National Center for Advancing Translational Sciences:

Catalyzing Translational Innovation

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

NIH COUNCIL OF COUNCILS
JANUARY 22, 2013

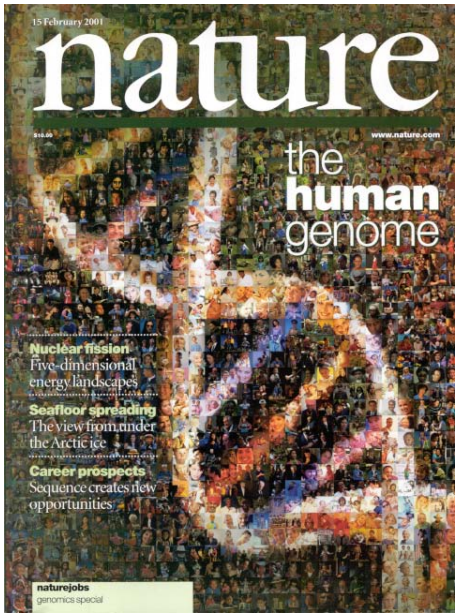
NCATS

NIH National Center for Advancing Translational Sciences

“Houston, we have a problem.”

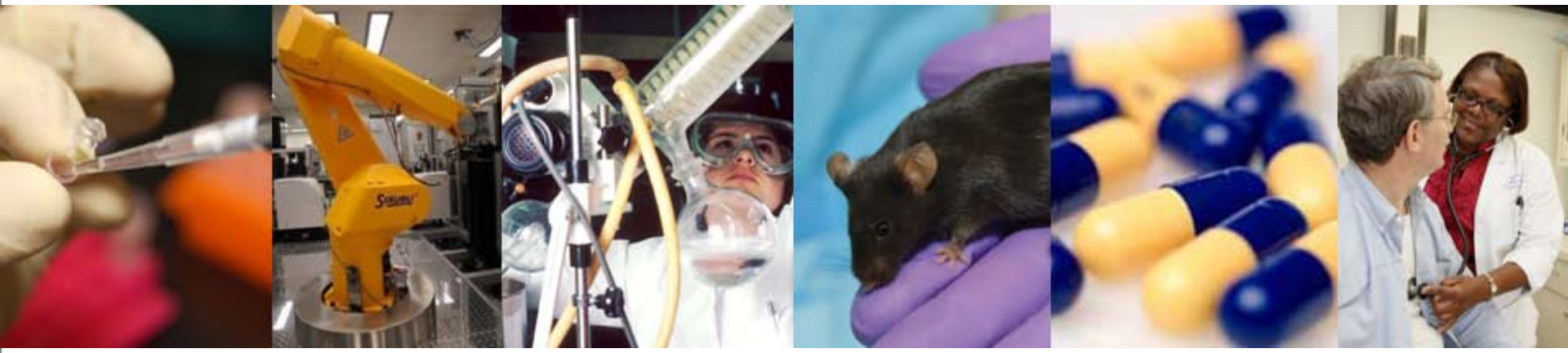
Fundamental science unprecedentedly advanced, but:

- Inefficient transition to interventions that tangibly improve human health
- Drug/device development system in crisis
- Clinical trials system in crisis
- Poor adoption of demonstrably useful interventions



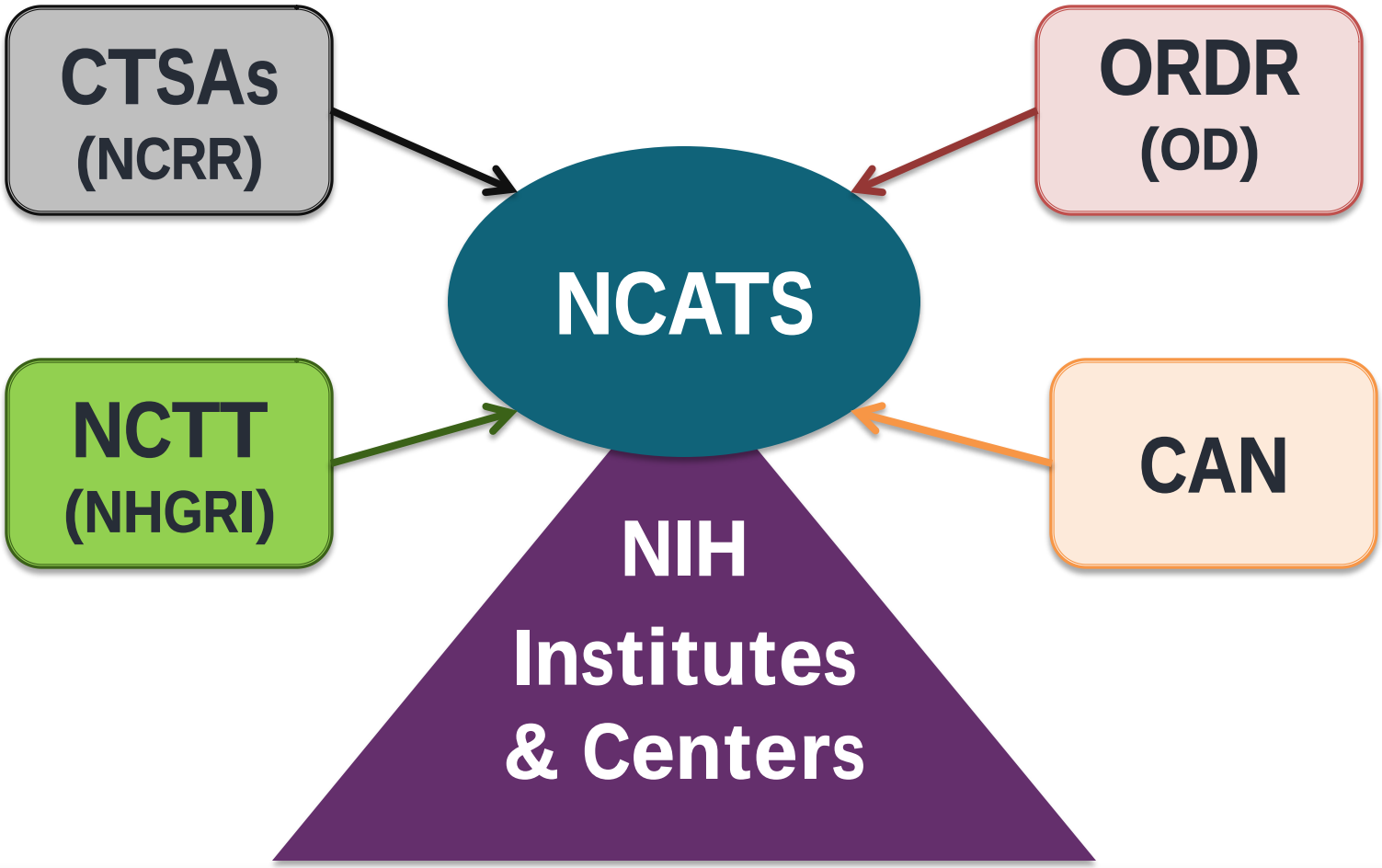
People unhealthier and funders of biomedical research enterprise (public and private) impatient

NCATS Mission

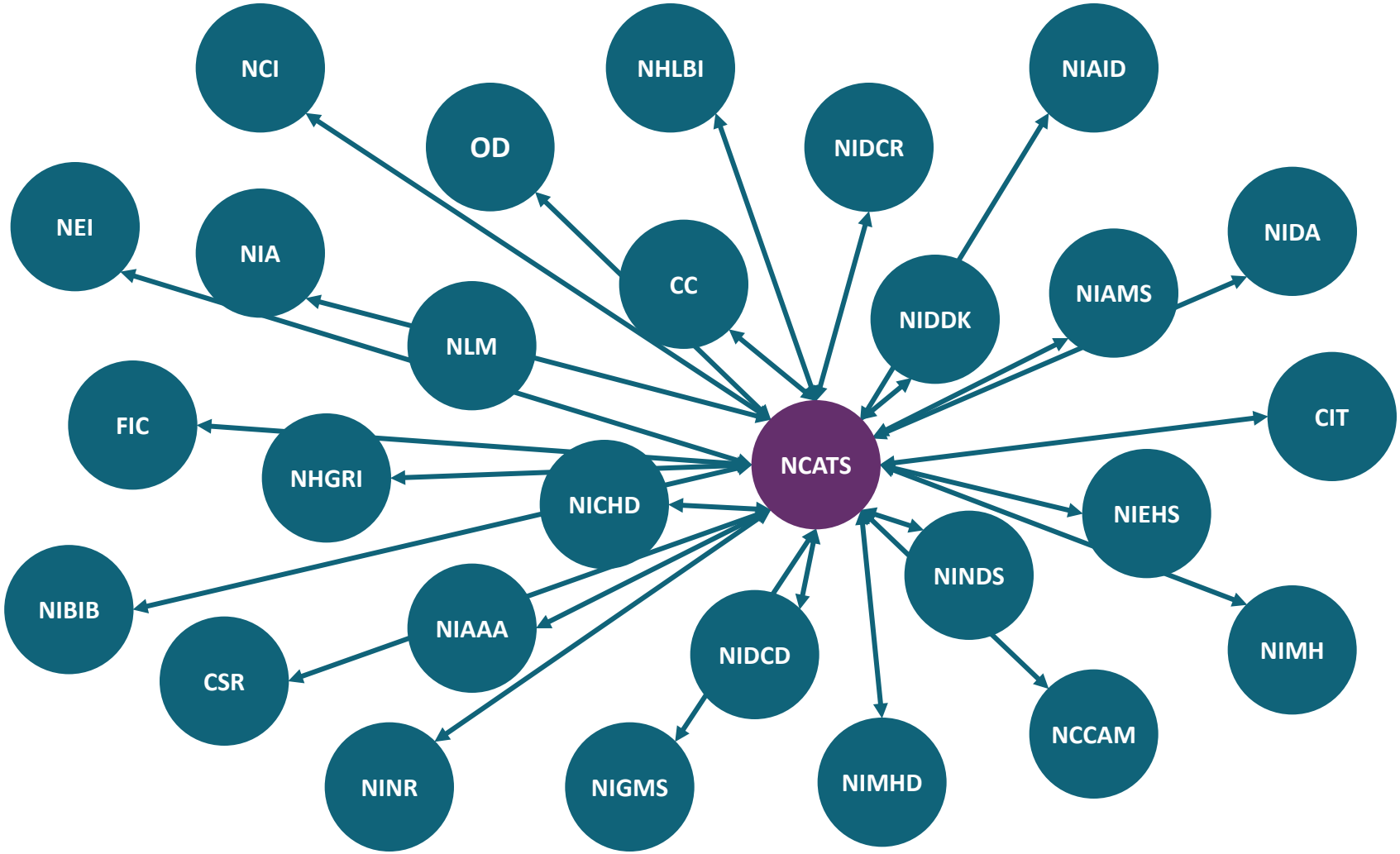


To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

NCATS: Established December 23, 2011



Catalyzing Collaborations Within NIH



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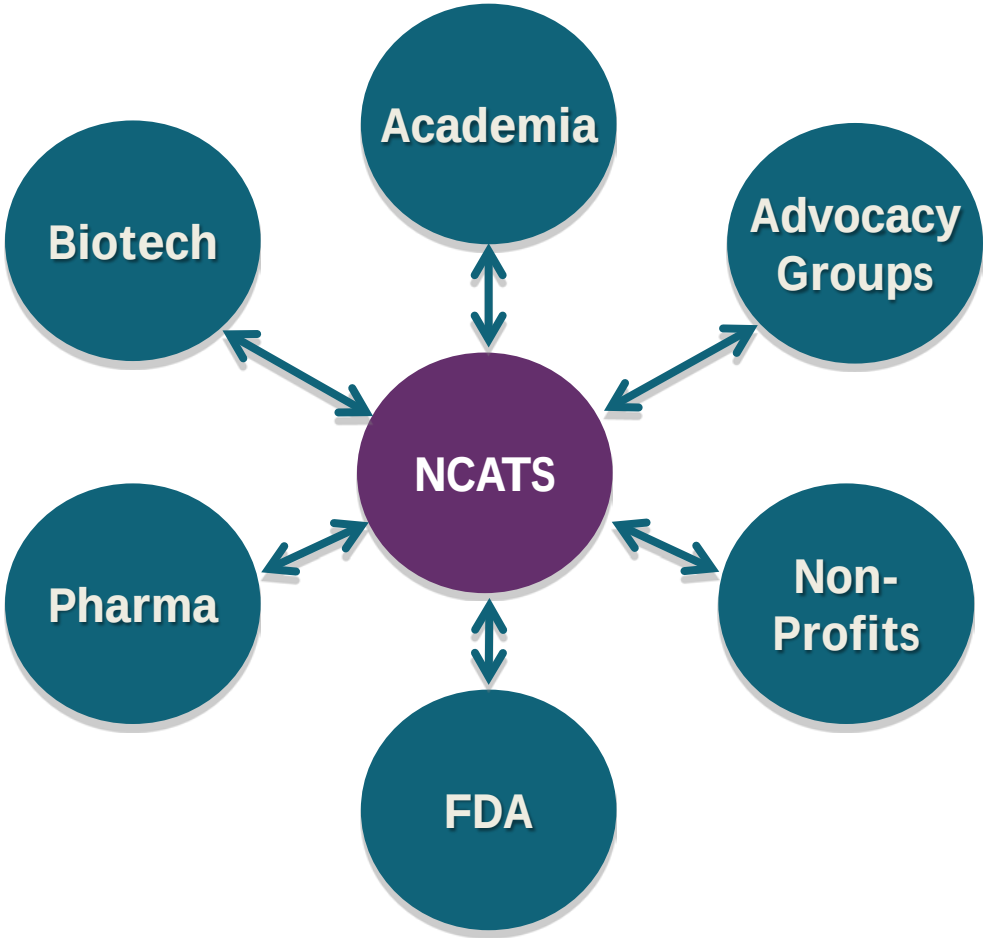
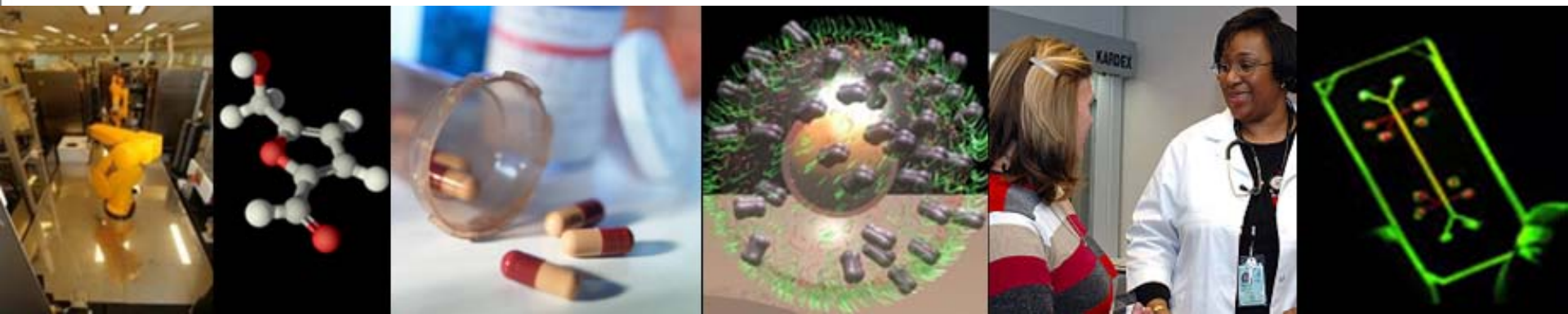
Catalyzing Collaborations Outside NIH



- Complements — does not compete — with the work of others
- Revolutionizes the process of translation by promoting innovative research
- Galvanizes and supports new partnerships
- Supports and augments regulatory science and its application
- Expands the precompetitive space

Examples of Translational Challenges

- Therapeutic target validation
- Chemistry
- Virtual drug design
- Preclinical toxicology
- Biomarkers
- Imaging
- Efficacy testing
- Rescuing and repurposing
- Adaptive clinical trial designs
- Post-marketing research



NCATS "3D's"

Develop
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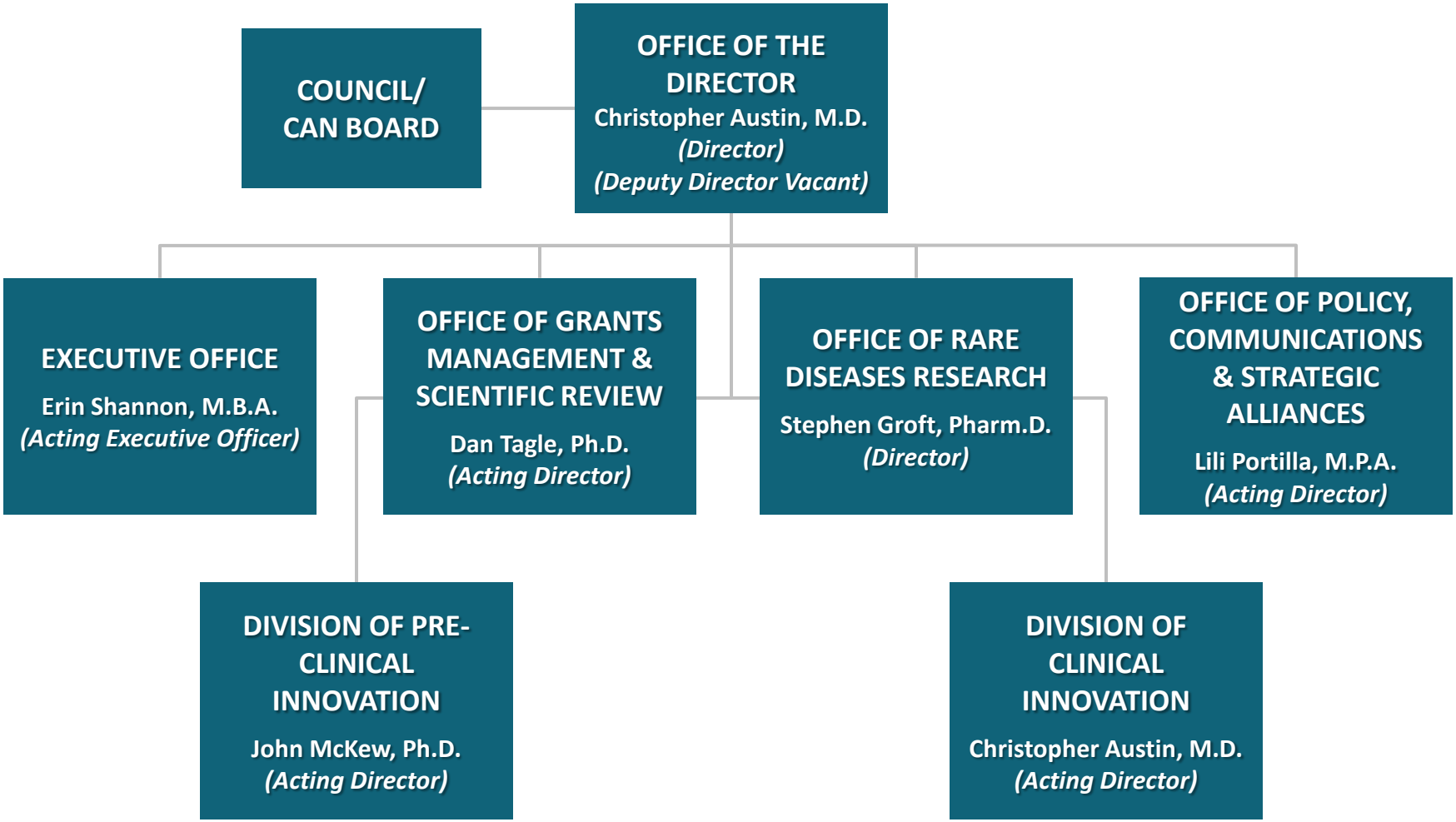
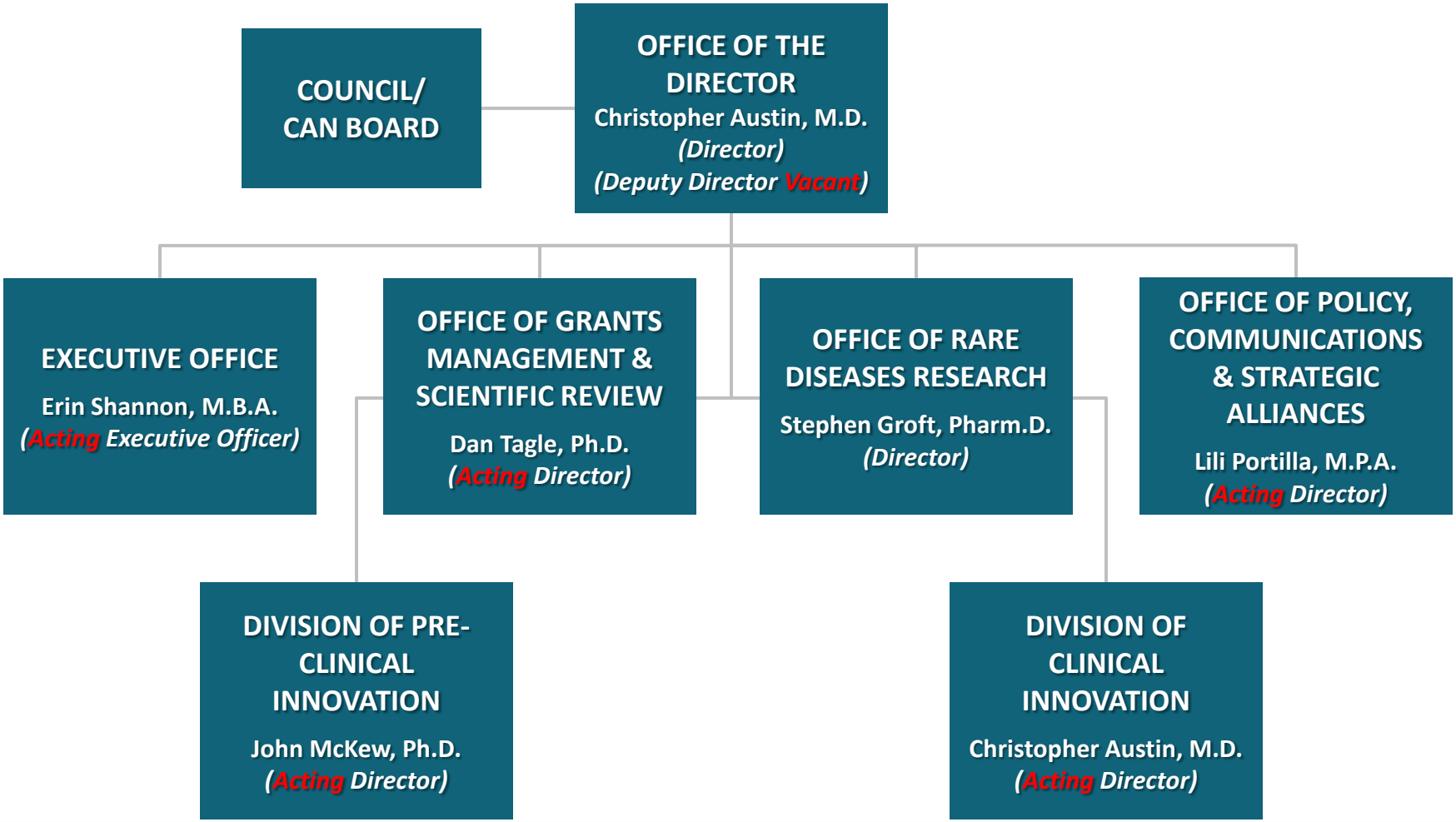
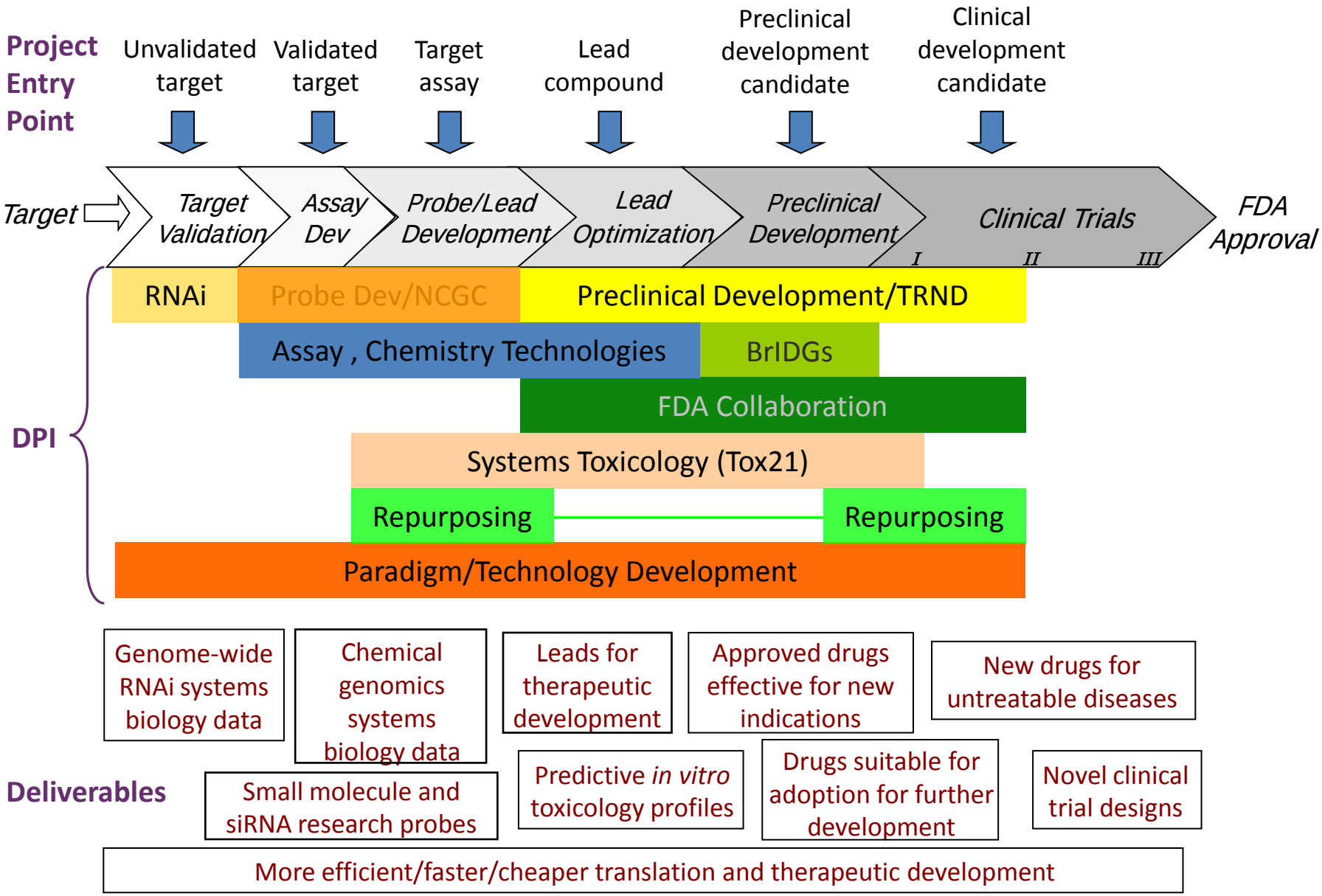
NCATS Organization



NCATS Organization



NCATS DPI: A Collaborative Pipeline



DPI Is Different in Science and Operation

- DPI is administratively intramural
  - » No independent PIs, no tenure system
  - » All projects are collaborations, (n = 300 currently), 90% of which are with extramural investigators/foundations/companies
  - » Projects are selected via solicitation/review
- Science is intermediary between mechanistic research and commercialization
  - » "Adaptor" function
  - » Each project has tangible deliverable and technology/paradigm development components
- DPI is disease agnostic, works across disease spectrum
  - » Common mechanisms and principles to make translation better/faster/cheaper for all
- Focuses on new technologies, enabling tools, dissemination

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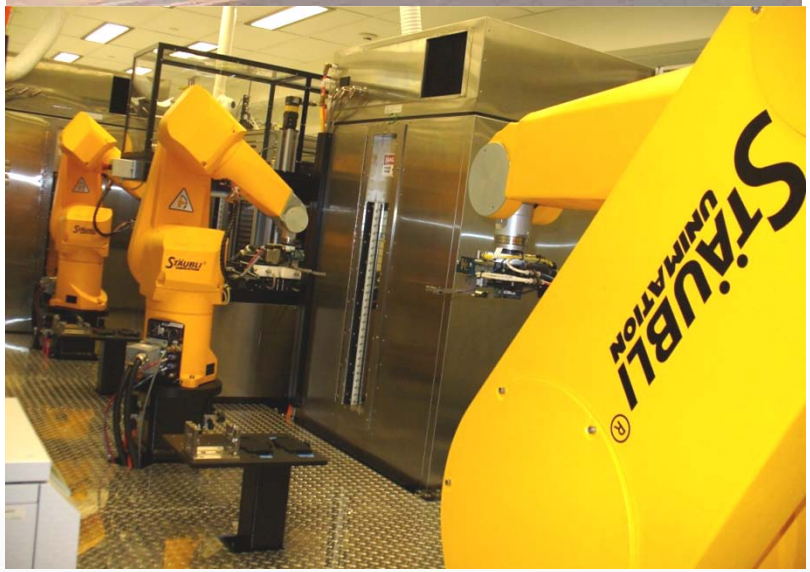
NCATS NIH Chemical Genomics Center

- Founded 2004
- 85 scientists
- > 200 collaborations with investigators worldwide
- Assay development, high-throughput screening (HTS), chemical informatics, medicinal chemistry : “target to lead”
- Focus is unprecedented targets, rare/neglected diseases
- Mission
  - Chemical probes/leads
  - New technologies/paradigms to improve efficiency and success rates of target-to-lead stage of drug development
  - Chemical genomics: general principles of small molecule — target interactions

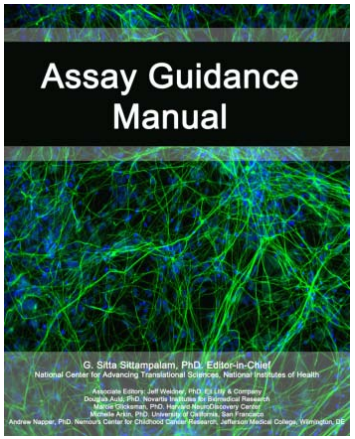


Assay Guidance Manual eBook

http://www.ncbi.nlm.nih.gov/books/NBK53196

Originally developed as quantitative biology manual for HTS and lead optimization at Eli Lilly & Co.

- A publically available resource for the drug discovery community
- "Tribal knowledge" of 100+ scientists at Lilly and other organizations
- Current version is edited by 15 experts from pharma, academia and life science companies.
- eBook at NLM/NCBI, contributions to expand content being continually added
- As an eBook on NLM, is a dynamic resource for information
- Fits with NCATS mission — know-how is a valuable public resource



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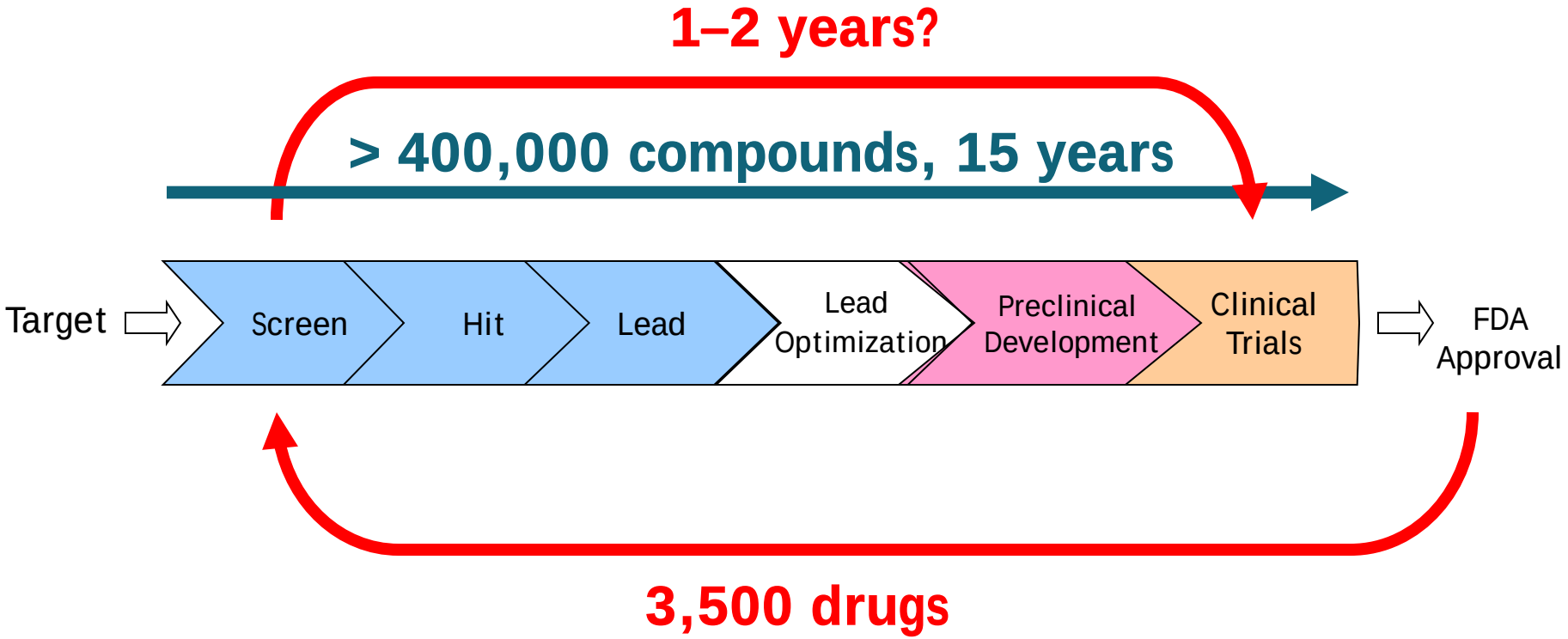
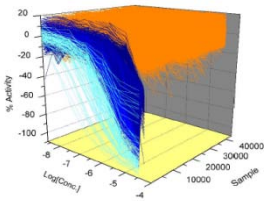
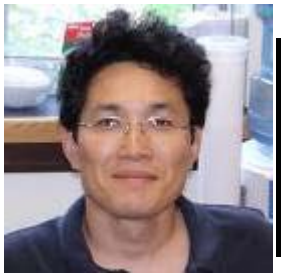
Two approaches to therapeutics at NCATS

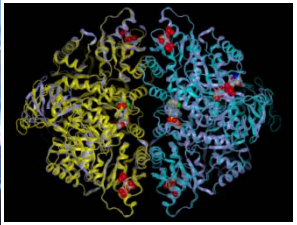


Development of Human Pyruvate Kinase Activators as Anti-Cancer Agents

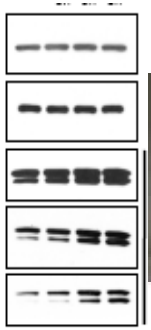
Doug Auld, Matt Boxer, Min Shen
NIH Chemical Genomics Center







Hee-Won Park
U. of Toronto, SGC



Lew Cantley, Harvard
Matt Vander Heiden, MIT
Heather Christofk, UCLA

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nature chemical biology

ARTICLE

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Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis

Dimitrios Anastasiou[1,2,13], Yimin Yu[3,13], William J Israelsen[3,13], Jian-Kang Jiang[4], Matthew B Boxer[4], Bum Soo Hong[5], Wolfram Tempel[5], Svetoslav Dimov[5], Min Shen[4], Abhishek Jha[6], Hua Yang[7], Katherine R Mattaini[3], Christian M Metallo[8], Brian P Fiske[3], Kevin D Courtney[1,2,9], Scott Malstrom[3], Tahsin M Khan[3], Charles Kung[7], Amanda P Skoumbourdis[4], Henrike Veith[4], Noel Southall[4], Martin J Walsh[4], Kyle R Brimacombe[4], William Leister[4], Sophia Y Lunt[3], Zachary R Johnson[3], Katharine E Yen[7], Kaiko Kunii[7], Shawn M Davidson[3], Heather R Christofk[1], Christopher P Austin[4], James Inglese[4], Marian H Harris[10], John M Asara[1,11], Gregory Stephanopoulos[6], Francesco G Salituro[7], Shengfang Jin[7], Lenny Dang[7], Douglas S Auld[4], Hee-Won Park[5,12], Lewis C Cantley[1,2], Craig J Thomas[4] & Matthew G Vander Heiden[3,9]*

[1]Department of Medicine, Division of Signal Transduction, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA. [2]Department of Systems Biology, Harvard Medical School, Boston, Massachusetts, USA. [3]Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology Cambridge, Massachusetts, USA. [4]National Institutes of Health (NIH) Chemical Genomics Center, National Center for Advancing Translational Sciences, NIH, Bethesda, Maryland, USA. [5]Structural Genomics Consortium, University of Toronto, Toronto, Ontario, Canada. [6]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. [7]Agios Pharmaceuticals, Cambridge, Massachusetts, USA. [8]Department of Bioengineering, University of California, San Diego, California, USA. [9]Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA. [10]Department of Pathology, Children's Hospital, Boston, Massachusetts, USA. [11]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA. [12]Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada. [13]These authors contributed equally to this work. *e-mail: mvh@mit.edu

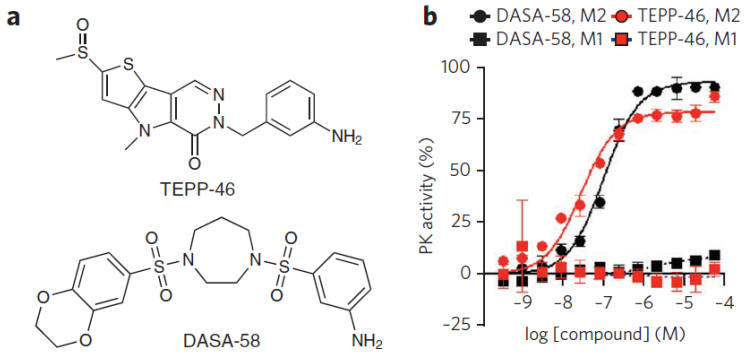


Figure 2 | TEPP-46 and DASA-58 isoform specificity *in vitro* and in cells.

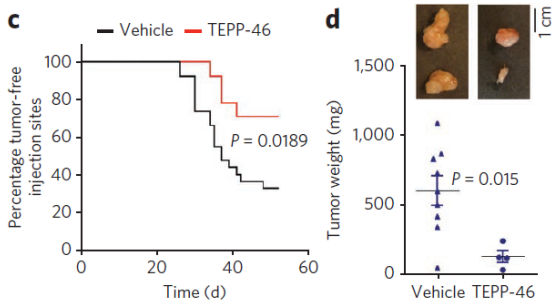
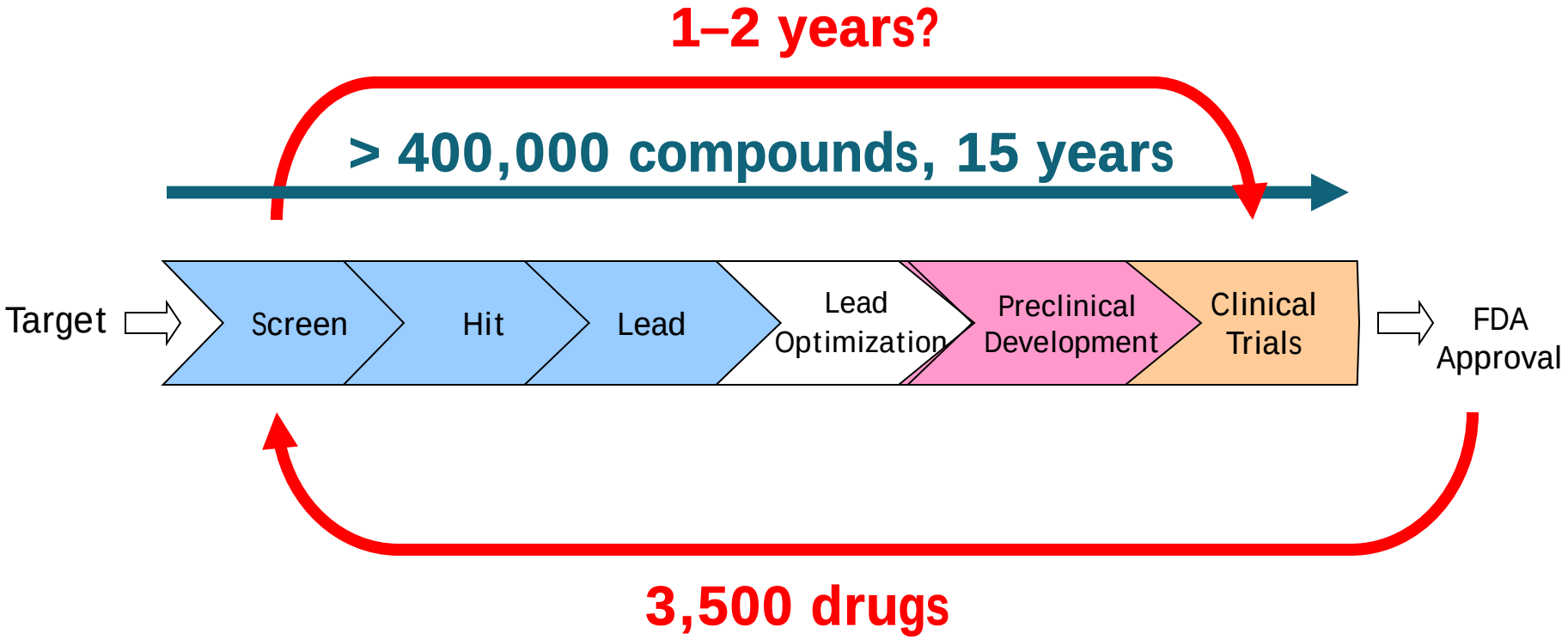


Figure 6 | PKM2 activators impair xenograft growth.

Two approaches to therapeutics at NCATS



Enabling Comprehensive Drug Repurposing

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

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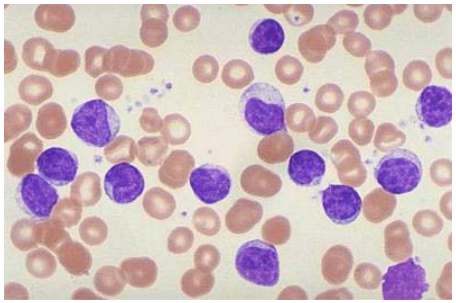
Repurposing Case Study: Refractory CLL



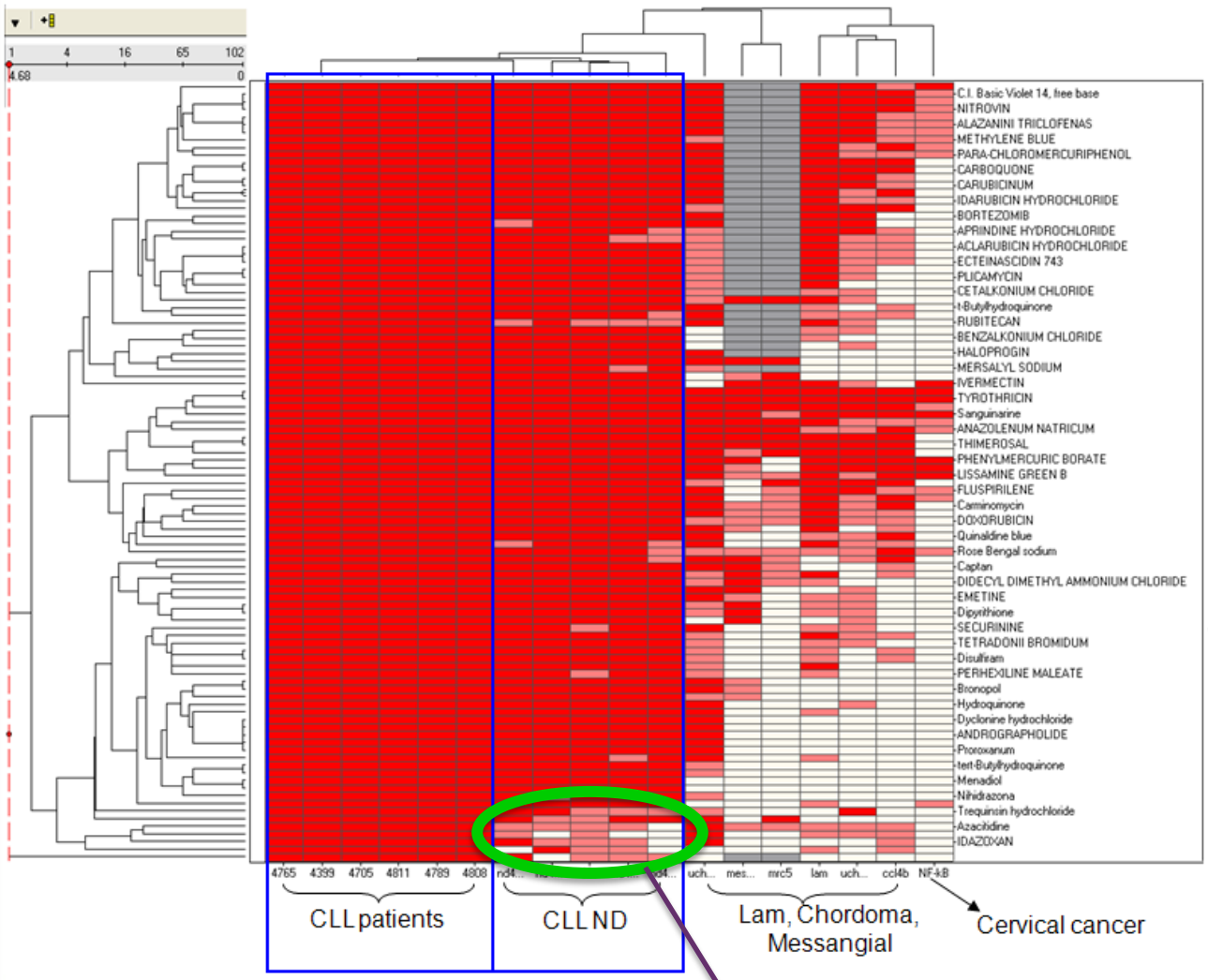
CLL — Chronic Lymphocytic Leukemia

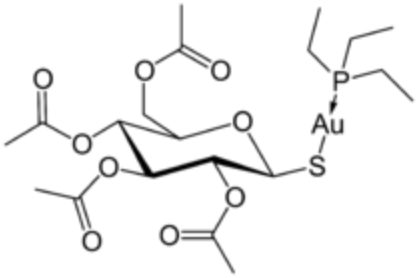
- 30% of all leukemias
- ~15,000 people new diagnoses/year in U.S.
- Standard of care: chemotherapy (e.g., fludarabine, anti-CD20 mab [Rituxan])
- Relapse virtually universal

NCATS Pharmaceutical Collection CLL Screen

- CLL and normal donor B cells obtained from patients at NIH Clinical Center
  - » Adrian Wiestner, NHLBI
  - » Cells from six CLL patients and five normal donors
- NCATS Pharmaceutical Collection screened at 9 concentrations, 1 nM to 57 uM
  - » Readout: cell viability (ATP measurement)
  - » Desired compound profile = differential cell killing

102 CLL Pan-Actives vs. Normal B Cells





Auranofin

Kill CLL but not normal donor B cells

The Learning Collaborative: Capitalizing on Strengths

KU THE UNIVERSITY OF KANSAS
The Institute for Advancing Medical Innovation

- Bench-to-bedside translation in drug repurposing
- National leadership in medicinal and pharmaceutical chemistry
- Pharma experience

NIH National Center for Advancing Translational Sciences

- Focus on rare and neglected diseases
- Industrial scale HTS, cheminformatics, medicinal chemistry, drug development capabilities
- Pharma experience

LEUKEMIA & LYMPHOMA SOCIETY®

- ~400 active research projects
- Worldwide network of blood cancer experts
- Track record of commercial partnerships
- Pharma experience

Discovering New Therapeutic Uses for Existing Molecules Program

- Pilot program matching NIH researchers with compounds deprioritized by pharma for efficacy/business reasons
- Creation of template agreements to streamline negotiations between researchers and pharmaceutical companies
- 58 compounds from eight companies

- **Abbott**
- **AstraZeneca**
- **Bristol-Myers Squibb Company**
- **Eli Lilly and Co.**
- **GlaxoSmithKline**
- **Janssen Pharmaceutical Research & Development, L.L.C.**
- **Pfizer Inc.**
- **Sanofi**

Therapeutics Discovery Pilot: Timeline

- June 2012: Funding announcement issued
- August 2012: Approximately 160 pre-applications received (X02)
- December 2012: Full applications received
- June 2013: Awards to be issued
- Program will be evaluated for success:
  - » Does the use of template agreements speed negotiation time?
  - » Does the pilot advance disease understanding?
  - » Does the pilot result in promising new therapeutics?

Therapeutics for Rare and Neglected Diseases (TRND) Program

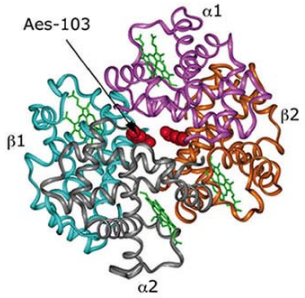
- Model: Comprehensive drug development collaboration between DPI and extramural labs with disease-area/target expertise
- Projects
  - » May enter at various stages of preclinical development
  - » Disease must meet FDA orphan or WHO neglected tropical disease criteria
  - » Taken to stage needed to attract external organization to adopt to complete clinical development/registration, max 2a
  - » Milestone driven
  - » Therapeutic modalities: small molecules, proteins
  - » Serve to develop new generally applicable platform technologies and paradigms
- Eligible applicants
  - » Academic, non-profit, government lab, biotech/pharma
  - » Ex-U.S. applicants accepted

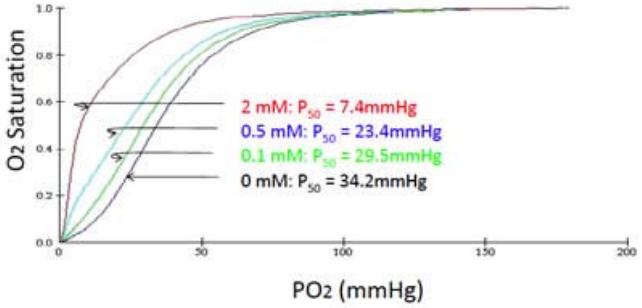
TRND Portfolio

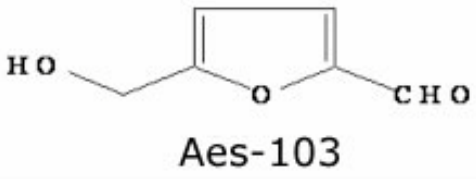
Collaborator	Organization Name(s)	Partner Type(s)	Agent	Therapeutic Area / Disease
TRND Pilot Project	NPC-SOAR, Washington Univ., Einstein College of Medicine, NICHD, NHGRI	Disease Foundation, Academic, DIR	Repurposed Approved Drug	Niemann-Pick C
TRND Pilot Project	New Zealand Pharmaceuticals, NHGRI	Biotech, DIR	Intermediate Replacement	Hereditary Inclusion Body Myopathy
TRND Pilot Project	Aes-Rx, NHLBI	Biotech, DIR	NME	Sickle Cell Disease
TRND Pilot Project	Leukemia & Lymphoma Society, Kansas Univ. Cancer Center	Disease Foundation, Academic	Repurposed Approved Drug	Chronic Lymphocytic Leukemia
Reeves, Erica	ReveraGen BioPharma	Small Business	NME	Duchenne Muscular Dystrophy
Campbell, David	Afraxis, Inc.	Small Business	NME	Fragile X Syndrome
Garvey, Edward	Viamet Pharmaceuticals, Inc.	Small Business	NME	Cryptococcal Meningitis
Liu, Paul	NHGRI	DIR	Repurposed Approved Drug	Core Binding Factor Leukemia
Kimberlin, David	University of Alabama	Academic	Nucleotide Analog Pro-drug	Neonatal Herpes Simplex
Trapnell, Bruce	Cincinnati Children's Hospital	Academic	Biologic	Autoimmune Pulmonary Alveolar Proteinosis
Bloch, Kenneth	Massachusetts General Hospital	Academic	NME	Fibrodysplasia Ossificans Progressiva
Liu, Julie	CoNCERT Pharmaceuticals	Small Business	NME	Schistosomiasis
Davis, Robert	Lumos Pharma	Small Business	NME	Creatine Transporter Defect
Sazani, Peter	AVI BioPharma, Inc.	Small Business	Oligo (PMO)	Duchenne Muscular Dystrophy

TRND Project on Sickle Cell Disease

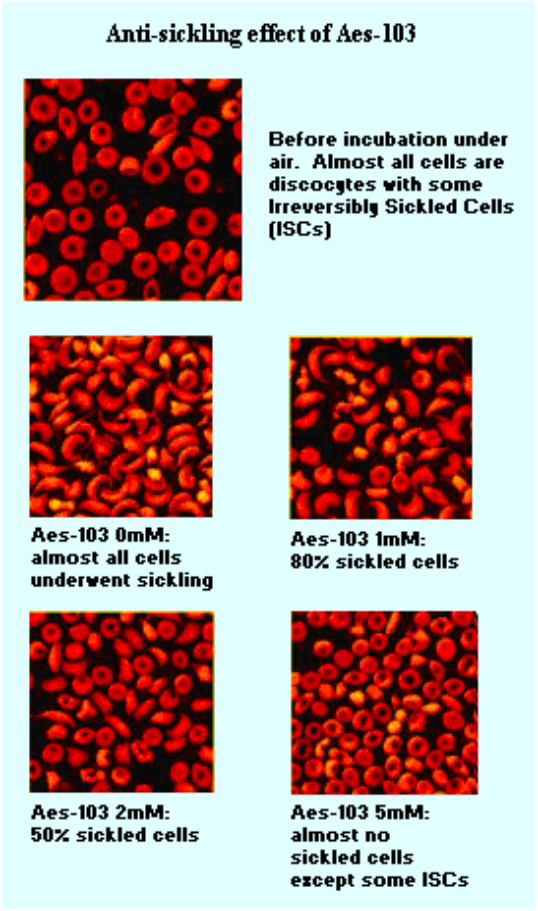
- Collaborator: AesRx, Boston-based biotech
- Compound: 5-hydroxymethyl-2-furfural (5-HMF, or Aes-103)
  - Binds to sickle hemoglobin and increases its oxygen affinity







- Roadblocks in drug development encountered by collaborator
  - Animal toxicology studies
  - CMC (Chemistry, Manufacturing, and Quality Control)
  - Regulatory: interactions with FDA, IND filing
- TRND collaborating with AesRx on
  - IND-enabling pre-clinical animal toxicology studies
  - API manufacturing and impurity characterization
  - Preparing and filing of IND
  - Proof-of-concept clinical trials
- API (Aes-103) manufactured: CROs supported by RAID program and TRND
- Phase I-II clinical trials performed at CRO and NIH Clinical Center



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Toxicology Technology Development: The Tox21 Program

FDA

Tox21

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

NIH National Institutes of Health
Turning Discovery Into Health

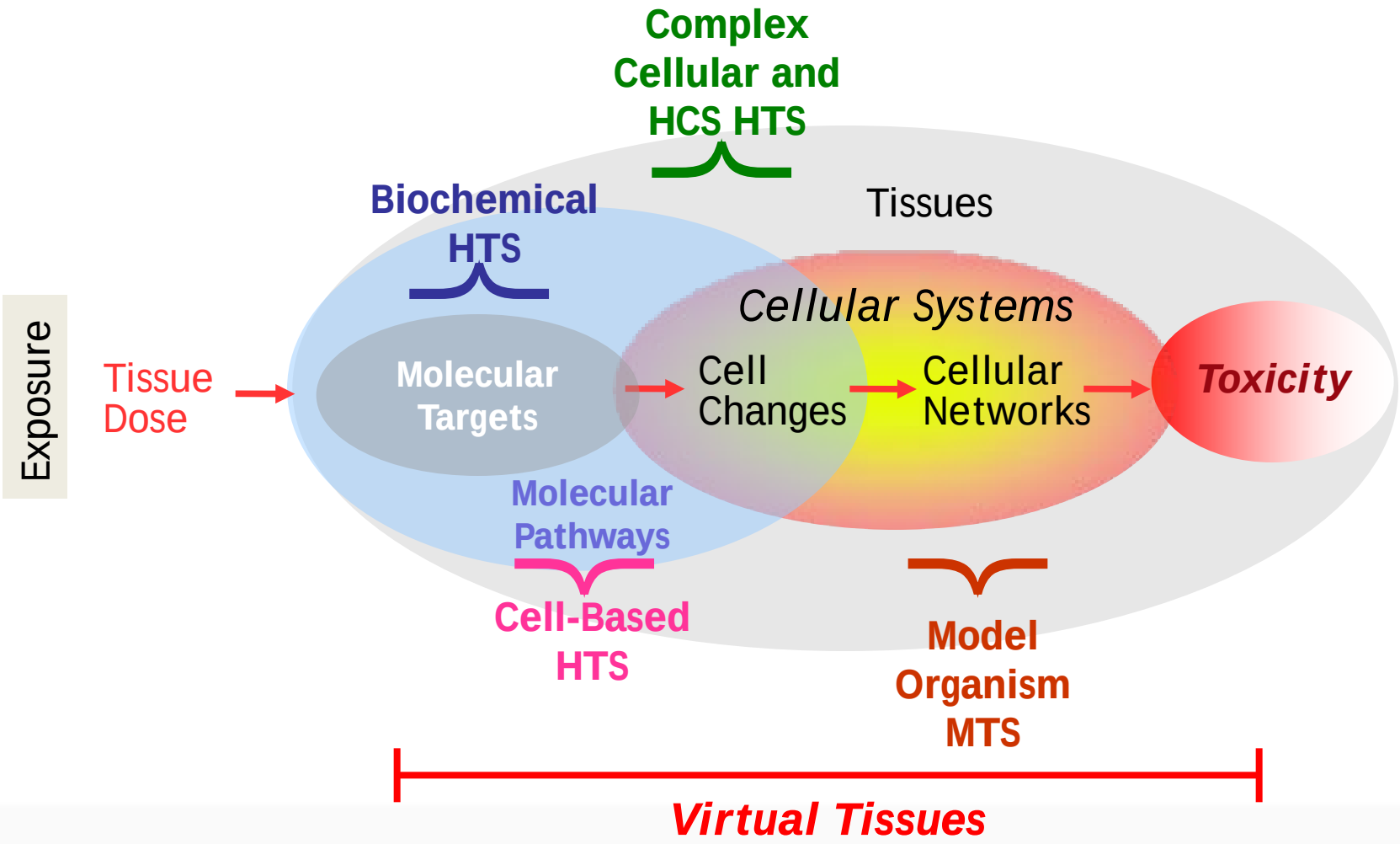
NIEHS
National Institute of Environmental Health Sciences

National Toxicology Program
Department of Health and Human Services

NIH National Center for Advancing Translational Sciences

NCGC
NIH Chemical Genomics Center

Tox21: Predicting Toxicity



Tissue Chip for Drug Screening: Microsystems Initiative

Aims to develop tissue chips that mimic human physiology to screen for safe, effective drugs using best ideas in engineering, biology, toxicology

- NIH investment (funded through CAN + Common Fund) = $70M/5 years
  - » (CAN = Cures Acceleration Network)
- DARPA investment = $75M/5 years
- FDA investment = regulatory and toxicology expertise
- NCATS and DARPA independently manage and fund separate but highly coordinated programs

NIH National Center for Advancing Translational Sciences

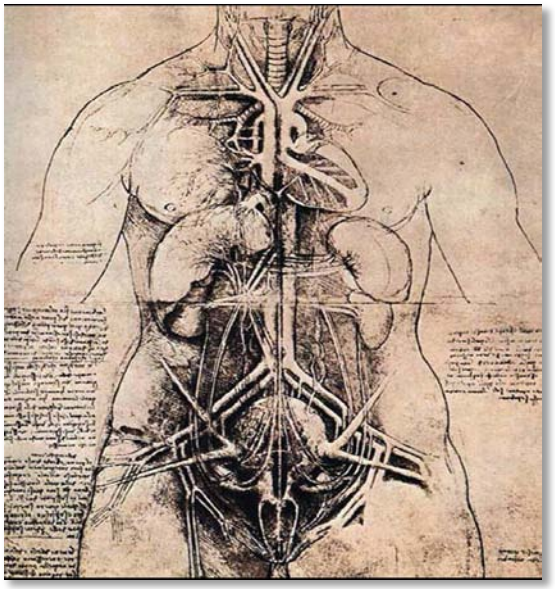
NIH National Institutes of Health
Turning Discovery Into Health

DARPA

FDA

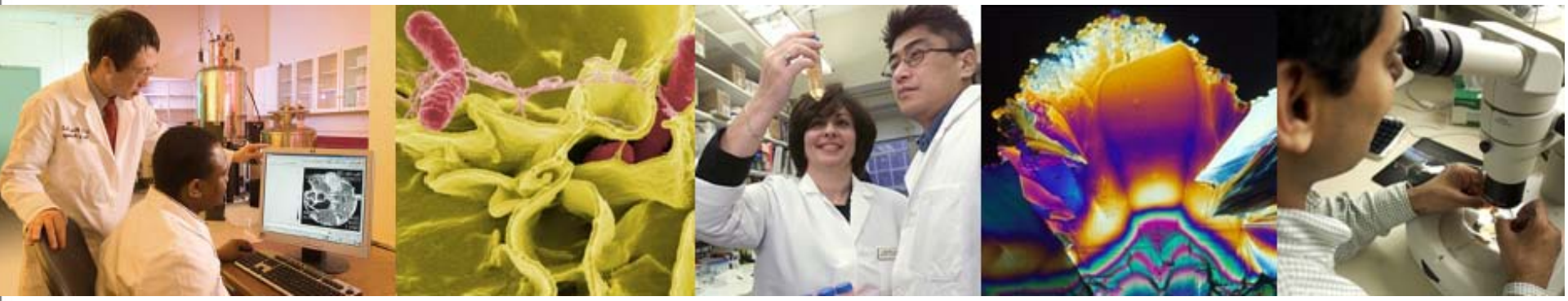
Tissue Chips Program

GOAL: Develop an *in vitro* platform that uses human tissues that will be predictive of efficacy, pharmacokinetics, safety and toxicity of promising therapies in humans and suitable for regulatory science use.



- All 10 human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Integumentary
- Physiologically relevant, genetically diverse and pathologically meaningful
- Modular, reconfigurable platform for easy integration
- Tissue viability for at least 4 weeks
- Community-wide access

Division of Clinical Innovation (DCI)



Clinical and Translational Science Awards (CTSAs)

- Support a national consortium of medical research institutions
- Work together to improve the way clinical and translational research is conducted nationwide
- Aim to accelerate the research translation process

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Translational and Clinical Science — Time for a New Vision

Elias A. Zerhouni, M.D.

N Engl J Med 2005; 353:1621-1623 | October 13, 2005

"The CTSAs will advance the assembly of institutional academic 'homes' that can provide integrated intellectual and physical resources for the conduct of original clinical and translational science."

Evolving CTSA Vision

- National leadership to enhance quality, safety and efficiency in translational research
- Innovation in translational research methods, resources and services that catalyze the spectrum of translational research
- Facilitate training and career development of robust translational workforce for interdisciplinary team research
- Flexible academic, community and industry collaboration and partnership models built on shared commitment to translation
- *A national network for translational medicine*

CTSA Collaborative Research

THE LANCET

High-performance neuroprosthetic control by an individual with tetraplegia

Jennifer L Collinger, Brian Wodlinger, John E Downey, Wei Wang, Elizabeth C Tyler-Kabara, Douglas J Weber, Angus J C McMorland, Meel Velliste, Michael L Boninger, Andrew B Schwartz

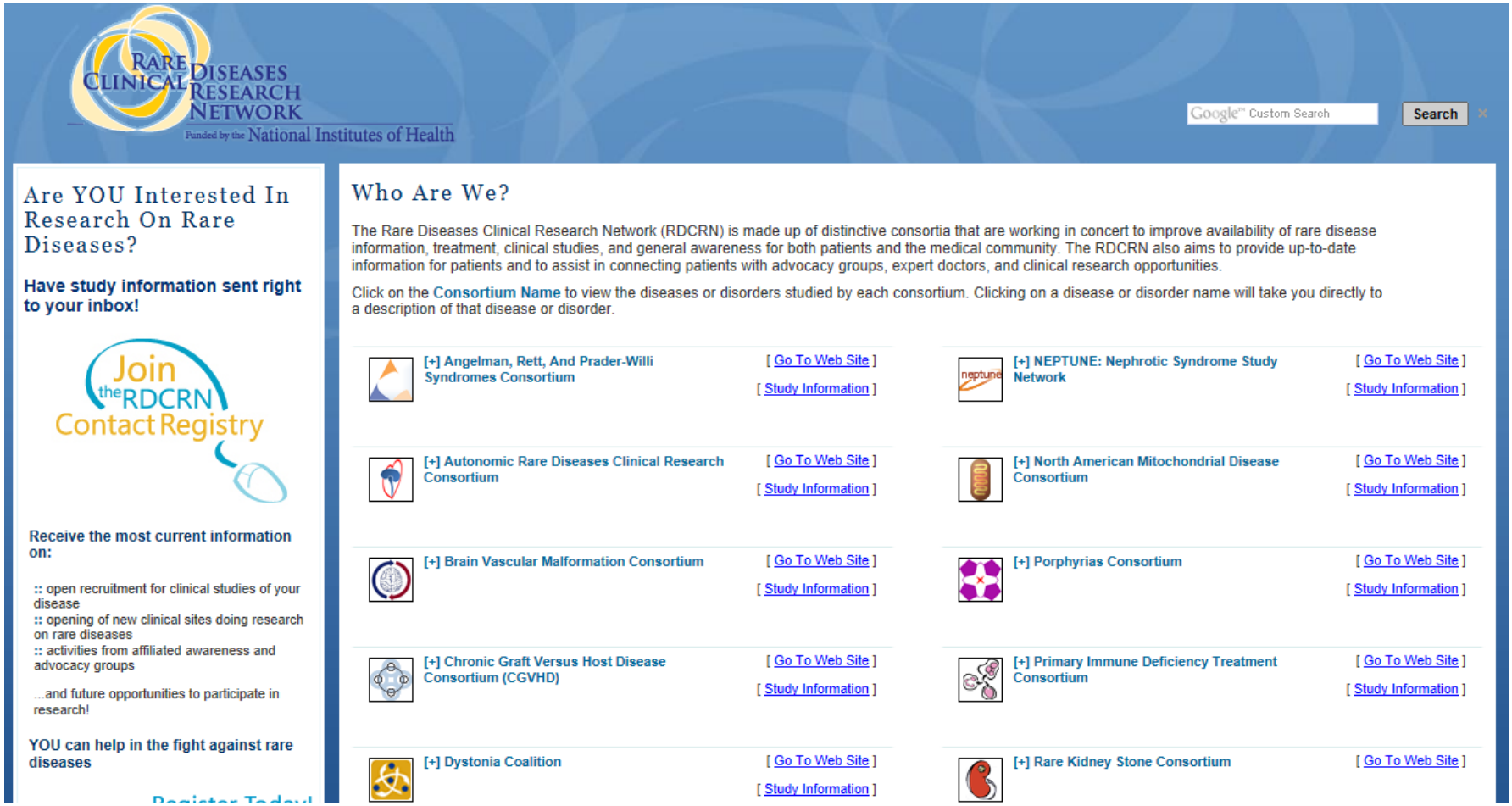
- Published in December 2012; current paper in press
- Brain-computer-interface (BCI) technology enables a quadriplegic to use only her thoughts to move a robotic arm
- Collaborative support from NIH, DARPA, VA and FDA
- University of Pittsburgh's CTSI provided:
  - » Critical mass needed for the team to work together early in the research process
  - » Help with protocol development
  - » Regulatory reporting and compliance expertise
  - » Early pilot work and KL2 mentored career development

Office of Rare Diseases Research (ORDR)

- Rare Diseases Clinical Research Network (RDCRN)
- Scientific Conferences Program
- NIH Clinical Center Bedside-to-Bench Program
- Genetic and Rare Disease Information Center (GARD)

NIH National Center for Advancing Translational Sciences

The Rare Disease Clinical Research Network



New NCATS Initiatives

- Address significant bottlenecks in the process of translation
- Highly collaborative across NIH, across other government agencies and with the private sector
- Quick to respond to needs of biomedical researchers

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NIH
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