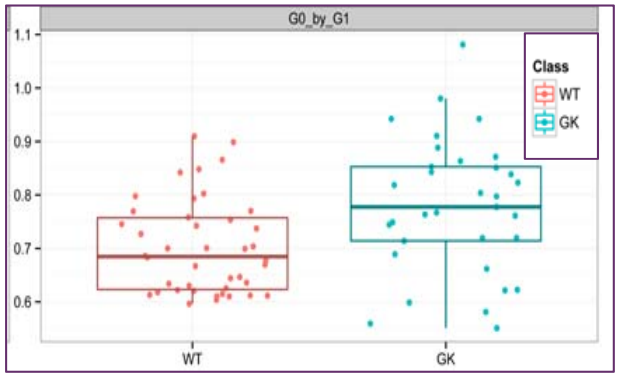
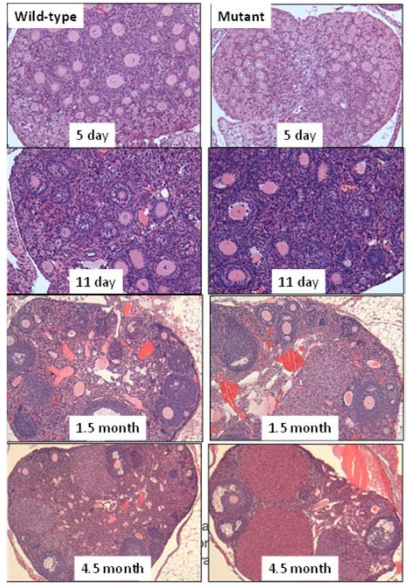
GalT-gene trapped mice



Ratio of non-galactosylated IgG (G0) to mono-galactosylated IgG (G1) in wild type (red boxes) vs GalT-gene trapped (GalT-"knockout") (GK, blue boxes) mice

WT vs mutant mouse ovary histopathology



NCATS Assay Development & Screening Technology Laboratory

- In collaborative relationships with disease foundations enable drug discovery strategies for early-stage (gateway) translation
  - A. Develop assays to phenocopy molecular hallmarks of pathology leveraging disease knowledge and advances in molecular biology
  - B. Analysis and progression strategies for evaluation of approved drugs, investigational agents, large diversity libraries and complex chemical libraries (e.g., NPEs)
- Training, grant support and outreach to strengthen competencies in translational research in new and established investigators
  - Foundation-sponsored Post-doctoral training opportunities

Jim Inglese

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

GFPD GLOBAL FOUNDATION for PEROXISOMAL DISORDERS

A1 THE ALPHA-1 PROJECT

Hannah's HOPE FUND

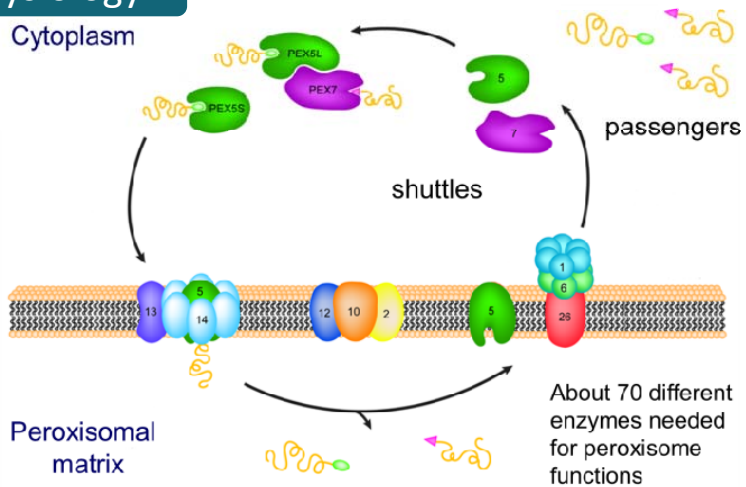
CureJM FOUNDATION

CMTA

Assay development strategies for PBD-ZSD

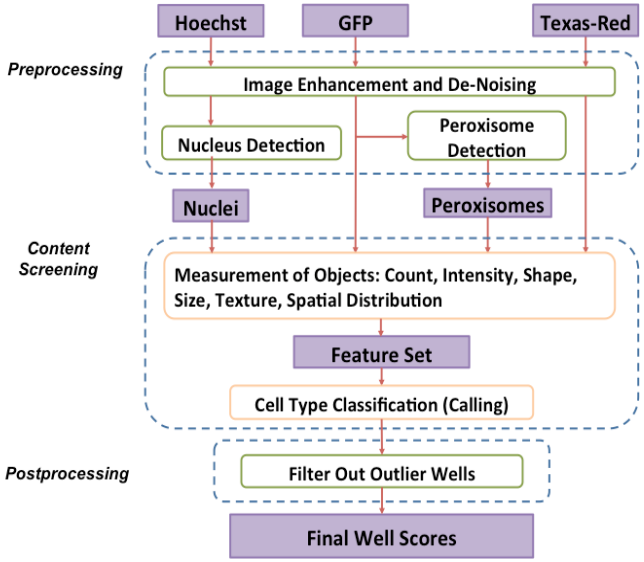
Pathophysiology

Increased VLCFA levels and decreased plasmalogen levels in blood & tissues

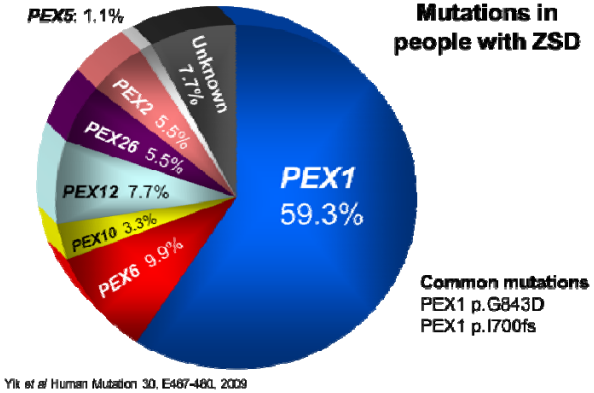


VLCFA β-oxidation

HCS assay development & data

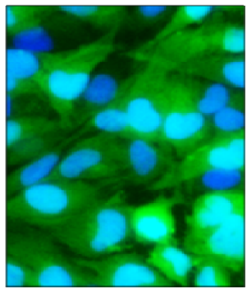


Genetic & molecular basis

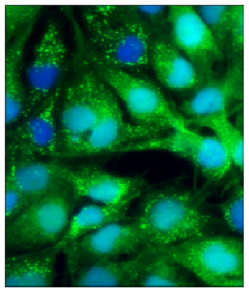


Inglese (NCATS), Hacia, Braverman

Skin fibroblasts modified to express GFP-PTS1 protein

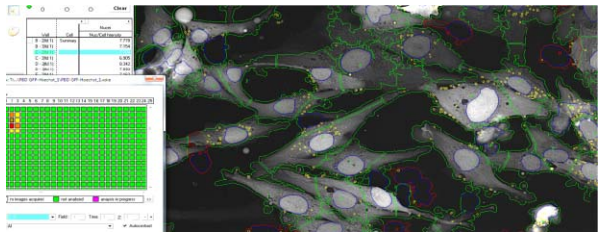


In cytoplasm of immortalized fibroblasts from patient *PEX1* p.G843D/I700fs



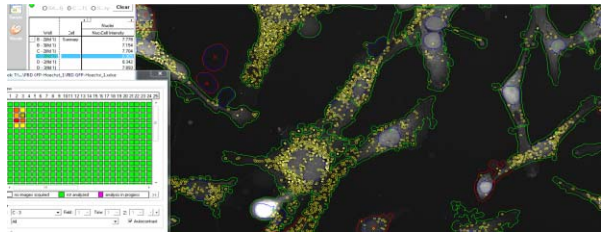
In peroxisomes of the same patient fibroblasts rescued by small molecule treatments

Negative Control Well Image



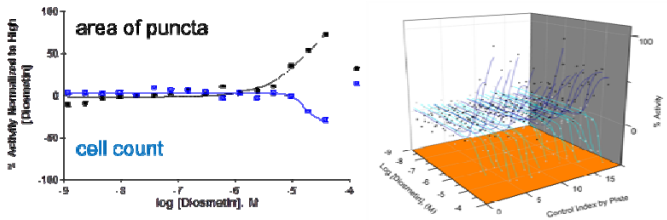
IN Cell Analyzer HCA System Software

Positive Control Well Image

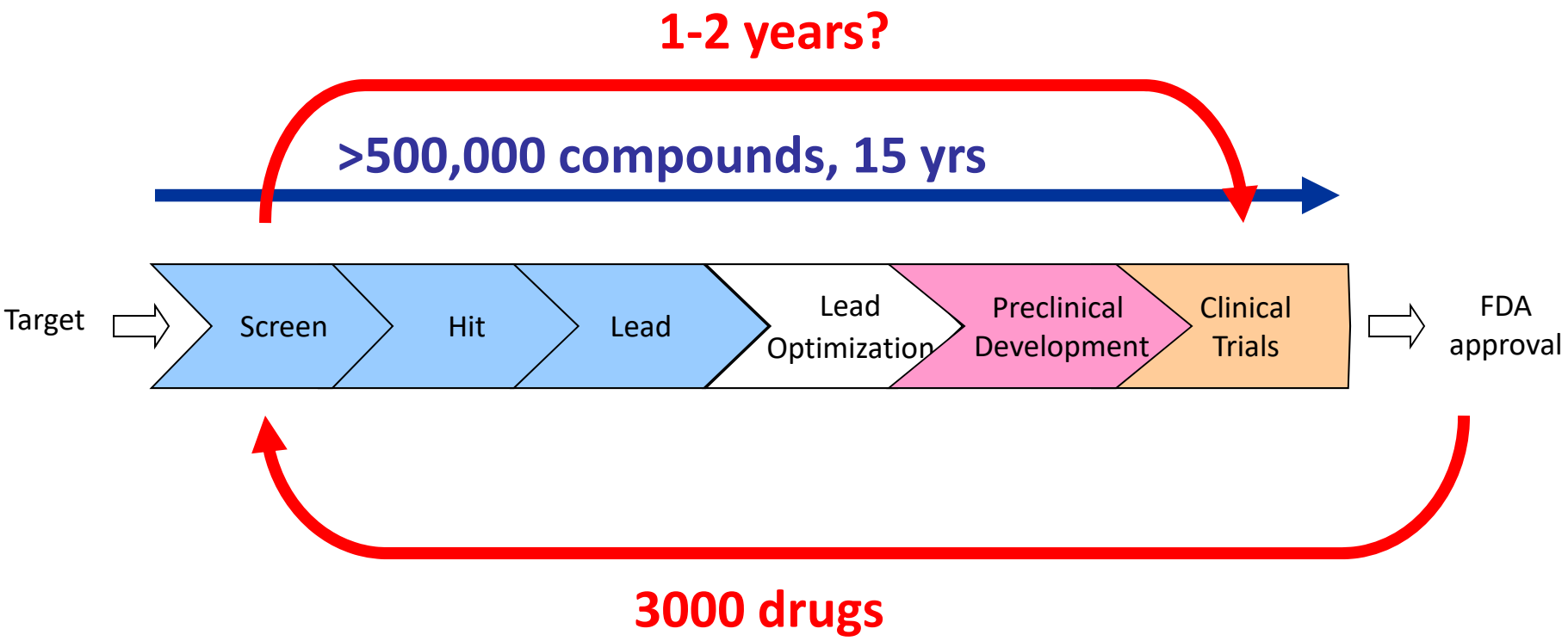


IN Cell Analyzer HCA System Software

Diosmetin Control



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

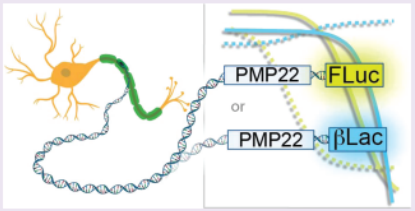
Sung-Wook Jang,[†] Camila Lopez-Anido,[§] Ryan MacArthur,[†] John Svaren,[§] and James Inglese*[,†,‡]

[†]National Center of Advancing Translational Sciences and [‡]National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, United States

[§]Department of Comparative Biosciences, and Waisman Center, University of Wisconsin, Madison, Wisconsin 53705, United States

Supporting Information

ABSTRACT: The structural integrity of myelin formed by Schwann cells in the peripheral nervous system (PNS) is required for proper nerve conduction and is dependent on adequate expression of myelin genes including peripheral myelin protein 22 (*PMP22*). Consequently, excess PMP22 resulting from its genetic duplication and overexpression has been directly associated with the peripheral neuropathy called Charcot-Marie-Tooth disease type 1A (CMT1A), the most prevalent type of CMT. Here, in an attempt to identify transcriptional inhibitors with therapeutic value toward CMT1A, we developed a cross-validating pair of orthogonal reporter assays, firefly luciferase (FLuc) and β-lactamase (βLac), capable of recapitulating PMP22 expression, utilizing the intronic regulatory element of the human *PMP22* gene. Each compound from a collection of approximately 3,000 approved drugs was tested at multiple titration points to achieve a pharmacological end point in a 1536-well plate quantitative high-throughput screen (qHTS) format. In conjunction with an independent counter-screen for cytotoxicity, the design of our orthogonal screen platform effectively contributed to selection and prioritization of active compounds, among which three drugs (fenretinide, olvanil, and bortezomib) exhibited marked reduction of endogenous Pmp22 mRNA and protein. Overall, the findings of this study provide a strategic approach to assay development for gene-dosage diseases such as CMT1A.



nature COMMUNICATIONS

ARTICLE

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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]

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

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; National Center for Advancing Translational Sciences; National Institutes of Health; Bethesda, MD USA; [2]Department of Medicine; Duke University; Durham, NC USA; [3]University of Virginia; Charlottesville, VA USA; [4]Chordoma Foundation; Durham, NC USA

[†]These authors contributed equally to this work.

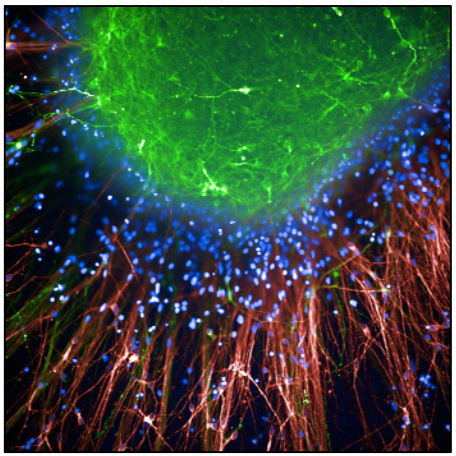
Keywords: chordoma, NCGC Pharmaceutical Collection, cell viability, caspase 3/7, U-CH1, U-CH2, qHTS

NIH National Center for Advancing Translational Sciences

NCATS Stem Cell Translation Laboratory

Overcoming systemic barriers to clinical application of iPSCs

- Part of NIH Common Fund Regenerative Medicine Program
- Goal: Bring iPS cells closer to clinical applications in drug discovery and regenerative medicine by developing characterization standards, improved iPSC differentiation protocols
- Cutting-edge technologies (e.g. qHTS, single cell proteomics, next-gen sequencing) and multidisciplinary team approach (e.g. biologists, chemists, engineers, bioinformaticians)
- SCTL is seeking new collaborations to help achieve common goals in iPS cell biology in a faster and more coordinated fashion (e.g. comprehensive cell characterization, functional maturation)

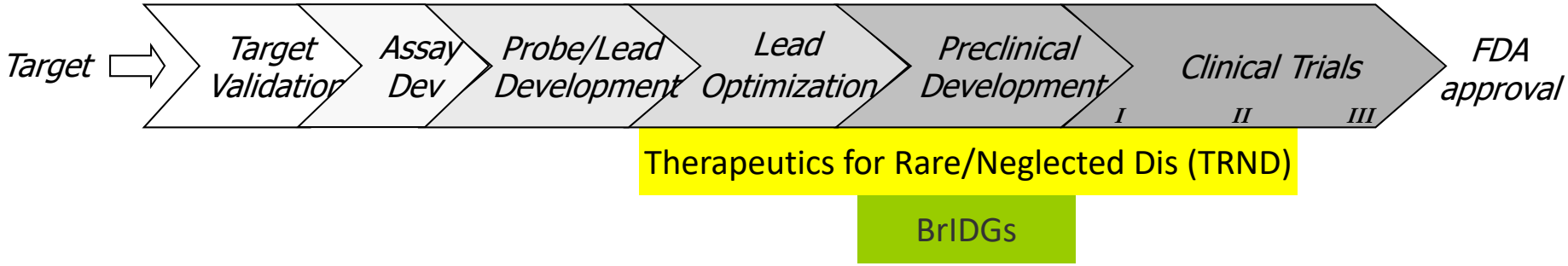


Ilyas Singeç

NIH National Center for Advancing Translational Sciences

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:

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

Ex-U.S. applicants accepted

NIH National Center for Advancing Translational Sciences

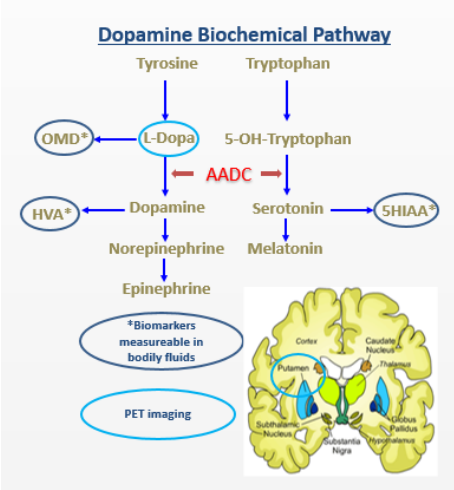
NCATS TRND Project

Aromatic L-Amino Acid Decarboxylase Deficiency

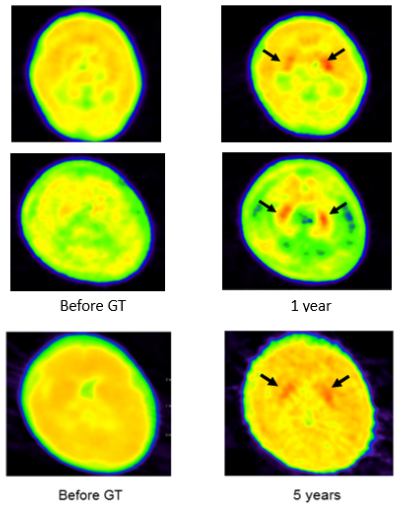
- Collaborator: Agilis Biotherapeutics
- Gene Therapy: single dose AAV-hAADC injection into putamen
- AADC: Profound Developmental Failure
  - Extremely limited muscle strength, control and movement
  - Seizure-like symptoms (oculogyric crises)
  - Lifelong care and frequent hospitalizations
  - Severe forms have catastrophic course (average life expectancy of 4-8 yrs)

- Challenges to develop AAV-AADC
  - Ultra-rare disease (underdiagnosed) – small market
  - Stereotactic surgery in infant brains
  - Regulatory: phase 1 and phase 2 human data outside of U.S.

- TRND collaboration catalyzing development of AAV-AADC
  - 18 AADC patients received GT with some remarkable clinical responses
  - Project initiation, May, 2016
  - GMP grade AAV-AADC manufacturing production
  - GLP bio-distribution and toxicology testing in rodents
  - Patient finding / epidemiology study
  - FDA EOP2 meeting July 2017



PET Imaging: *De Novo* Dopamine Production

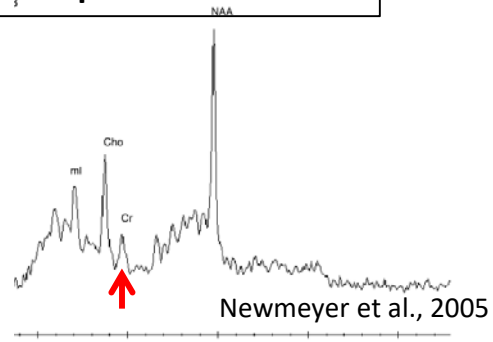


National Center for Advancing Translational Sciences

Development of LUM-001 as a Treatment for Creatine Transporter Deficiency (CTD)

- Collaborator: Lumos Pharma
- Disease: X-linked cerebral creatine deficiency caused by mutations in the creatine transporter encoded by the *SLC6A8* gene
  - ➢ Reduced creatine levels in brain leads to decreased levels of ATP needed as energy source
  - ➢ Severe intellectual disability and developmental delay
- No currently approved therapies

CTD patient brain MRS



Newmeyer et al., 2005

PreClinical Studies

Question: Does LUM-001 reach therapeutic concentrations in brain?

- *In vitro* cell uptake studies
- *In vivo* ^{14}C-LUM-001 PK/distribution study
- PK/ADME
- Bioanalytical method development
- CMC/formulation
- Toxicology

Clinical Studies

- Multi-site Natural History Study: Lumos, NCATS, UPenn, and Duke
- Centralized data management using NIH Clinical Trials Database and biological sample collection

Outcomes

- IND approved & Phase I initiated Oct. 2016
- Natural History study initiated Oct. 2016
- Lumos received funding to support further clinical development
  - Welcome Trust Award
  - VC funding

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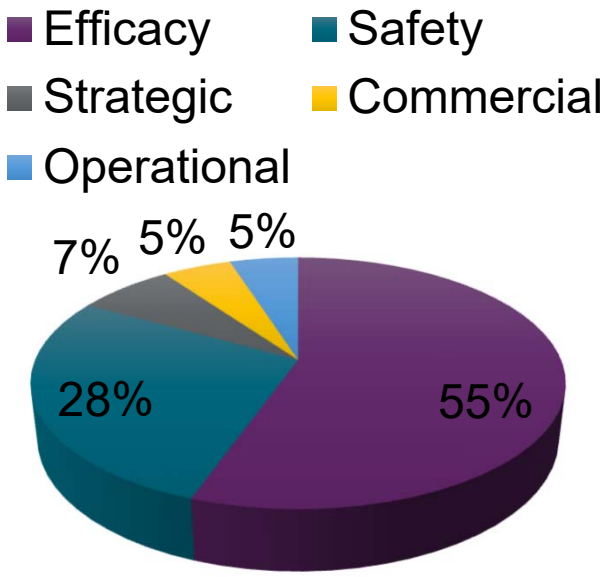
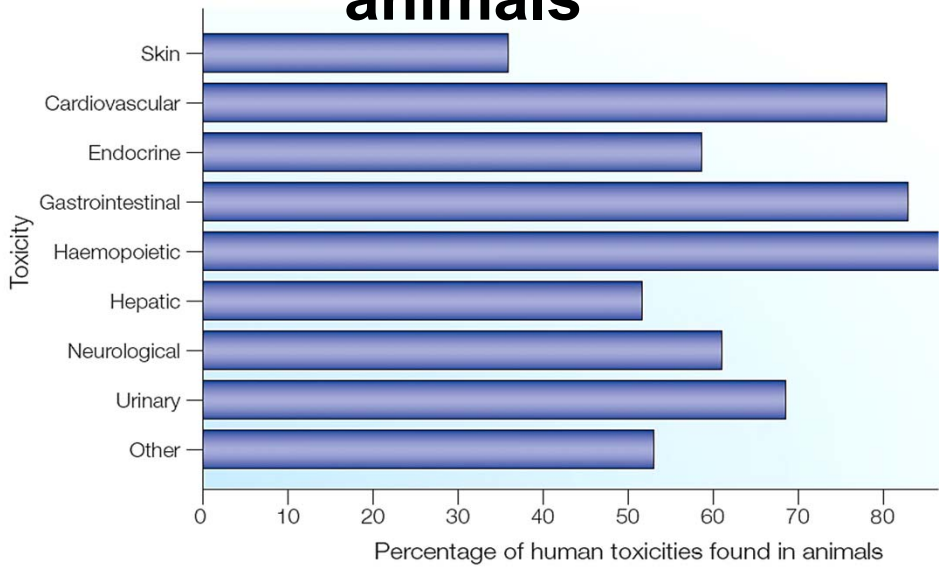
TRND Collaboration: Catalyzing Development

Why Drugs Fail in Development

Drug Failure Modes



Human toxicities found in animals



Arrowsmith and Miller, Nature Reviews Drug Discovery, Volume 12, 569 (2013)

Cook et al., Nature Reviews Drug Discovery, Volume 13, 419 (2014)

Human Tissue Chip Program

Goal: develop biochips to test for safe, effective drugs

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

NIH

Phase 1:
Individual chips

Phase 2:
Cell incorporation and organ integration

- Current focus:
  - Integration (DARPA and NIH); insight/expertise (FDA); compound testing, validation
  - Partnerships (MTA: GSK; Pfizer; AZ; MOU: IQ Consortium)
  - Adoptions of the tech to the community

nature medicine

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NATURE MEDICINE | NEWS

Channeling chip power: Tissue chips are being put to the test by industry

Cassandra Willyard

Nature Medicine **23**, 138–140 (2017) | doi:10.1038/nm0217-138
Published online 07 February 2017

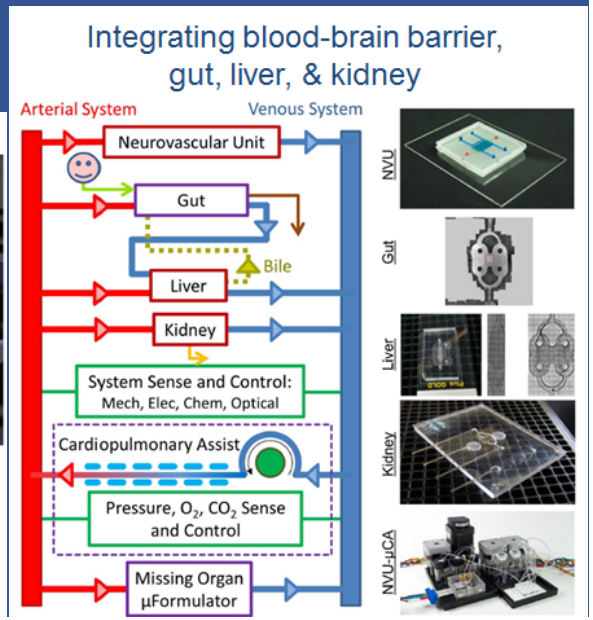
NEWS IN FOCUS

NATURE | VOL 523 | 16 JULY 2015

Miniature devices that mimic human organs could help to replace animals used in drug testing.

BIOTECHNOLOGY

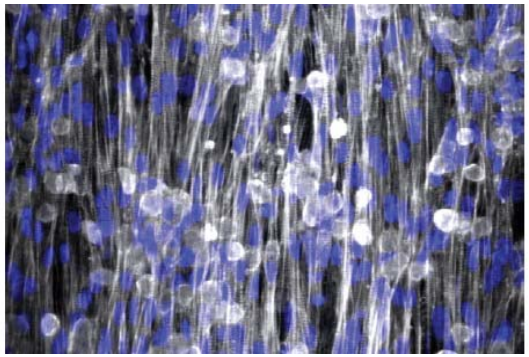
'Organs-on-chips' go mainstream



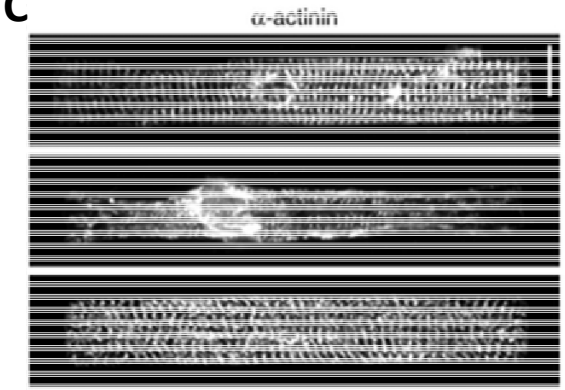
Barth Syndrome Heart on a Chip Model

A

B



C



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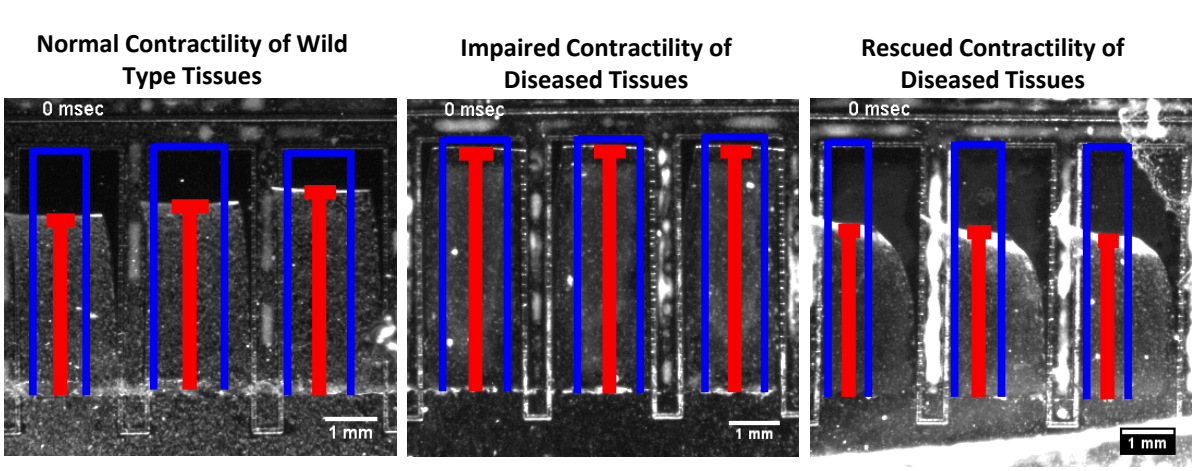
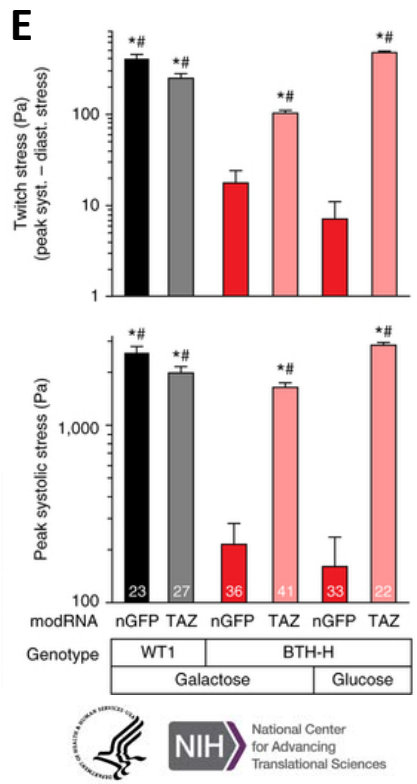


E



Barth Syndrome Heart on a Chip Model

ARTICLES

nature medicine

Modeling the mitochondrial cardiomyopathy of Barth syndrome with induced pluripotent stem cell and heart-on-chip technologies

Gang Wang[1,14], Megan L McCain[2,14], Luhan Yang[2,3], Aibin He[1], Francesco Silvio Pasqualini[2], Ashutosh Agarwal[2], Hongyan Yuan[2], Dawei Jiang[1], Donghui Zhang[1], Lior Zangi[1], Judith Geva[1], Amy E Roberts[1,4], Qing Ma[1], Jian Ding[1], Jinghai Chen[1], Da-Zhi Wang[1], Kai Li[1], Jiwu Wang[5,6], Ronald J A Wanders[7], Wim Kulik[7], Frédéric M Vaz[7], Michael A Laflamme[8], Charles E Murry[8–10], Kenneth R Chien[11], Richard I Kelley[12], George M Church[2,3], Kevin Kit Parker[2,13] & William T Pu[1,13]

Study of monogenic mitochondrial cardiomyopathies may yield insights into mitochondrial roles in cardiac development and disease. Here, we combined patient-derived and genetically engineered induced pluripotent stem cells (iPSCs) with tissue engineering to elucidate the pathophysiology underlying the cardiomyopathy of Barth syndrome (BTHS), a mitochondrial disorder caused by mutation of the gene encoding tafazzin (*TAZ*). Using BTHS iPSC-derived cardiomyocytes (iPSC-CMs), we defined metabolic, structural and functional abnormalities associated with *TAZ* mutation. BTHS iPSC-CMs assembled sparse and irregular sarcomeres, and engineered BTHS 'heart-on-chip' tissues contracted weakly. Gene replacement and genome editing demonstrated that *TAZ* mutation is necessary and sufficient for these phenotypes. Sarcomere assembly and myocardial contraction abnormalities occurred in the context of normal whole-cell ATP levels. Excess levels of reactive oxygen species mechanistically linked *TAZ* mutation to impaired cardiomyocyte function. Our study provides new insights into the pathogenesis of Barth syndrome, suggests new treatment strategies and advances iPSC-based *in vitro* modeling of cardiomyopathy.

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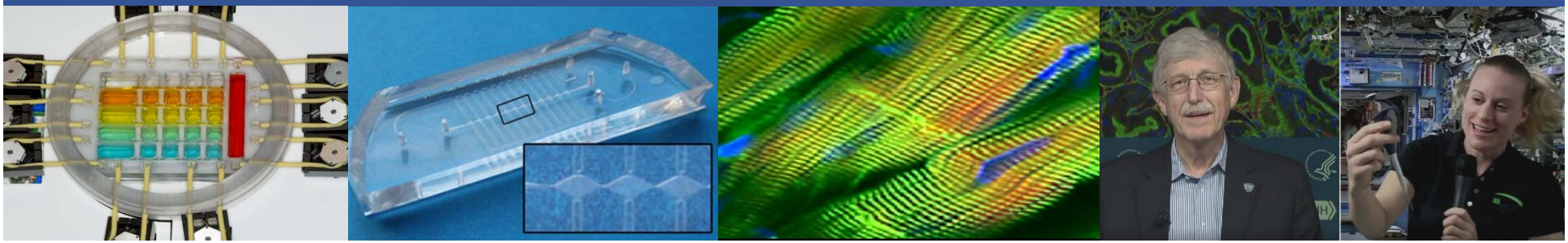
Next Phase Tissue Chip Initiatives

- Tissue Chip Testing Centers *(2016-2018)*
  - Tech transfer and testing at 2 independent centers (Texas A&M and MIT)
- Tissue Chips for Disease Modeling *(2017–2022)*
  - Develop tissue chip models of human diseases, particularly rare
    - Using human primary or induced pluripotent stem cell sources
  - Use to test effectiveness of candidate therapeutics
- Tissue Chips in Space *(2017–2021)*
  - Partnership with Center for the Advancement of Science in Space (CASIS)
  - Adapt, refine chips for on-flight experiments at the International Space Station U.S. National Laboratory
    - To understand diseases (e.g. bone, muscle, aging) prevalent on earth and accelerated in space



International Rare Diseases Research Consortium (IRDiRC)

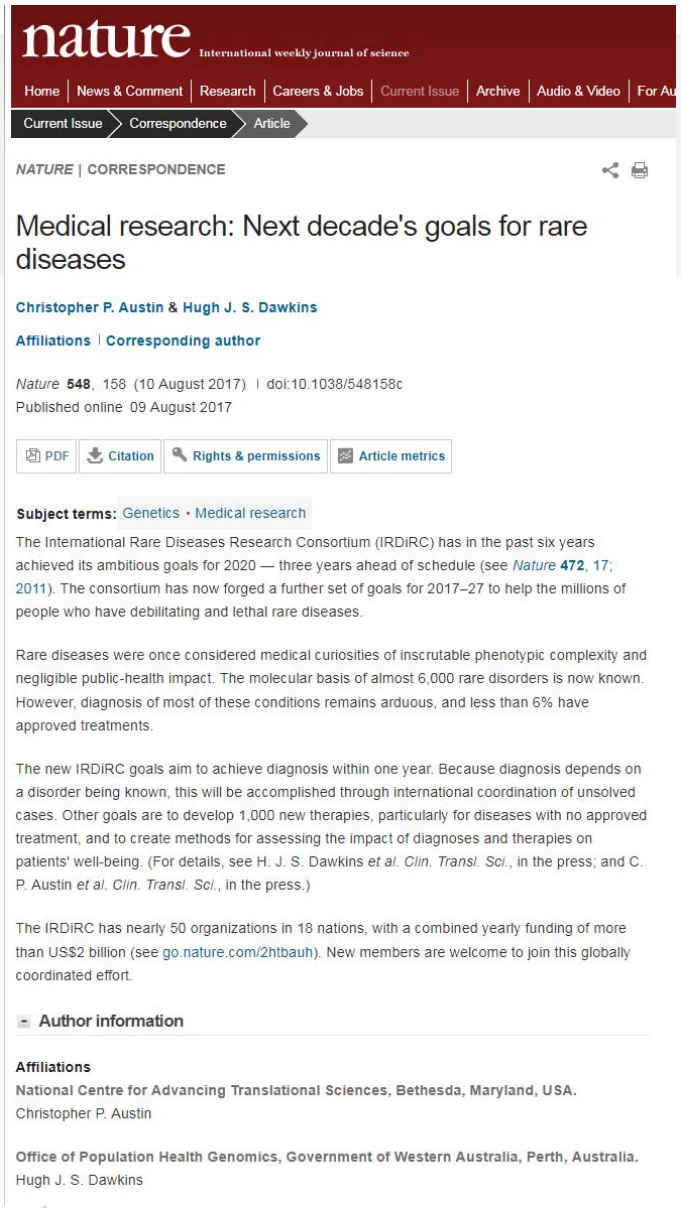
- Established 2011 to maximize global coordination and cooperation in rare disease research
  - Members from Europe, North America, Asia, Australia, Middle East
  - Each funder supports its own research
- Initial focus on developing common scientific and policy frameworks
- 2011-2020 objectives:
  - 200 new therapies for rare diseases by 2020
  - Means to diagnose most rare diseases by 2020
  - *Achieved in 2017 → new objectives formulated*

IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

IRDiRC Consortium Assembly

- Western Australia Department of Health
- European Organisation for Treatment & Research on Cancer, EORTC
- Canadian Institutes for Health Research
- Genome Canada
- BGI
- Chinese RD Research Consortium
- WuXi AppTec
- E-Rare 2 Consortium
- European Commission
- Academy of Finland
- Agence Nationale de la Recherche, ANR
- Fondation maladies rares
- French Muscular Dystrophiy Association, AFM
- Lysogene
- Children's New Hospitals Management Group
- Federal Ministry of Education and Research
- Shire
- Chiesi Pharmaceuticals
- Istituto Superiore de Sanita
- Telethon Foundation
- Japan Agency for Medical Research and Development, AMED
- National Institutes of Biomedical Innovation, Health and Nutrition, NIBIOHN
- Saudi Human Genome Project
- Netherlands Organisation for Health Research and Devevelopment
- Korea National Institute of Health
- National Institute of Health Carlos III, ISCIII
- Roche
- National Institute for Health Research
- Food and Drug Administration, FDA
- National Cancer Institute, NCI, NIH
- National Center for Advancing Translational Sciences, NCATS, NIH
- National Eye Institute, NEI, NIH
- National Human Genome Research Institute, NHGRI, NIH
- National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIAMS, NIH
- National Institute of Child Health and Human Development, NICHD, NIH
- National Institute of Neurological Disorders and Stroke, NINDS, NIH
- NKT Therapeutics
- Pfizer
- PTC Therapeutics
- Sanford Research
- EURORDIS
- National Organization for Rare Diseases
- Genetic Alliance

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM



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NATURE | CORRESPONDENCE

Medical research: Next decade's goals for rare diseases

Christopher P. Austin & Hugh J. S. Dawkins

Affiliations | Corresponding author

Nature **548**, 158 (10 August 2017) | doi:10.1038/548158c
Published online 09 August 2017

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Subject terms: Genetics • Medical research

The International Rare Diseases Research Consortium (IRDiRC) has in the past six years achieved its ambitious goals for 2020 — three years ahead of schedule (see *Nature* **472**, 17; 2011). The consortium has now forged a further set of goals for 2017–27 to help the millions of people who have debilitating and lethal rare diseases.

Rare diseases were once considered medical curiosities of inscrutable phenotypic complexity and negligible public-health impact. The molecular basis of almost 6,000 rare disorders is now known. However, diagnosis of most of these conditions remains arduous, and less than 6% have approved treatments.

The new IRDiRC goals aim to achieve diagnosis within one year. Because diagnosis depends on a disorder being known, this will be accomplished through international coordination of unsolved cases. Other goals are to develop 1,000 new therapies, particularly for diseases with no approved treatment, and to create methods for assessing the impact of diagnoses and therapies on patients' well-being. (For details, see H. J. S. Dawkins *et al. Clin. Transl. Sci.*, in the press; and C. P. Austin *et al. Clin. Transl. Sci.*, in the press.)

The IRDiRC has nearly 50 organizations in 18 nations, with a combined yearly funding of more than US$2 billion (see go.nature.com/2htbauh). New members are welcome to join this globally coordinated effort.

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Hugh J. S. Dawkins

IRDiRC Goals 2017–2027

VISION: Enable all people living with a rare disease to receive diagnosis, care, and therapy within one year of coming to subspecialty medical attention

GOAL 1: All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline.

GOAL 2: 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options.

GOAL 3: Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients.

IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

More information on IRDiRC

- http://www.irdirc.org/
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- Co-Chair: Hugh Dawkins, hugh.dawkins@health.wa.gov.au
- Secretariat: Lilian Lau, lilian.lau@irdirc.org

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

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