The National Center for Advancing Translational Sciences

Catalyzing Translational Innovation

CHRISTOPHER P. AUSTIN, M.D.
DIRECTOR, NCATS
UNIVERSITY OF MINNESOTA
OCTOBER 21, 2014

NCATS

NIH National Center for Advancing Translational Sciences

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?

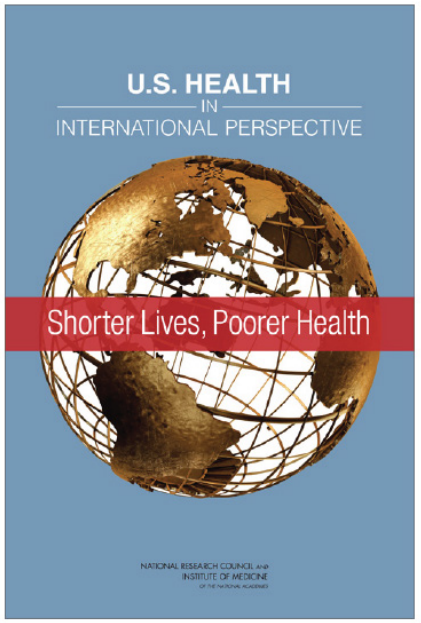
Translational Science is the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process.

NCATS studies translation as a scientific and organizational problem.

The Best of Times, the Worst of Times

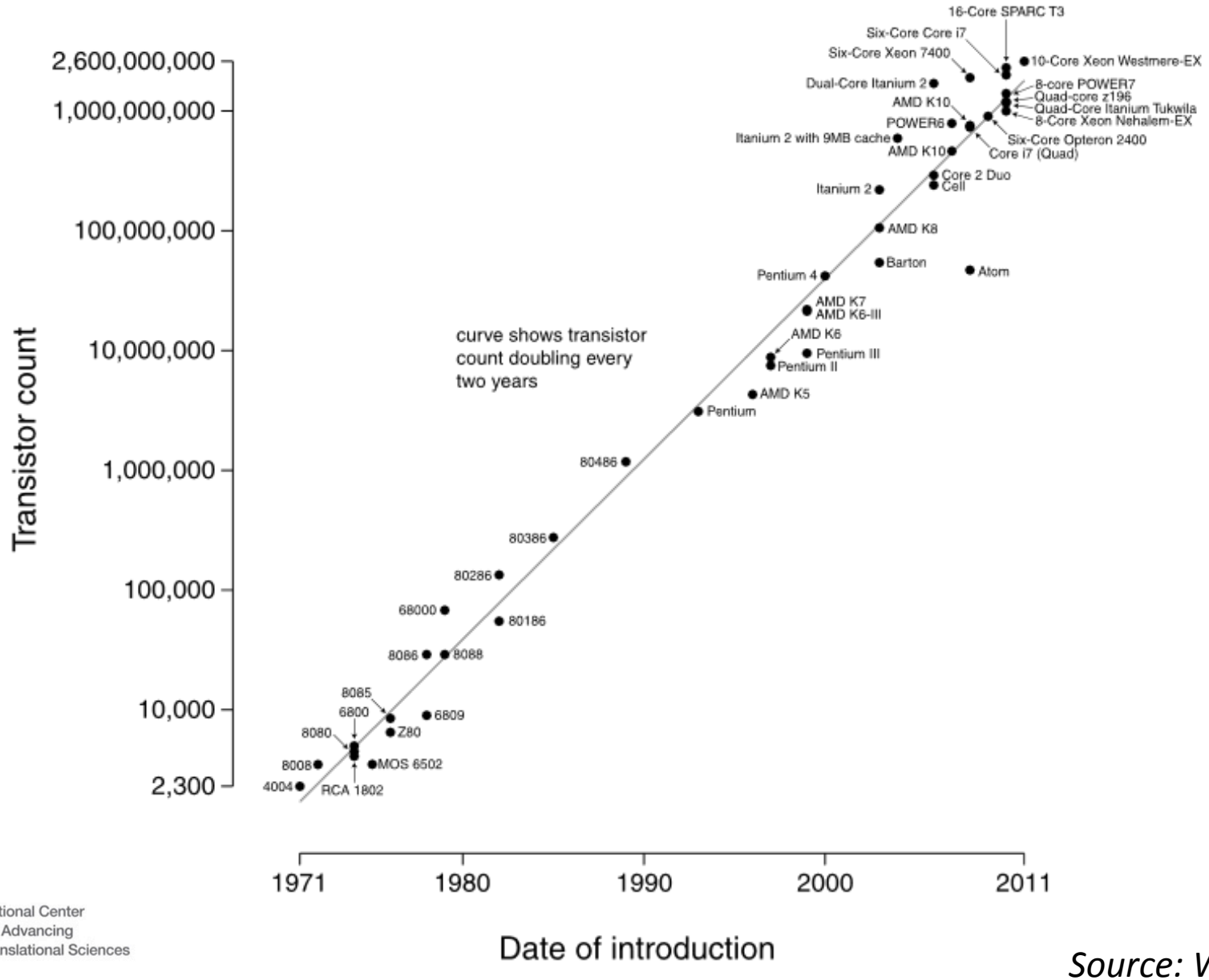
Fundamental science unprecedentedly advanced, but:

- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Drug/device/diagnostic development 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

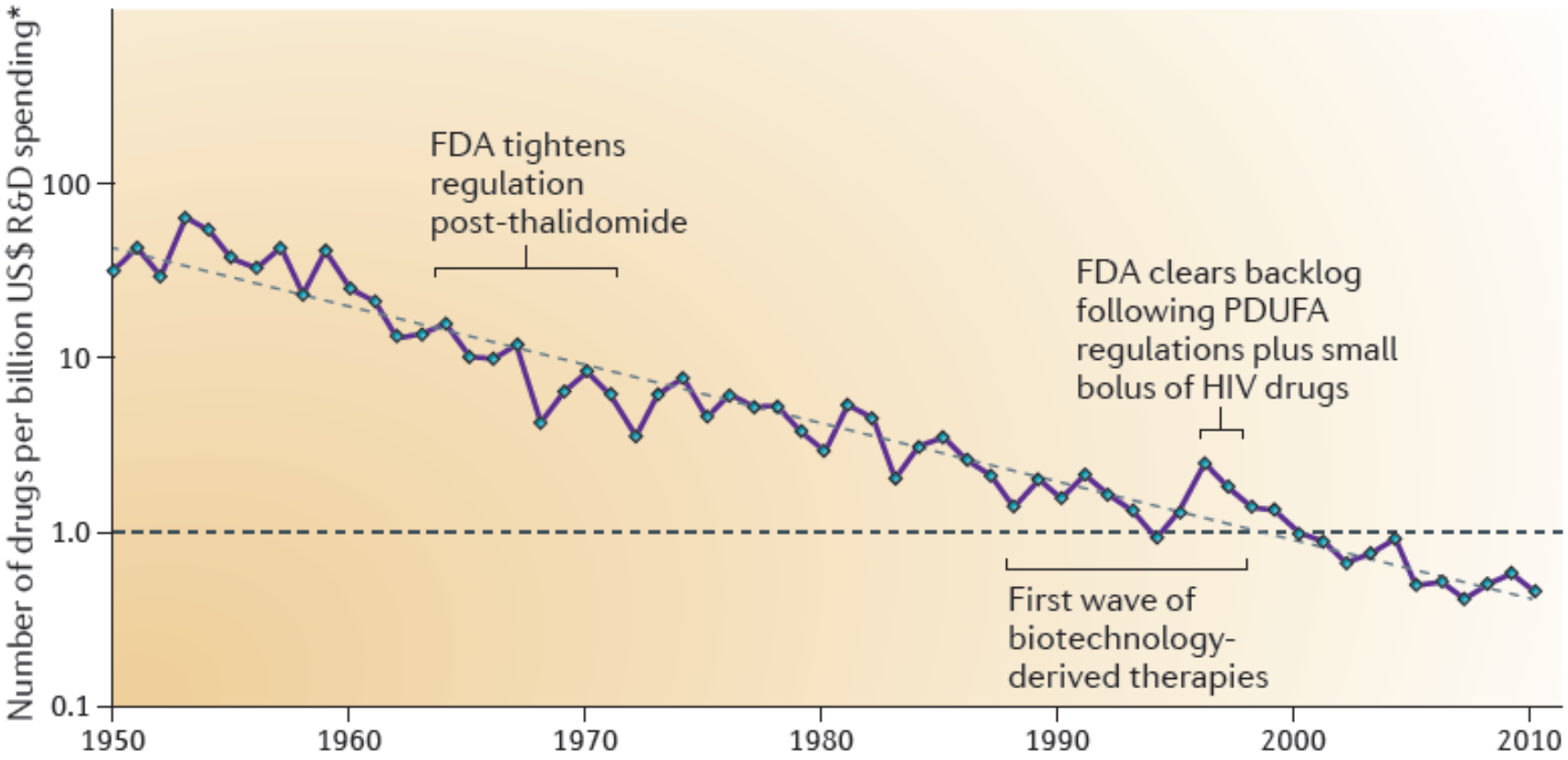
Moore's Law



National Center for Advancing Translational Sciences

Source: Wikipedia

Eroom's Law

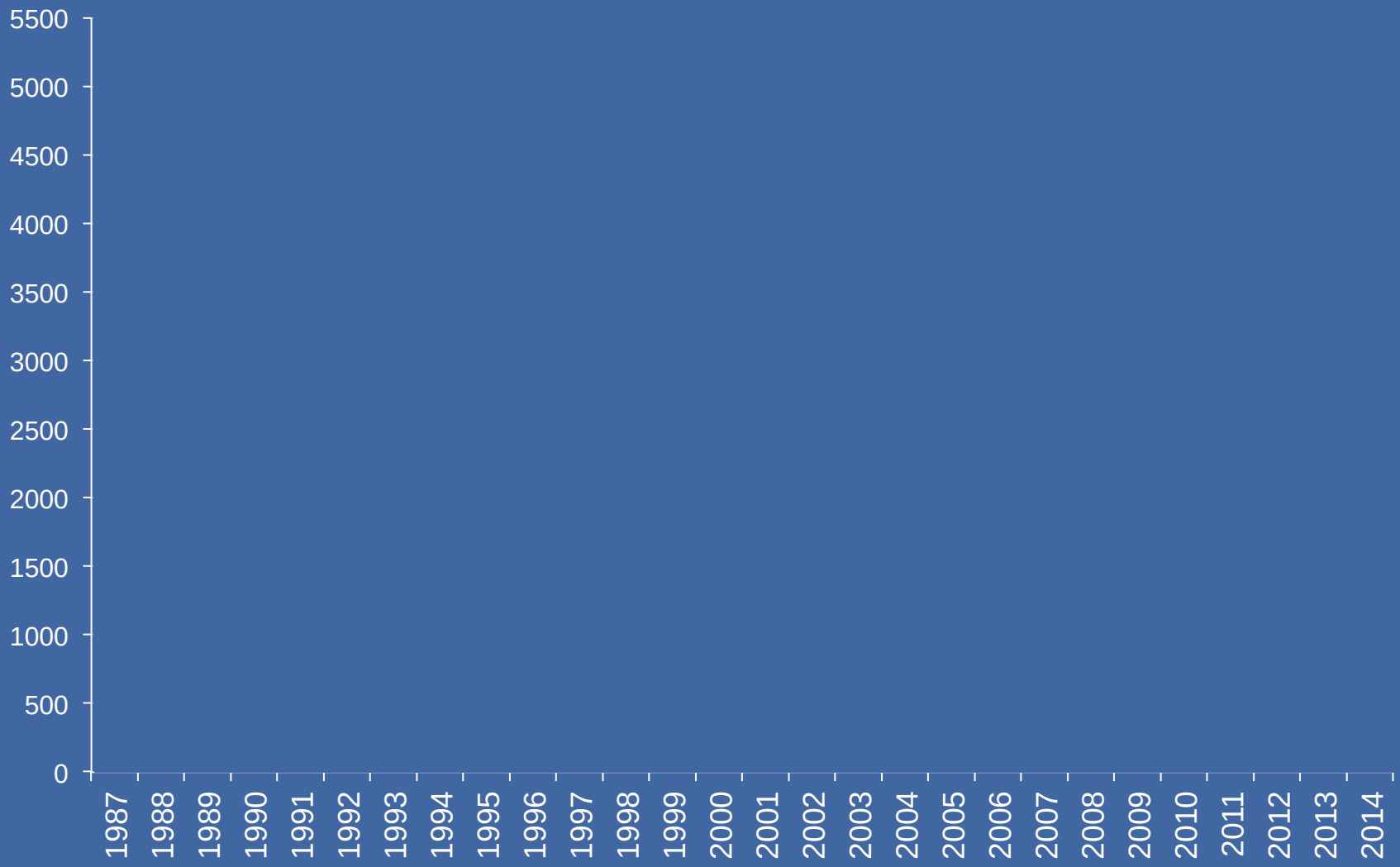


The number of new drugs approved by the FDA per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years since 1950.

NIH National Center for Advancing Translational Sciences

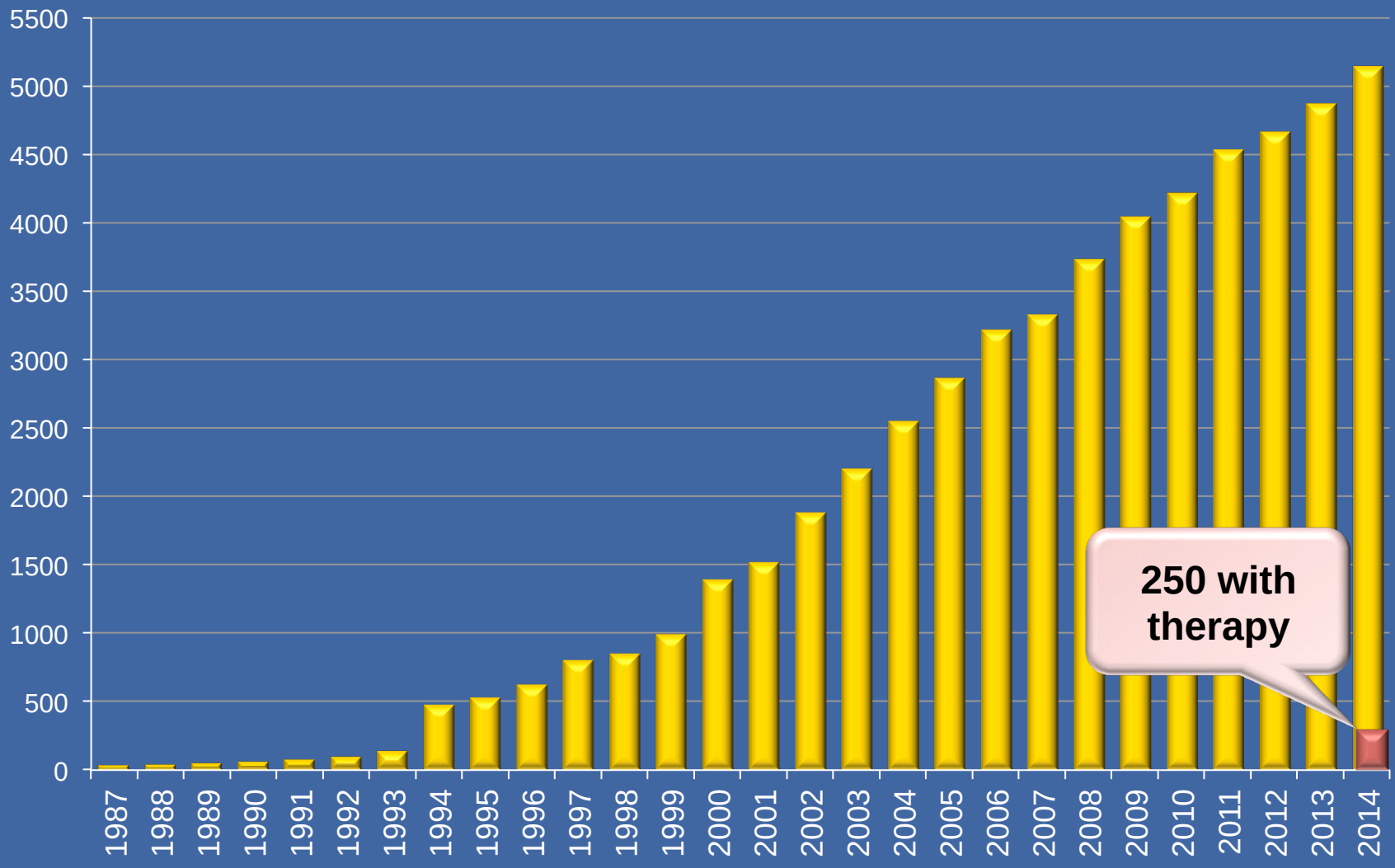
Scannell et al., *Nature Reviews Drug Discovery* 11:191, 2012

Disorders with Known Molecular Basis



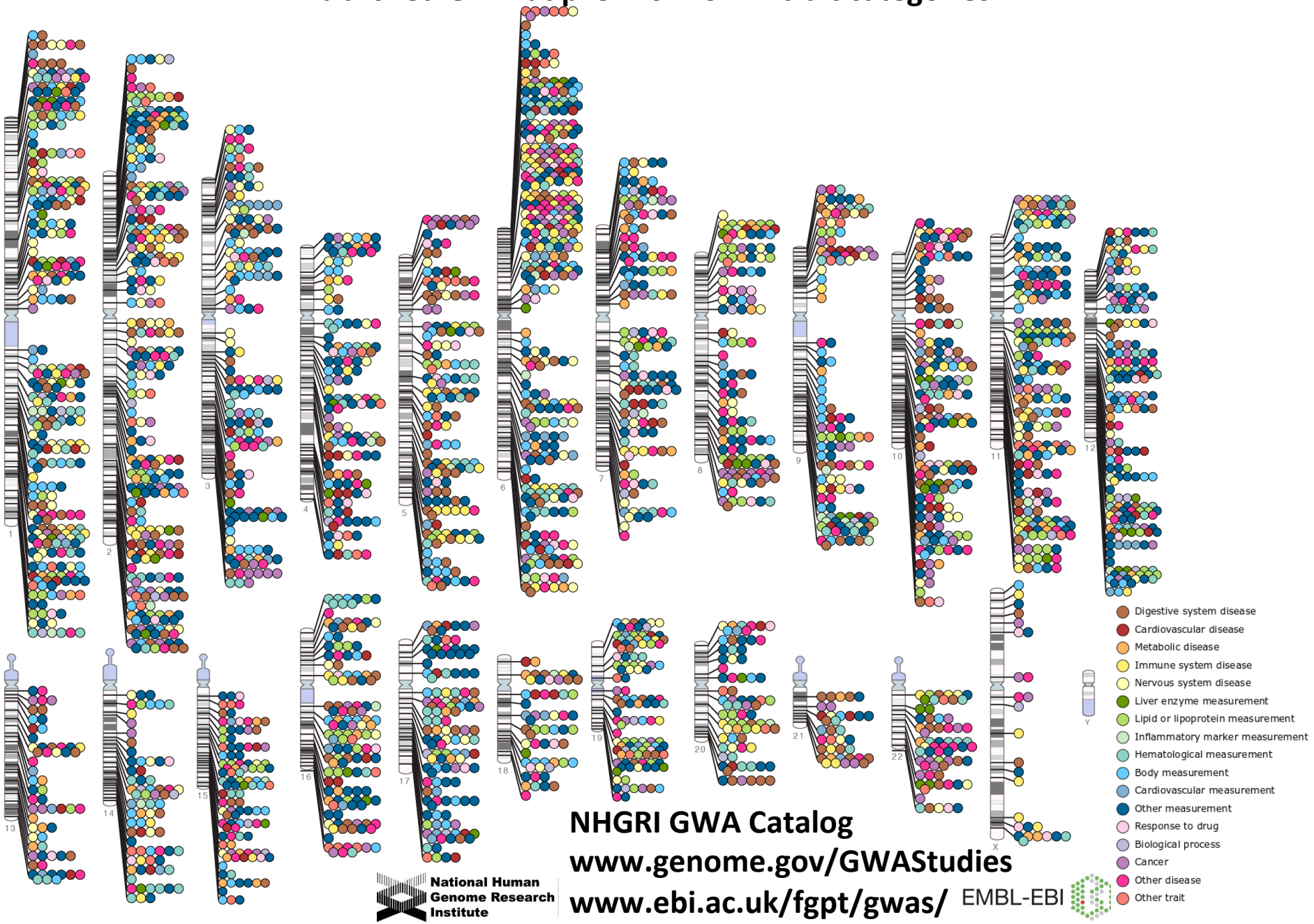
Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome

Disorders with Known Molecular Basis



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

Published Genome-Wide Associations through 12/2012
Published GWA at $p \leq 5X10^{-8}$ for 17 trait categories

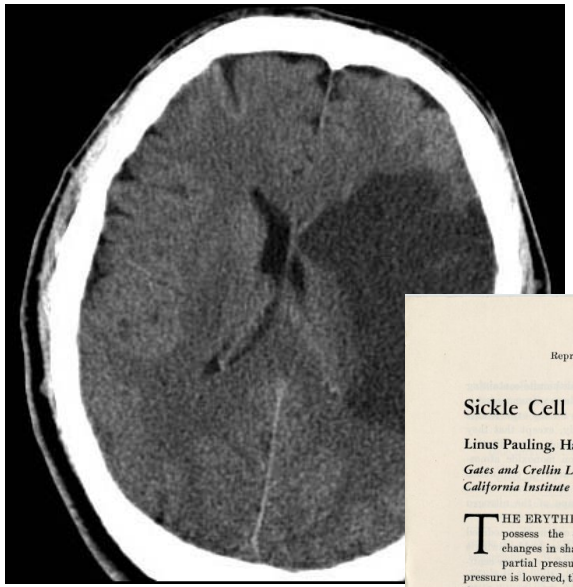


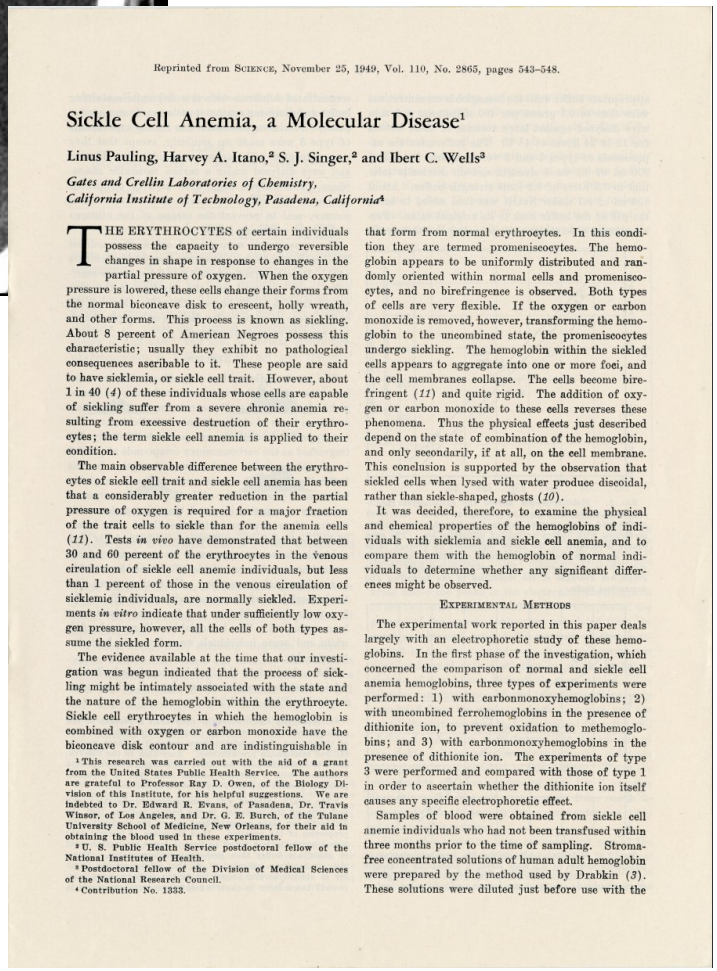
National Human Genome Research Institute

NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/

EMBL-EBI

What I learned as a neurologist, and then again as a geneticist





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

Sickle Cell Anemia, a Molecular Disease[1]

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

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

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

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

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

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

EXPERIMENTAL METHODS

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

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

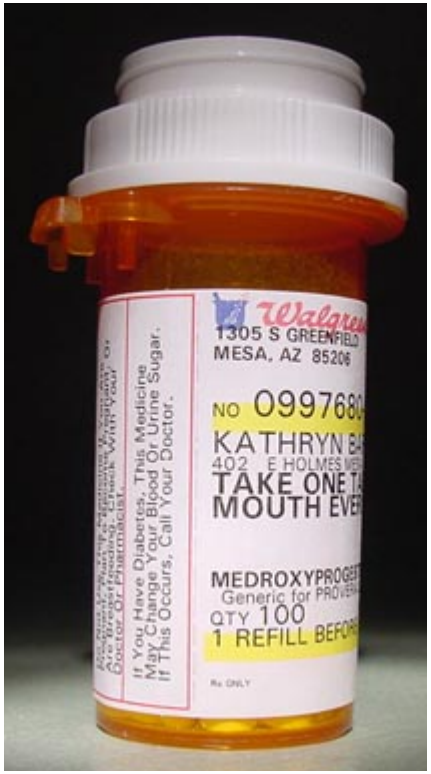
[1] This research was carried out with the aid of a grant from the United States Public Health Service. The authors are grateful to Professor Ray D. Owen, of the Biology Division of this Institute, for his helpful suggestions. We are indebted to Dr. Edward R. Evans, of Pasadena, Dr. Travis Winsor, of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

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

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

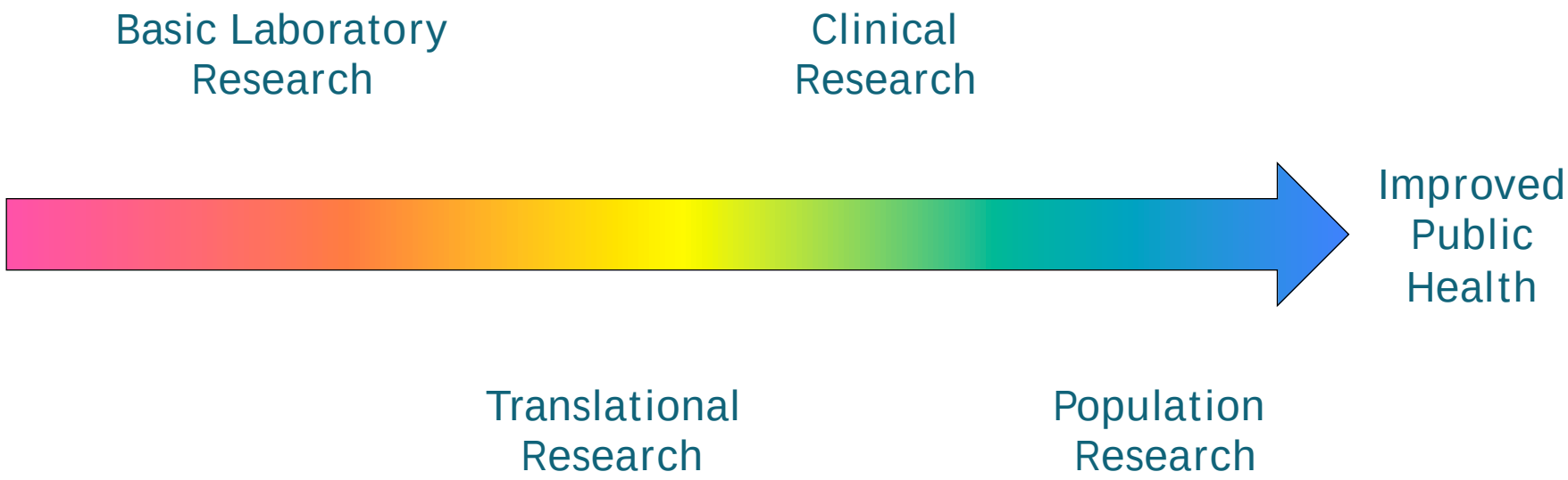
[4] Contribution No. 1333.

≠

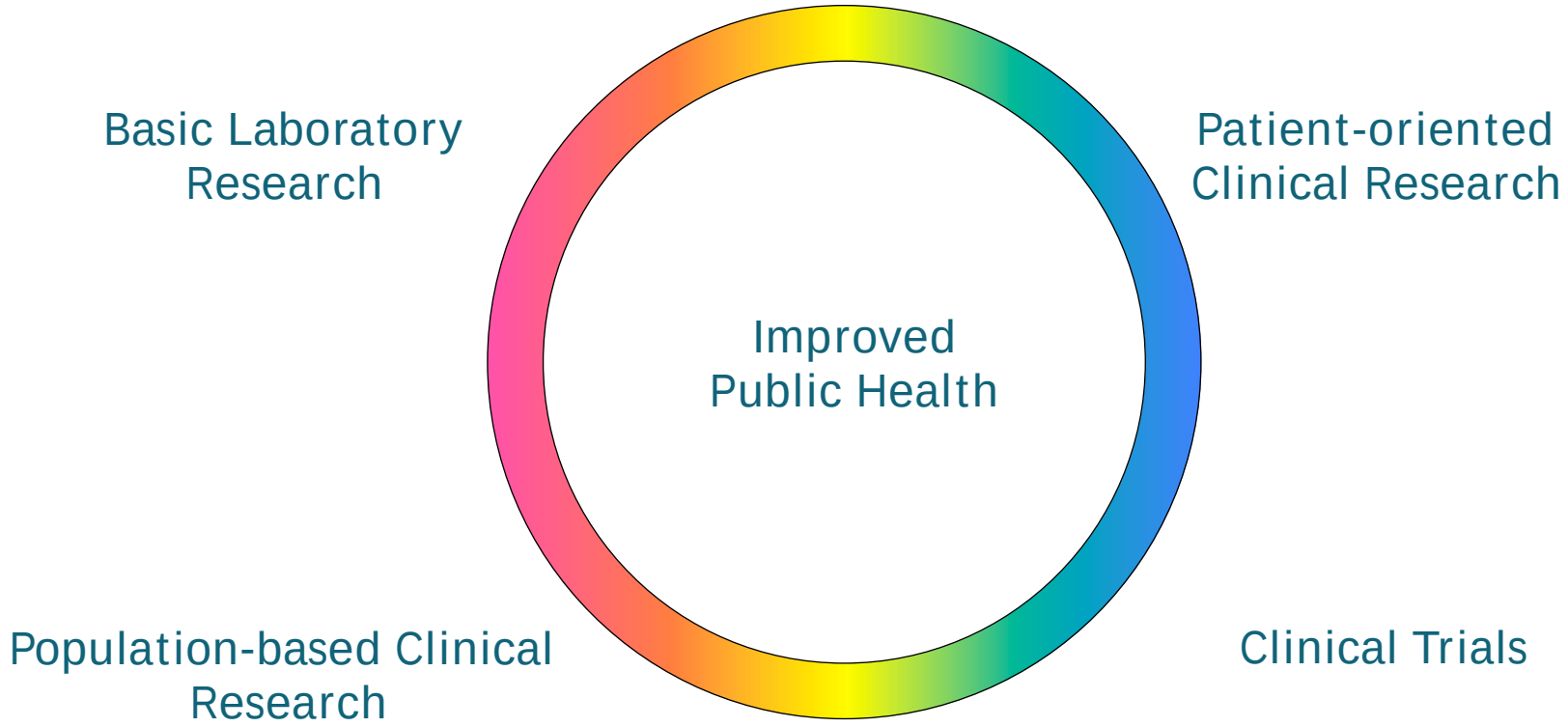


NIH National Center for Advancing Translational Sciences

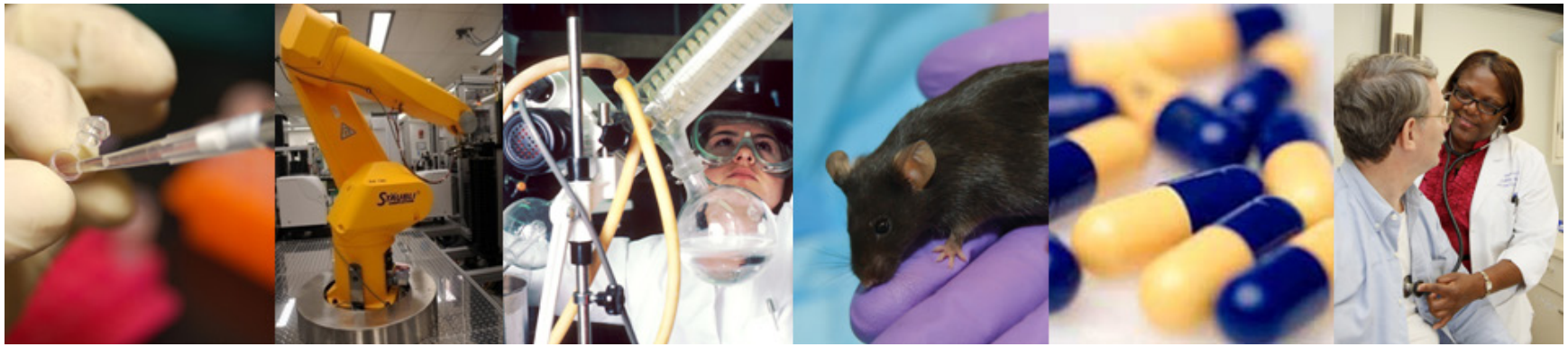
Standard Model



The Way It Should Work

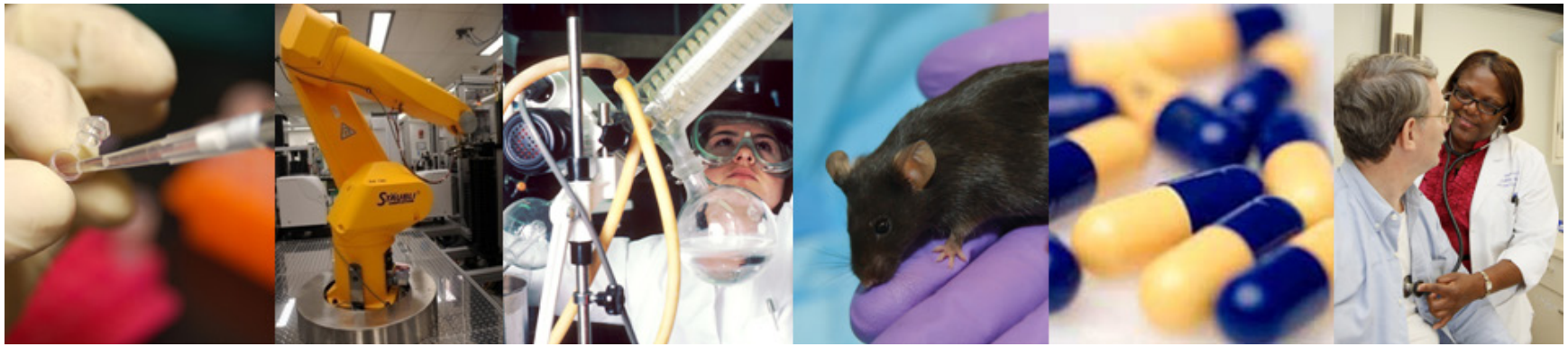


NCATS Mission



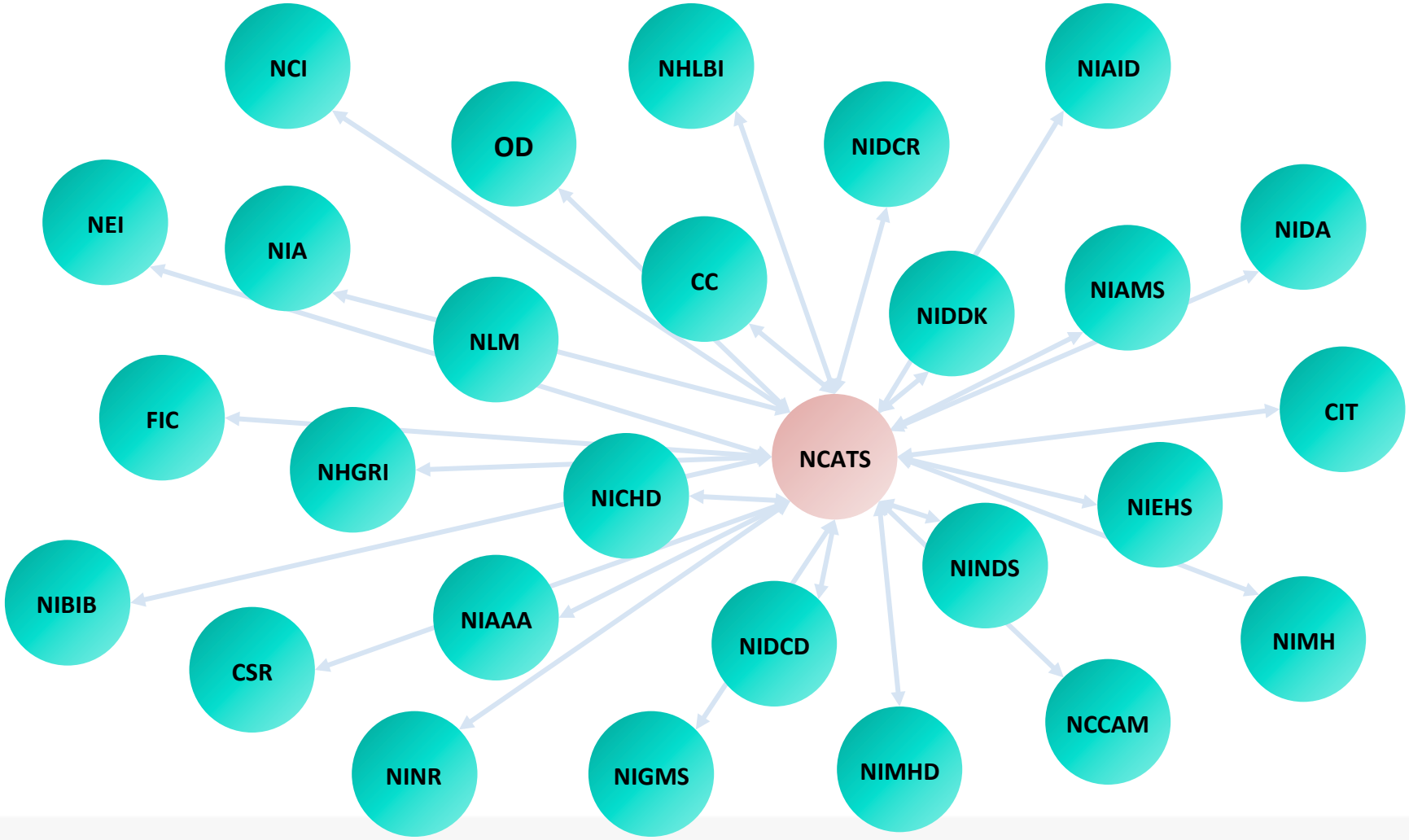
To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

NCATS Mission: an informal but important modification

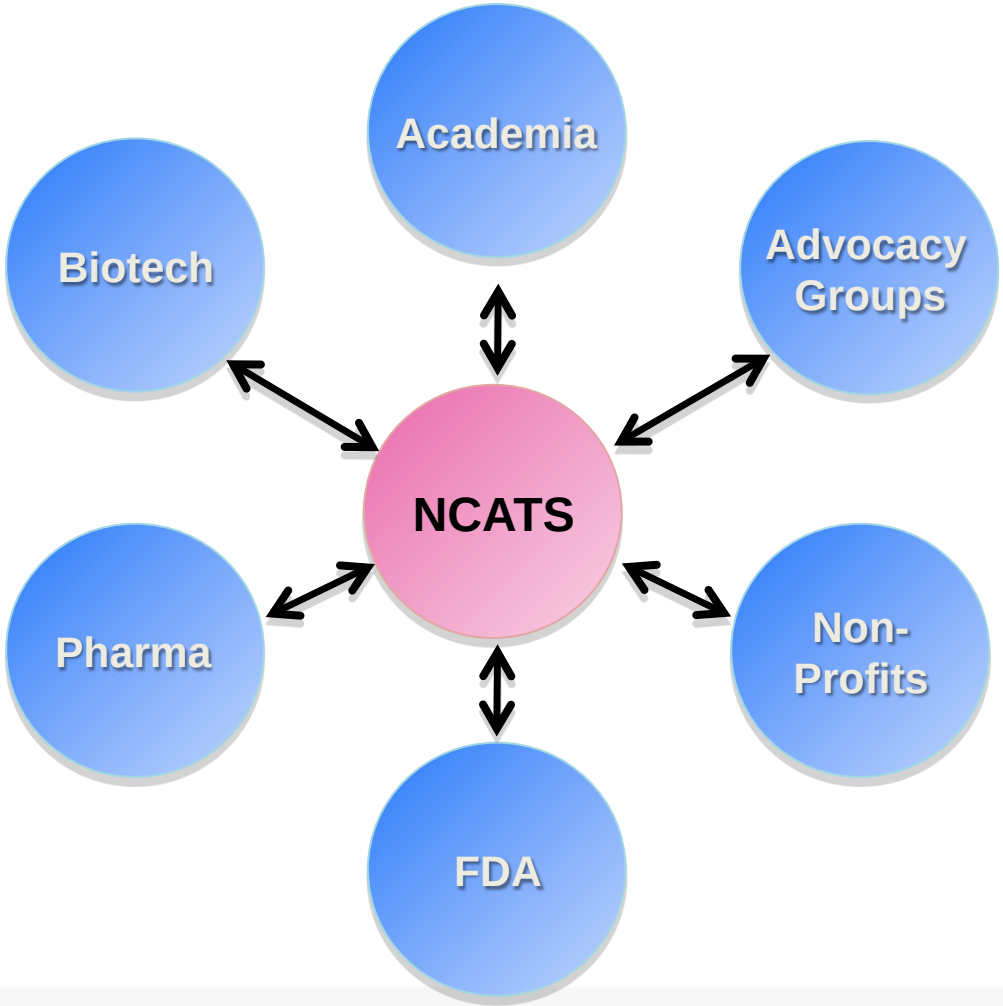


To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of interventions that tangibly improve human health across a wide range of human diseases and conditions.

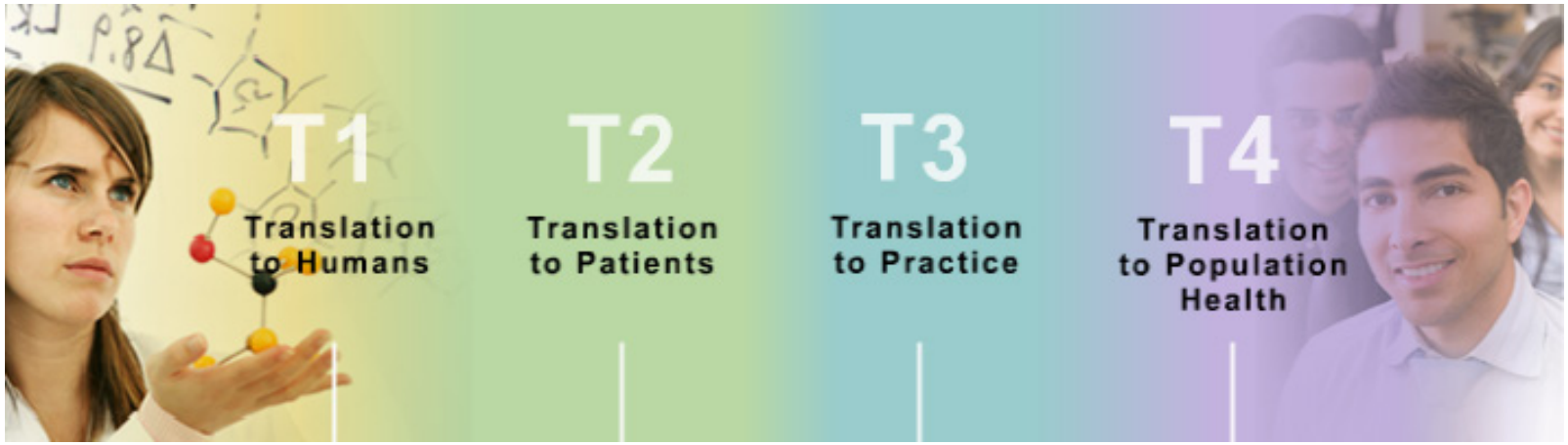
Catalyzing Collaborations Within NIH



Catalyzing Collaborations Outside NIH



Catalyzing Collaboration within NCATS Across the Translational Spectrum



NIH
National Center for Advancing Translational Sciences

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 of)

Some of the operational 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

NCATS "3D's"

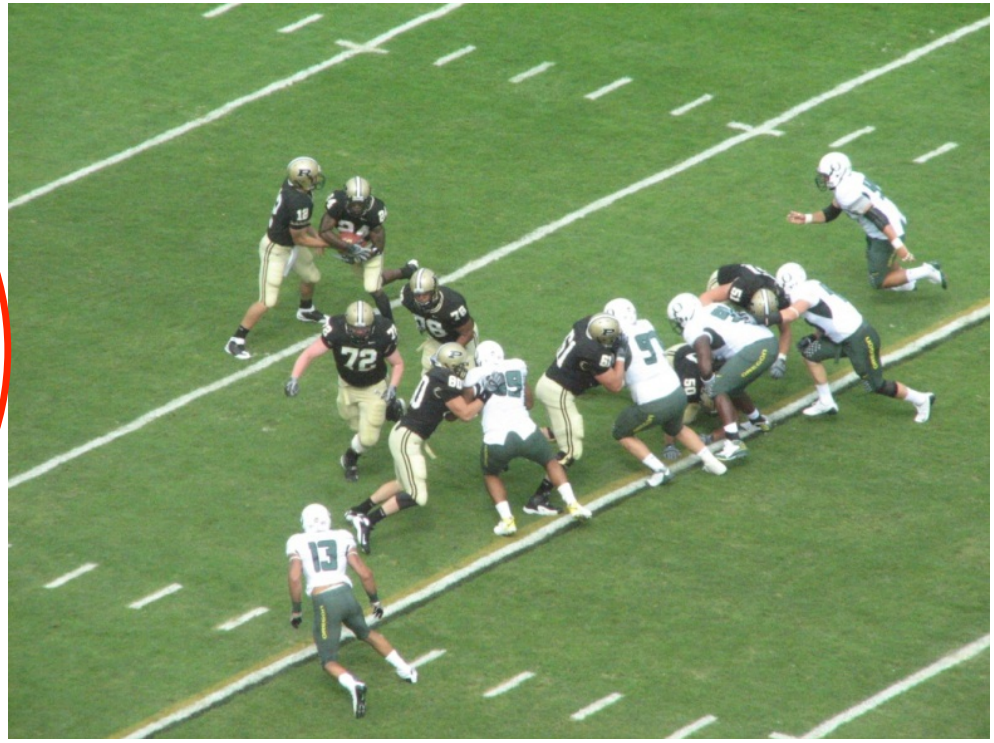
evelop

emonstrate

isseminate

Translation is a team sport

Requires top performers with a wide variety of different expertise to work together to a common goal



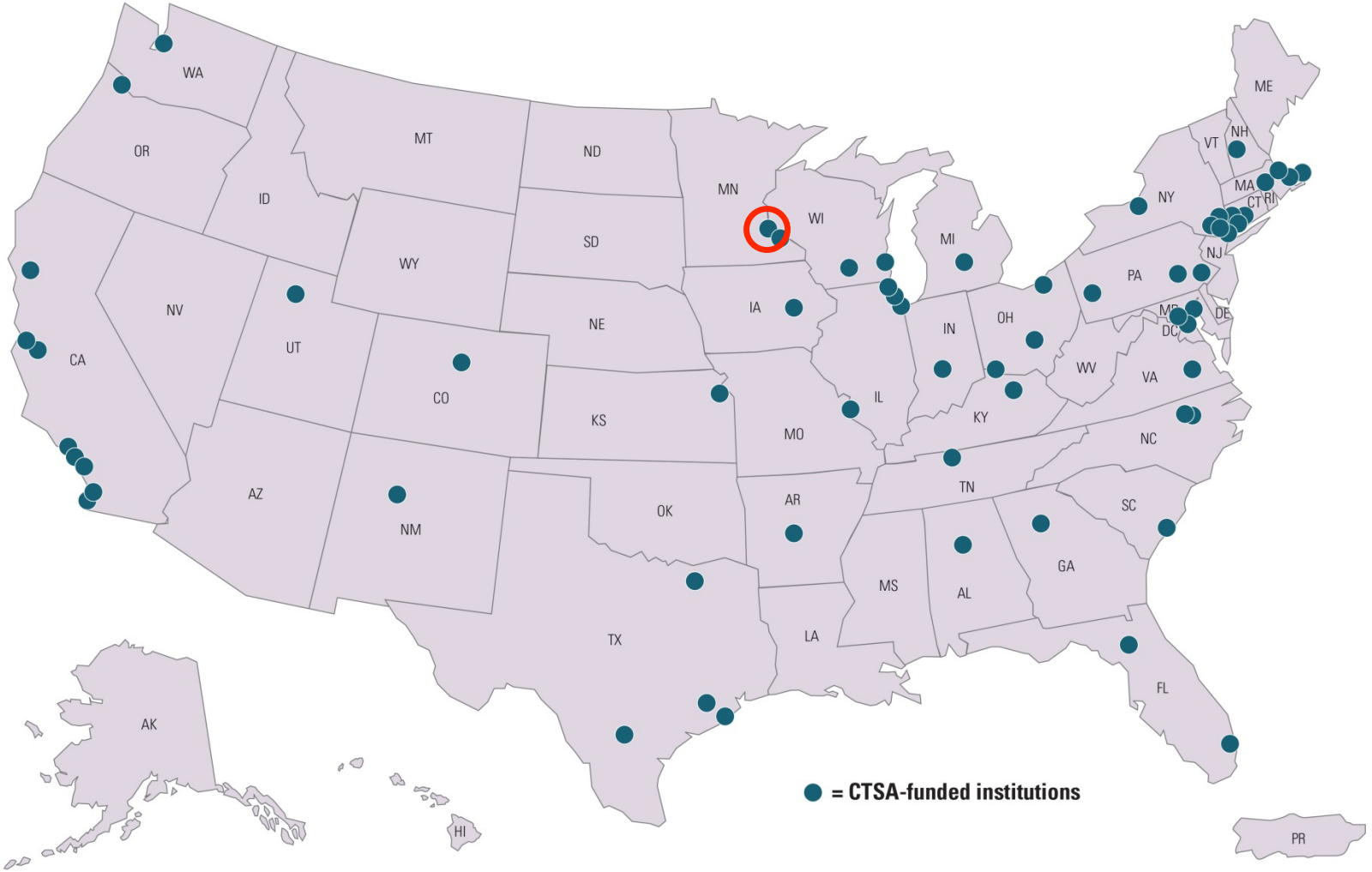
NCATS Scientific Initiatives

- Clinical Translational Science
  - Clinical and Translational Science Awards
  - Rare Disease Clinical Research Network
  - New Therapeutic Uses program
- Preclinical Translational Science
  - NIH 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

NCATS Division of Clinical Innovation

- Drive development, demonstration, and adoption of shared technologies, practices, and policies to logarithmically improve the efficiency of clinical translation
- Improve and instantiate methods and practice of rigorous clinical phenotyping and investigation in research and care
- Instill innovation in training programs for all research team members required for end-to-end translation
- Advance robust academic collaborative discipline of translational research and medicine
- Expand new models for engagement, collaboration, and partnership of communities across the clinical translational spectrum

Clinical and Translational Science Awards
(CTSA) Program Sites



Evolution of the CTSA Program

- Established in 2006 to "re-engineer the clinical research enterprise" (Zerhouni)
- In December 2011, NIH established NCATS, with the CTSA program as its largest component
- June 2013 IOM report finds CTSA program a worthwhile investment that has resulted in the successful establishment of academic focal points for translational and clinical research, and that would benefit from a variety of revisions
- NCATS with advice from a Council Working Group and input from CTSA investigators is implementing the recommended changes to the CTSA program

Development of Strategic Goals

WG Focus Areas → Strategic Goal Recommendations

IOM Report Recommendations

- Formalize and standardize evaluation processes
- Advance innovation in education and training programs
- Ensure community engagement in all phases of research
- Strengthen clinical and translational science relevant to child health

WG Focus Areas

- Training and education
- Collaboration and partnerships
- Community engagement of all stakeholders
- Academic environment for translational science
- Translational science across the lifespan and unique populations

Strategic Goal Recommendations

- Workforce Development
- Collaboration and Engagement
- Integration
- Methods, and Processes

New Funding Opportunity Announcement

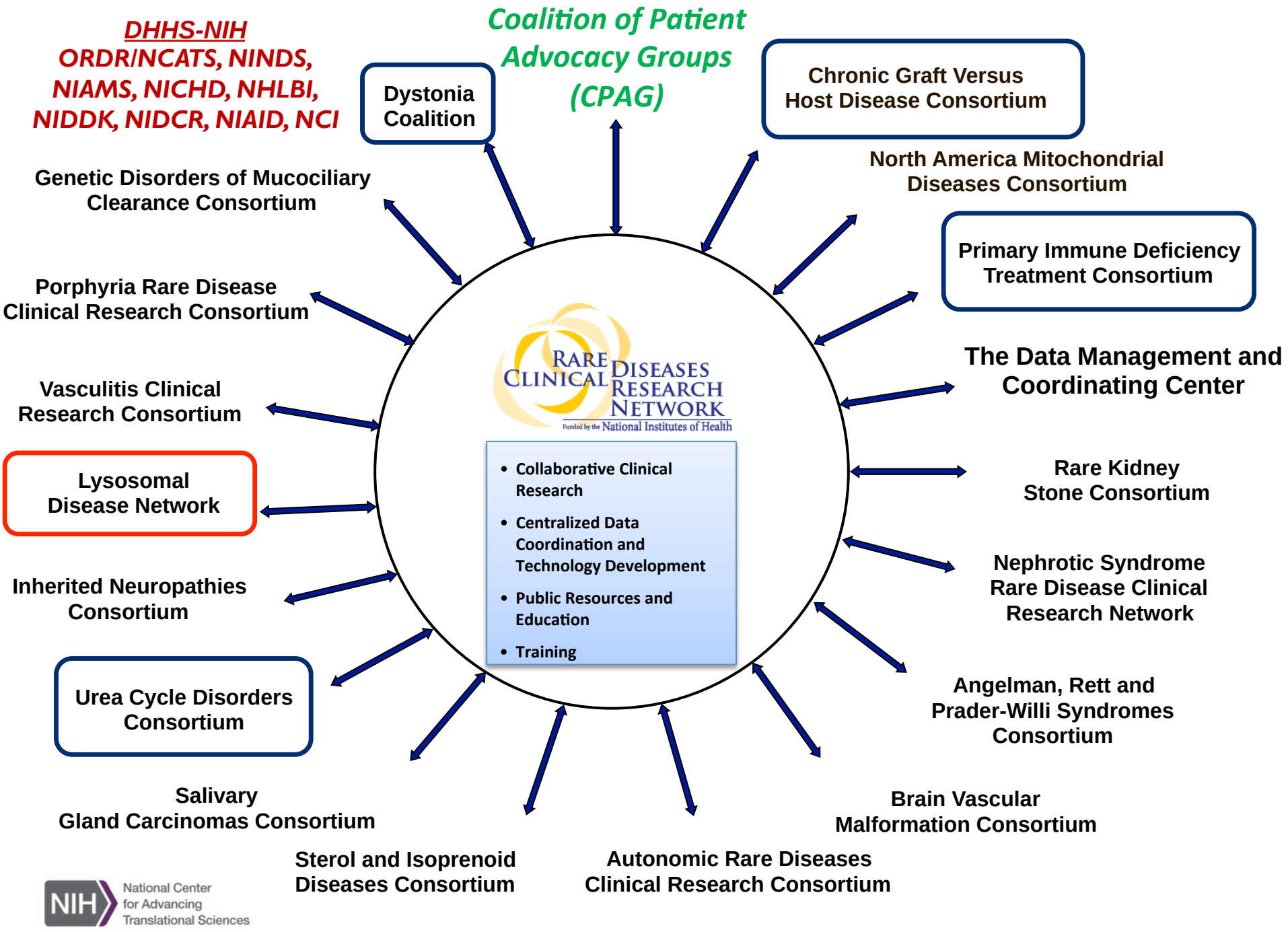
Clinical Innovation

NIH
National Center for Advancing Translational Sciences

Office of Rare Diseases Research (ORDR)

- Rare Diseases Clinical Research Network (RDCRN)
  - 17 consortia at 225 institutions worldwide
  - Studying >200 diseases with 83 active protocols, and
  - More than 85 patient advocacy groups participating
- Genetic and Rare Disease Information Center (GARD)
- Scientific Conferences Program
  - Identify Scientific Opportunities and Establish Research Agendas (1200 Conferences)
- Global Rare Disease Registry (GRDR) Data Repository
  - 15 GRDR patient registries + 19 existing registries
  - Ability to conduct pan-disease analysis and recruitment

NIH National Center for Advancing Translational Sciences


DHHS-NIH
ORDR/NCATS, NINDS, NIAMS, NICHD, NHLBI, NIDDK, NIDCR, NIAID, NCI
Coalition of Patient Advocacy Groups (CPAG)
Dystonia Coalition
Chronic Graft Versus Host Disease Consortium
North America Mitochondrial Diseases Consortium
Genetic Disorders of Mucociliary Clearance Consortium
Primary Immune Deficiency Treatment Consortium
Porphyria Rare Disease Clinical Research Consortium
The Data Management and Coordinating Center
Vasculitis Clinical Research Consortium
Rare Clinical Diseases Research Network
Funded by the National Institutes of Health
Lysosomal Disease Network
Rare Kidney Stone Consortium
Collaborative Clinical Research
Centralized Data Coordination and Technology Development
Public Resources and Education
Training
Inherited Neuropathies Consortium
Nephrotic Syndrome Rare Disease Clinical Research Network
Urea Cycle Disorders Consortium
Angelman, Rett and Prader-Willi Syndromes Consortium
Salivary Gland Carcinomas Consortium
Brain Vascular Malformation Consortium
Sterol and Isoprenoid Diseases Consortium
Autonomic Rare Diseases Clinical Research Consortium
NIH National Center for Advancing Translational Sciences

Lysosomal Disease Network
RDCRN at the University of Minnesota

- PI: Chester Whitley, M.D.
- Partnership between NCATS, NINDS and NIDDK
- Focused on eleven of the lysosomal diseases
- Goal is to solve the major challenges in diagnosis, disease management, and therapy for these complex, rare disorders

NIH
National Center for Advancing Translational Sciences

Discovering *New Therapeutic Uses* for Existing Molecules Program *(NTU)*

- Problem: 80% of drugs that enter clinic never approved
- Opportunity: potential for new treatments via ID of new indications for deprioritized investigational drugs
- Program: matches investigational agents from pharma deprioritized for lack of efficacy or business reasons with new indication ideas from academia
  - NIH provided: template Collaborative Research Agreements (CRAs) and Confidential Disclosure Agreements (CDAs), FOAs, review, funding, oversight
  - Pharmaceutical partners provided: compounds, biologics, in kind support, pertinent data
  - Academic researchers provided: deep understanding of disease biology, new concepts to test, access to appropriate patient populations

New Therapeutic Uses Program

Pilot Program Awards Issued June 2013

- 9 projects in 8 diseases

Disease	Academic Partner	Pharma Partner
Alzheimer's Disease	Yale	AstraZeneca
Alcoholism	U Rhode Island/NIAAA	Pfizer
Calcific Aortic Stenosis	Mayo Clinic	Sanofi
Duchenne Muscular Dystrophy	Kennedy Krieger/UWash	Sanofi
Lymphangioleiomyomatosis	Baylor	AstraZeneca
Peripheral Artery Disease	U Virginia	AstraZeneca
Smoking Cessation	VCU/Pittsburgh	Janssen
Schizophrenia (2)	Indiana U	Lilly
	Yale	Pfizer

- Translational Innovation Success Measures
  - Does use of template agreements speed negotiation time?
  - Does crowdsourcing of indications generate new ideas?
  - Do studies result in new indications/approvals?

New Therapeutic Uses Program

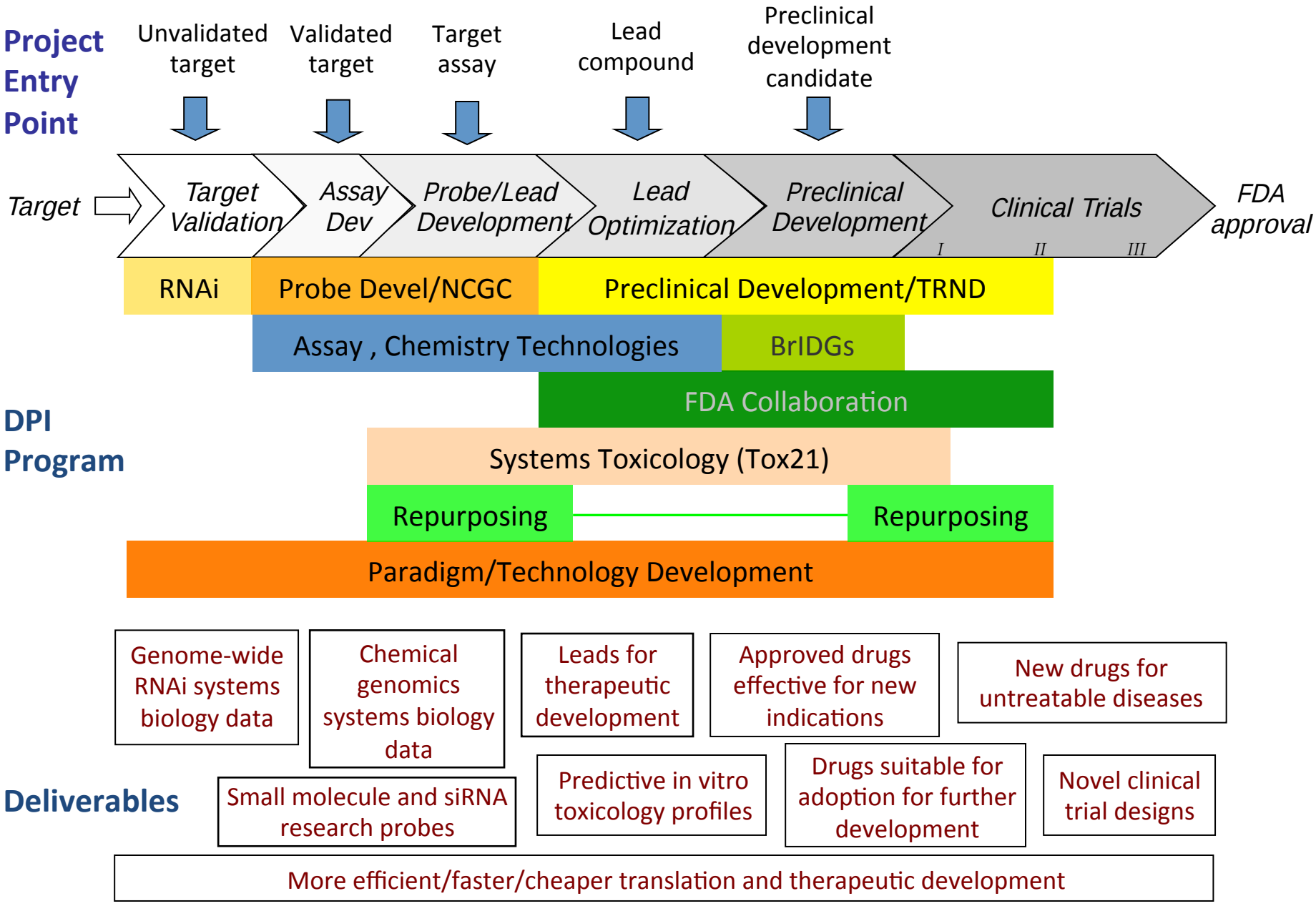
Pilot Program Awards Issued June 2013

- 9 projects in 8 diseases

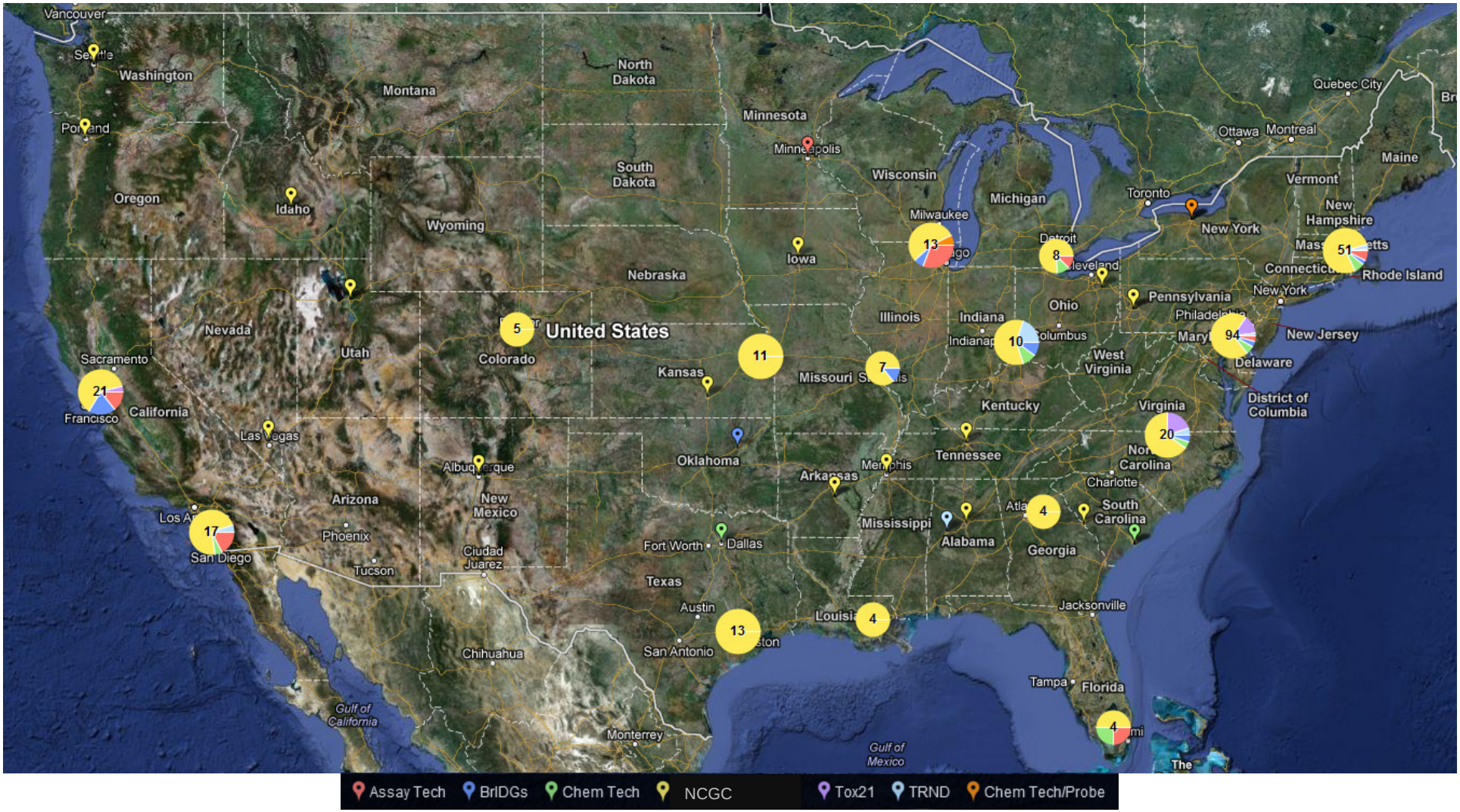
Disease	Academic Partner	Pharma Partner
Alzheimer's Disease	Yale	AstraZeneca
Alcoholism	U Rhode Island/NIAAA	Pfizer
Calcific Aortic Stenosis	Mayo Clinic	Sanofi
Duchenne Muscular Dystrophy	Kennedy Krieger/UWash	Sanofi
Lymphangioleiomyomatosis	Baylor	AstraZeneca
Peripheral Artery Disease	U Virginia	AstraZeneca
Smoking Cessation	VCU/Pittsburgh	Janssen
Schizophrenia (2)	Indiana U	Lilly
	Yale	Pfizer

- Translational Innovation Success Measures
  - Does use of template agreements speed negotiation time? YES
  - Does crowdsourcing of indications generate new ideas? YES
  - Do studies result in new indications/approvals? DATA IN 2015

NCATS DPI: A Collaborative Pipeline



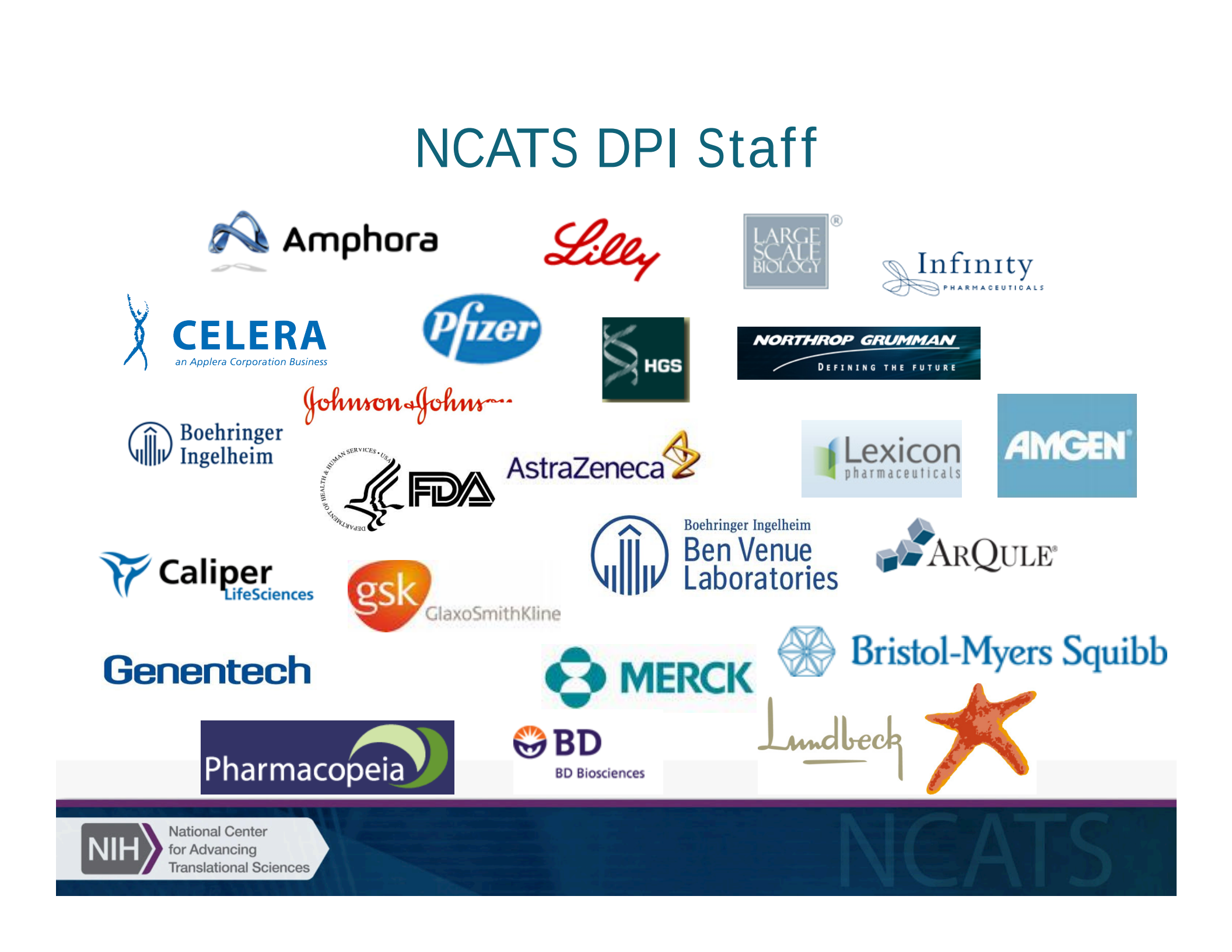
All DPI Projects are Collaborations



DPI currently has >300 collaborations with investigators all over the U.S….

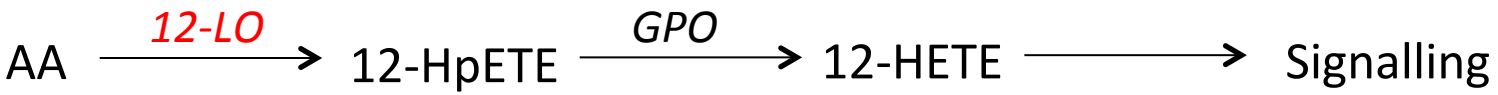
NIH National Center for Advancing Translational Sciences

NCATS DPI Staff



Chemical Probe Development Case Study: *Inhibitors of 12-Lipoxygenase*

- 12-hLO identified >30 years ago, but lack of selective inhibitors limited the understanding of its physiological function(s)



- NCGC collaboration with Ted Holman (UCSC) developed assay, HTS, cheminformatics, medchem optimization, leading to first potent, enantiomer selective 12-LO inhibitor (ML127)
- The ML127 pharmacological probe has allowed dissection of 12-LO functions *in vitro* and *in vivo*
- Therapeutic development for diabetes and thrombosis
  - Collaborators:
    - Ted Holman (UCSC)
    - Jerry Nadler (EVMS)
    - Michael Holinstat (TJU)
  - Developed the most potent, selective and drug-like inhibitors for 12-LOX to date
  - Signed Research Collaboration Agreement with Sanofi to further characterize our inhibitors

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†

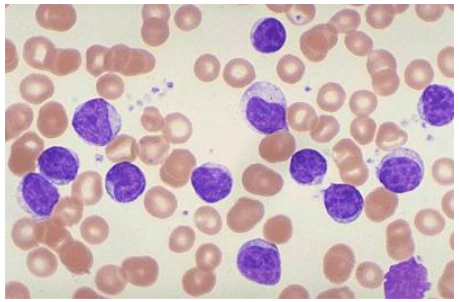
Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across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

NIH National Center for Advancing Translational Sciences

Repurposing Case Study: Refractory CLL

CLL — Chronic Lymphocytic Leukemia

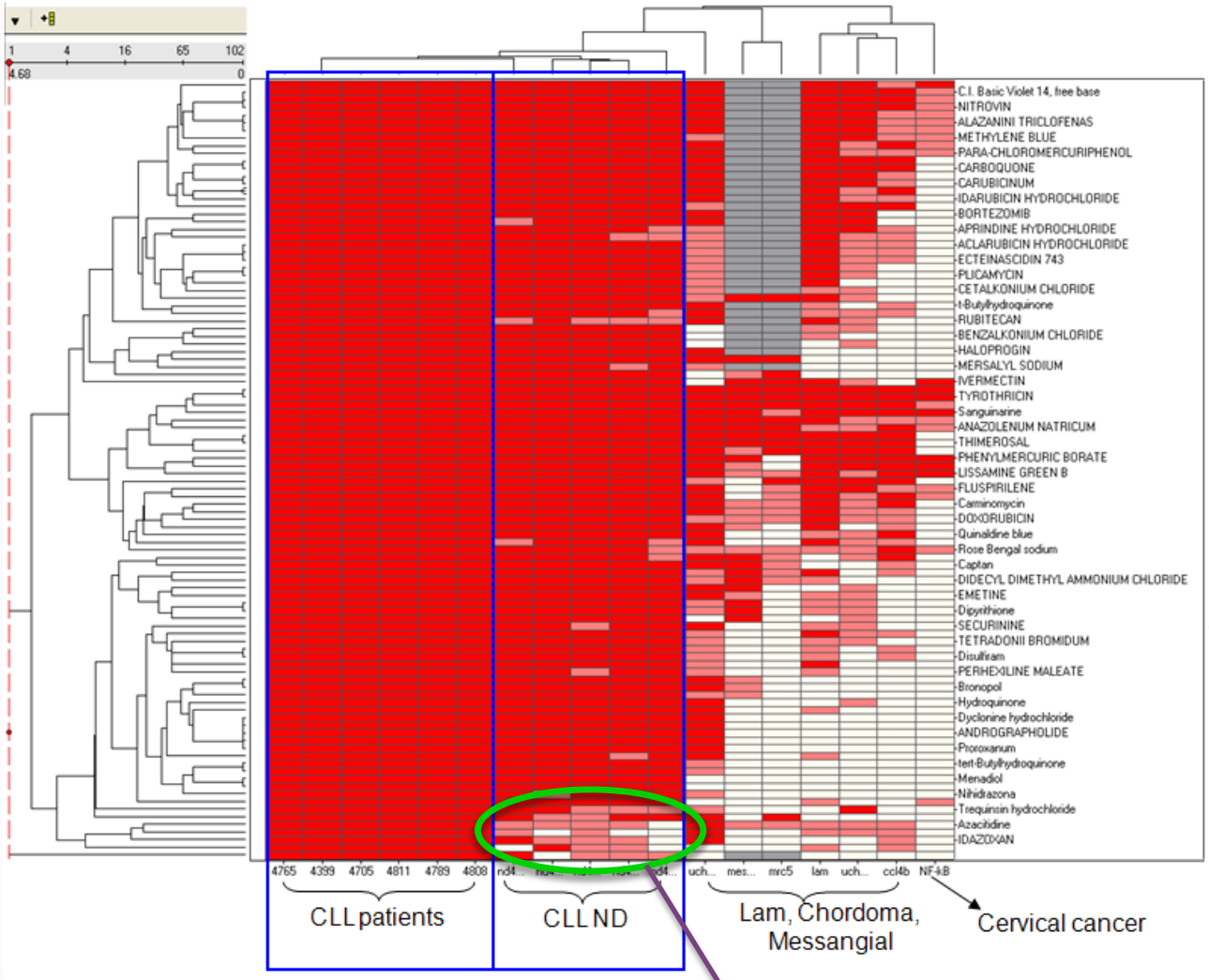


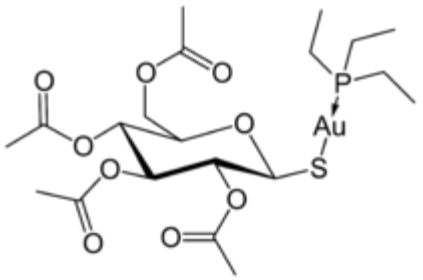
- 30% of all leukemias
- ~15,000 people new diagnoses/year in U.S.
- Standard of care: chemotherapy (e.g., fludarabine, anti-CD20 mab [Rituxan])
- Relapse virtually universal

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

NIH
National Center for Advancing Translational Sciences

Developing new medicines for blood cancers: The Learning Collaborative

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

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

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

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

NIH
National Center for Advancing Translational Sciences

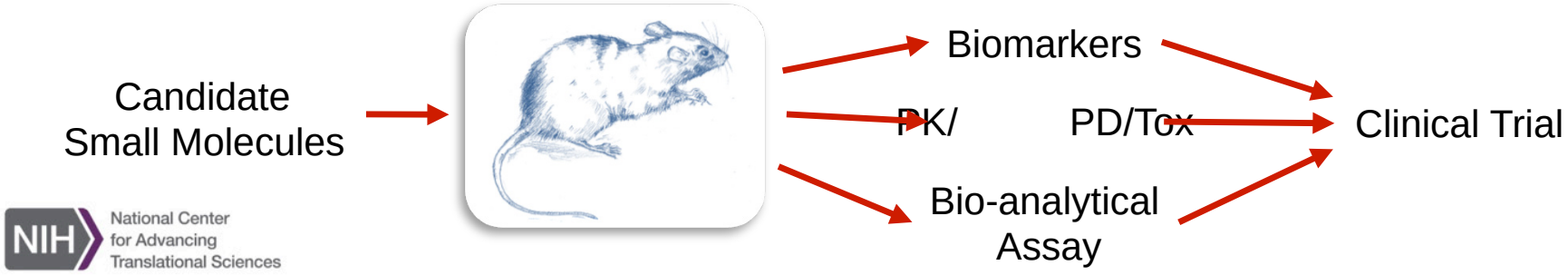
TRND
Scope

- Medicinal chemistry optimization
- Evaluation of functional activity, potency, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy
- Biomarker development
- Definition or optimization of dose and schedule for *in vivo* activity
- Development of pharmacology assays
- Conduct of pharmacology studies with a pre-determined assay
- Acquisition of bulk substance (GMP and non-GMP)
- Development of suitable formulations
- Development of analytical methods for bulk substances
- Production of dosage forms
- Stability assurance of dosage forms
- Range-finding initial toxicity
- Investigational New Drug (IND)-directed toxicology, with correlative pharmacology and histopathology
- Planning of clinical trials
- Regulatory and IND filing support
- First-in-Human clinical trials, as needed to support external adoption

TRND
Niemann Pick Type C Collaboration

- Drug: IT Cyclodextrin
- Collaborators
  - NIH: (Denny Porter, NICHD - Clinical
    Bill Pavan, NHGRI - Genetics)
  - Washington University (Dan Ory - Biochemistry)
  - 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-ß-cyclodextrin (HP-ß-CD) selected by TRND as pre-clinical candidate
  - December 2012: IND filed
  - February 2013: Phase I initiated and 1st patient dosed using ICV injections
  - May 2013: ICV trial clinical hold
  - July 2013: Response submitted to switch to IT lumbar injections for dosing
  - August 2013: Clinical hold lifted
  - September 2013 - present: IT trial on-going



NIH National Center for Advancing Translational Sciences

NPC Project Team

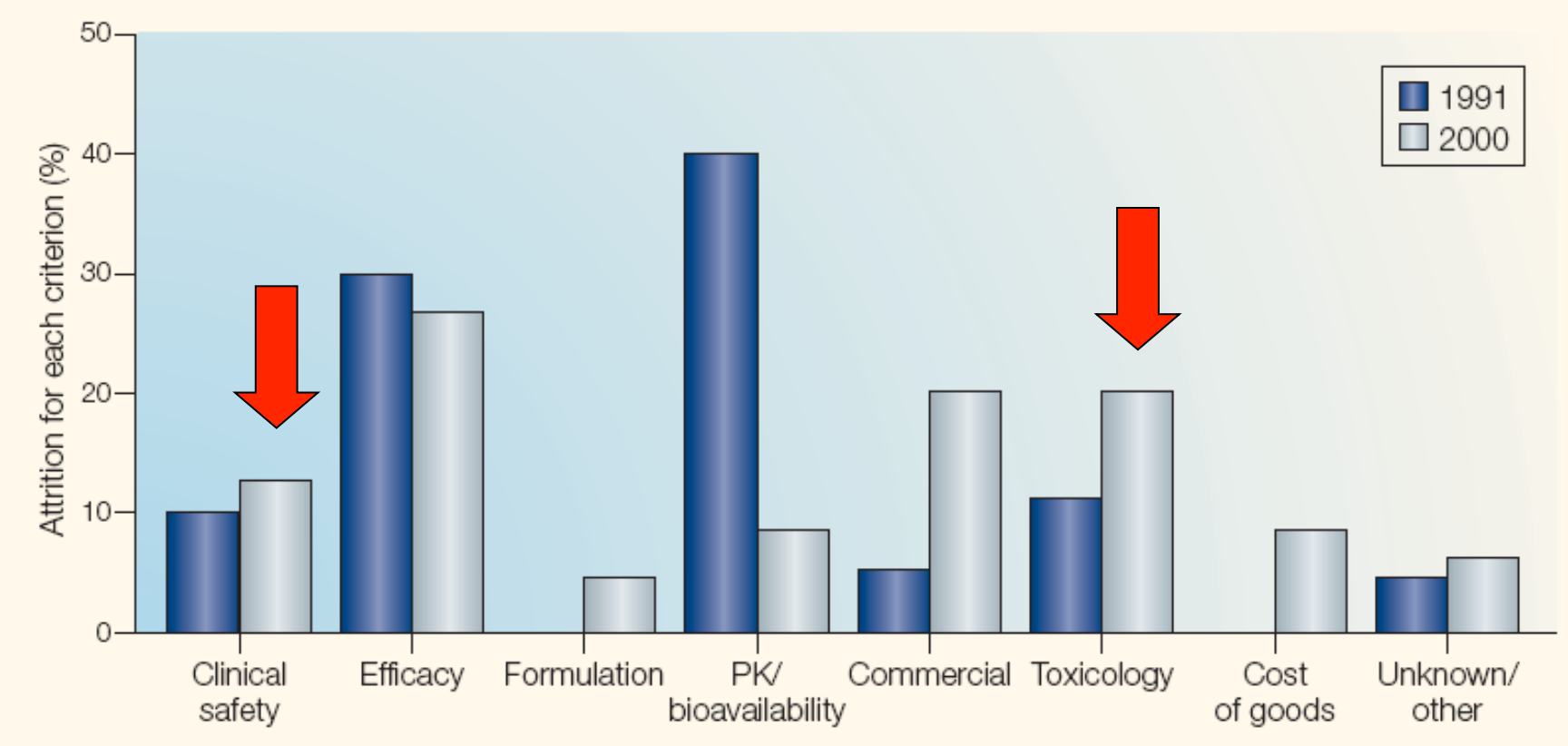
20 members with expertise spanning genetics, biochemistry, cell biology, animal models, pharmacology, drug development, regulatory, neurology, neurosurgery

9 organizations:

- NIH-NCATS/TRND
- NIH-NICHD
- NIH-NHGRI
- NIH-NINDS
- Albert Einstein College of Medicine
- University of Pennsylvania
- Washington University in St Louis
- Johnson & Johnson Pharmaceuticals
- RRD International (regulatory consultants to TRND)

NIH National Center for Advancing Translational Sciences

Toxicity is a common reason for drug development failure



Preclinical (21%) + Clinical (12%) Tox = 33% of all failures

NIH National Center for Advancing Translational Sciences

Kola and Landis, *Nature Reviews Drug Discovery* 3, 711-716, 2004.

Microphysiological Systems (MPS) Program *(aka, Tissue Chip, Organs-on-Chips)*

- Goal
  - Develop organoids on chips to screen for compound toxicity, efficacy
    - Liver, heart, lung, other cell types
    - Integrate platform systems
    - Designed for multiple different readouts
- NIH, DARPA contributing ~$70M each over 5 years
  - NCATS and DARPA independently manage, fund separately but highly coordinated program
  - FDA provides regulatory science guidance
- Awards announced in 2012
  - Supporting the best ideas in engineering, biology, and toxicology

NIH National Institutes of Health
Turning Discovery Into Health

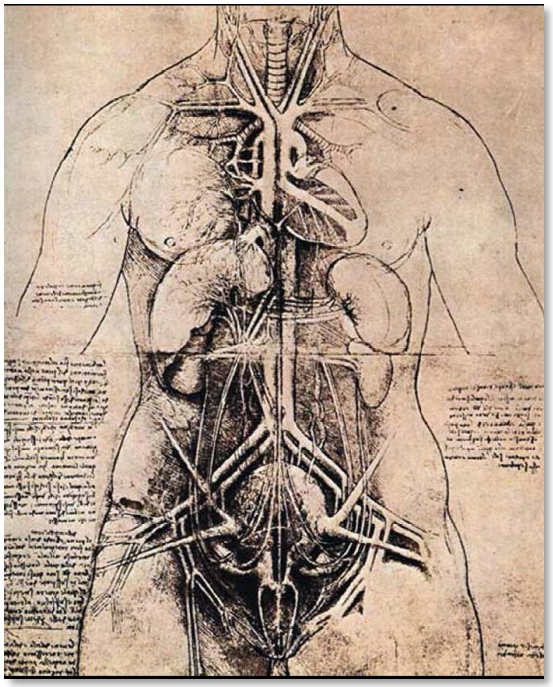
DARPA

FDA

NIH
National Center for Advancing Translational Sciences

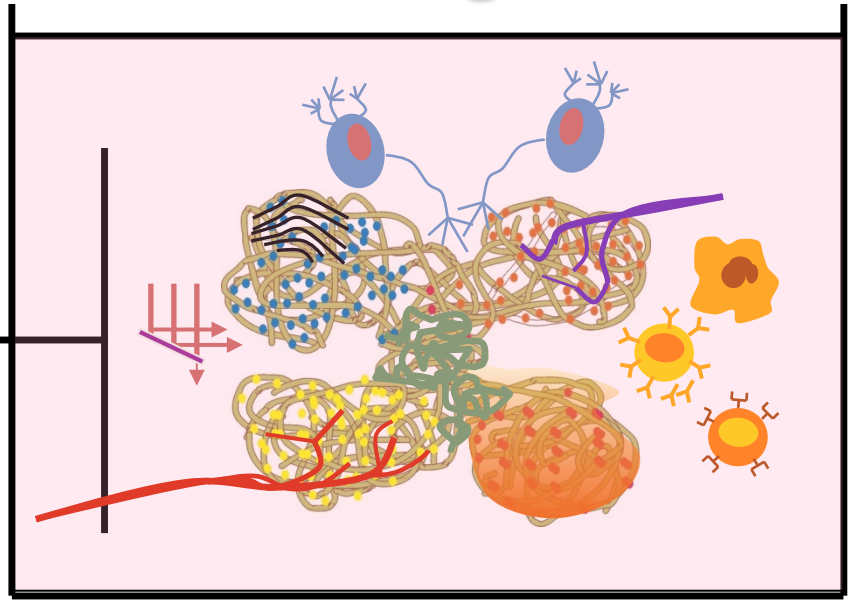
Microphysiological Systems Program

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

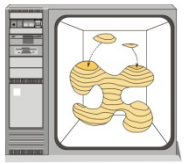


- All ten human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Integumentary
  - Musculoskeletal
  - Nervous
  - Reproductive
  - Respiratory
  - Urinary
- Physiologically relevant, genetically diverse,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

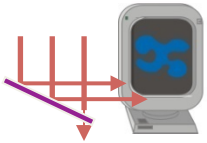
Microphysiological Systems from Common Building Blocks



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

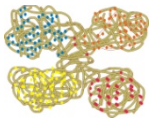


Functional Readout
- real-time, label-free, non-destructive sensing
- imaging

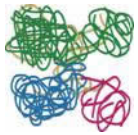


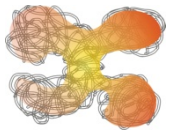
Scaffold
- purified ECM
- synthetic polymers
- composites

Cells
- stem/progenitor
- differentiated
- mixed cell types

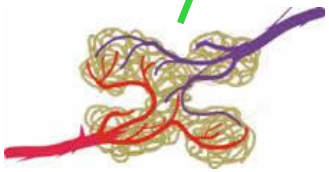


Structure
- porosity
- topography
- stiffness

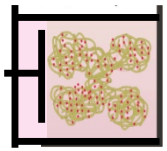




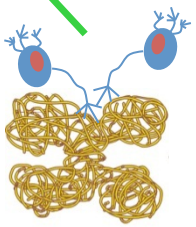
Spatial/Temporal Patterning
- cytokine gradients
- controlled release



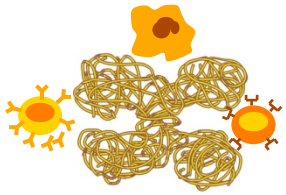
Perfusion
- embedded channels
- vascularization



Bioreactors
- optimized culture conditions
- biomechanical properties
- blood mimetics



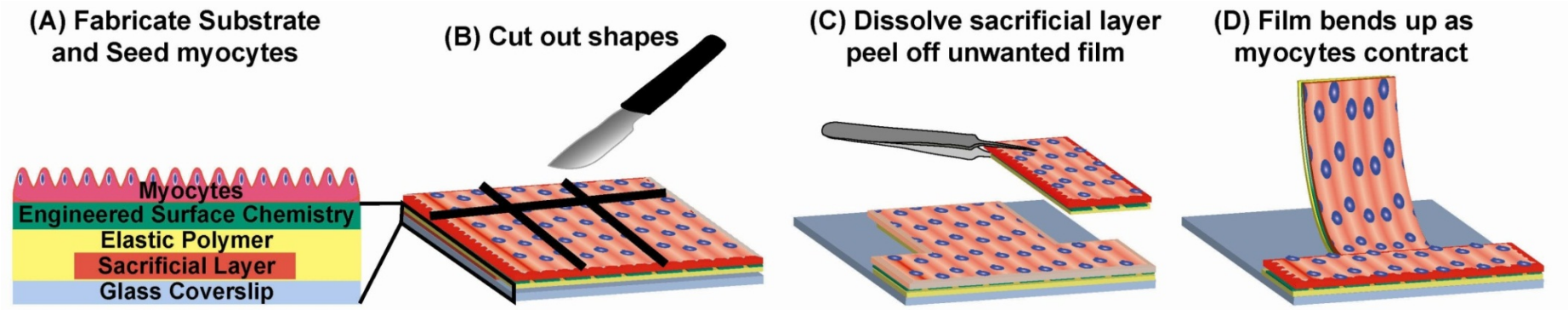
Innervation
- signal propagation
- coordinated response

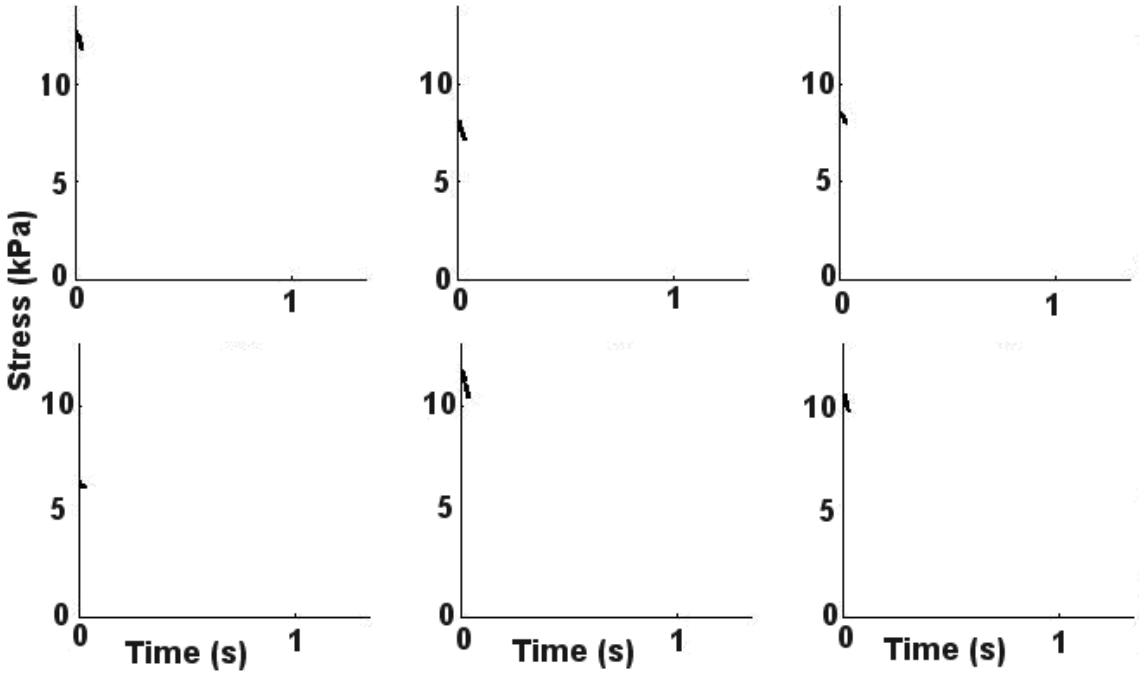


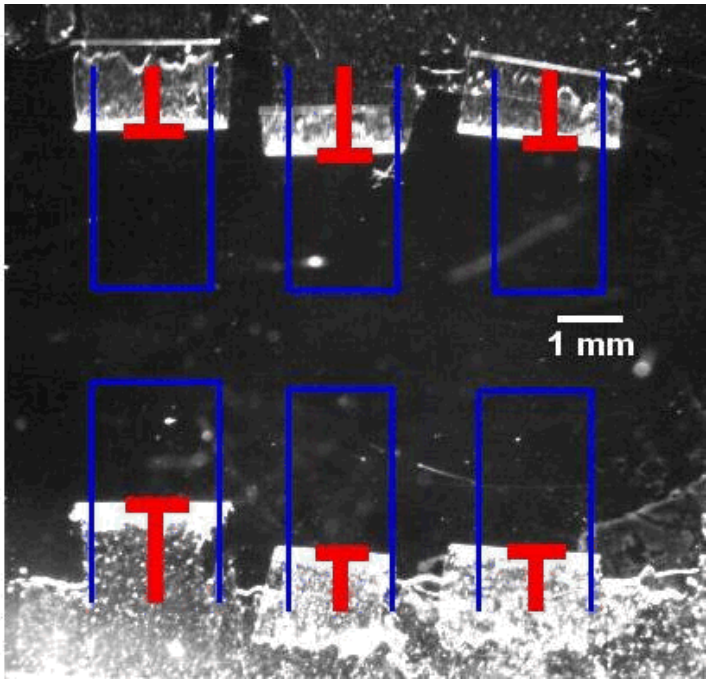
Host Response
- generalized inflammation
- specific immunity

NIH National Center for Advancing Translational Sciences

Engineered Cardiac Muscular Thin Films







Film length
Automatic projection tracking

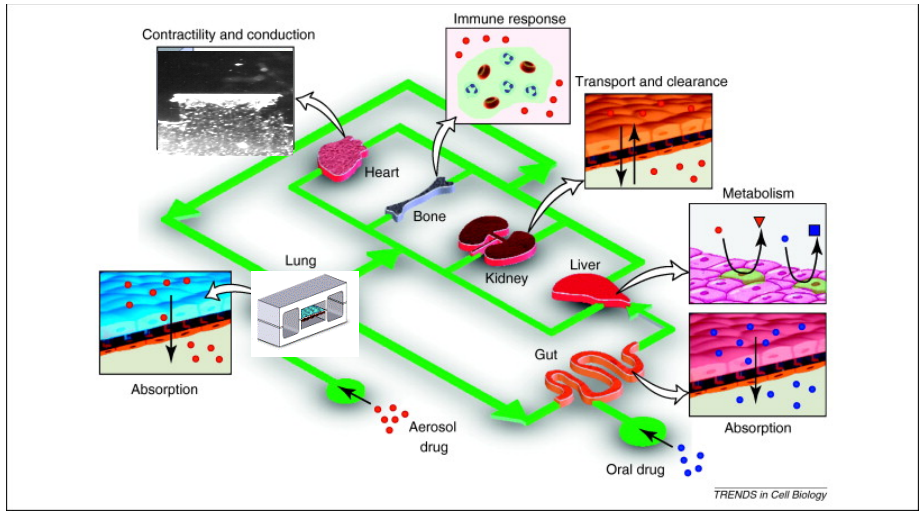
Data provided by Dr. Kit Parker, Wyss Institute

NIH National Center for Advancing Translational Sciences

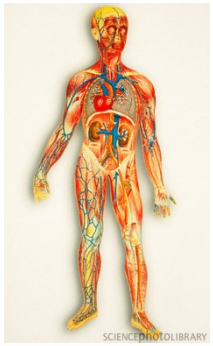
Science 2007;317:1366
Lab Chip 2011;11:4165

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

Body-on-a-Chip?



In vivo Correlation



- Absorption
- Distribution
- Metabolism
- Excretion
- Conc(t)
- Effect(t)
- Toxicity(t)
- Rare toxicities

Read outs

- Human biology
- Tissue/organ structure
- Cell histology
- Cell viability
- Mechanical properties
- Electrical properties
- Signaling pathways
- Cell metabolism
- Protein synthesis
- Gene expression
- Enzyme activities
- Ion channel properties

Take-home messages

- The opportunities (and needs) in translational science are huge and systematic, so require *systematic* solutions
- The scale of the opportunities/needs requires transformational change to deliver *logarithmic* improvements
  - » 21st c. needs cannot be solved with 20th c. structures
- NCATS has just begun to transform itself and its programs to meet these opportunities and needs for the benefit of patients

Program Leads at NCATS

- Preclinical Innovation: Anton Simeonov
  - » anton.simeonov@nih.gov
- Clinical Innovation: Petra Kaufmann
  - » petra.kaufman@nih.gov
- Office of Rare Diseases: Pamela McInnes
  - » pmcinnes@mail.nih.gov
- Tissue Chip: Dan Tagle
  - » tagled@mail.nih.gov
- New Therapeutic Uses: Christine Colvis
  - » ccolvis@mail.nih.gov
- Strategic Alliances: Lili Portilla
  - » portilll@mail.nih.gov

NIH
National Center for Advancing Translational Sciences

Learn More About NCATS

Website: www.ncats.nih.gov

Facebook: facebook.com/ncats.nih.gov

Twitter: twitter.com/ncats_nih_gov

YouTube: youtube.com/user/ncatsmedia

E-Newsletter: ncats.nih.gov/news-and-events/e-news/e-news.html

Email us! info@ncats.nih.gov

National Center for Advancing Translational Sciences