The National Center for Advancing Translational Sciences

Catalyzing Translational Innovation

CHRISTOPHER P. AUSTIN, M.D.
DIRECTOR, NCATS
NHGRI COUNCIL
FEBRUARY 10, 2014

NCATS

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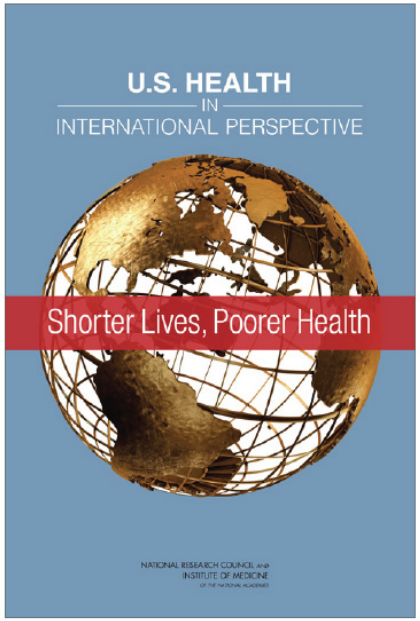
The Best of Times, the Worst of Times

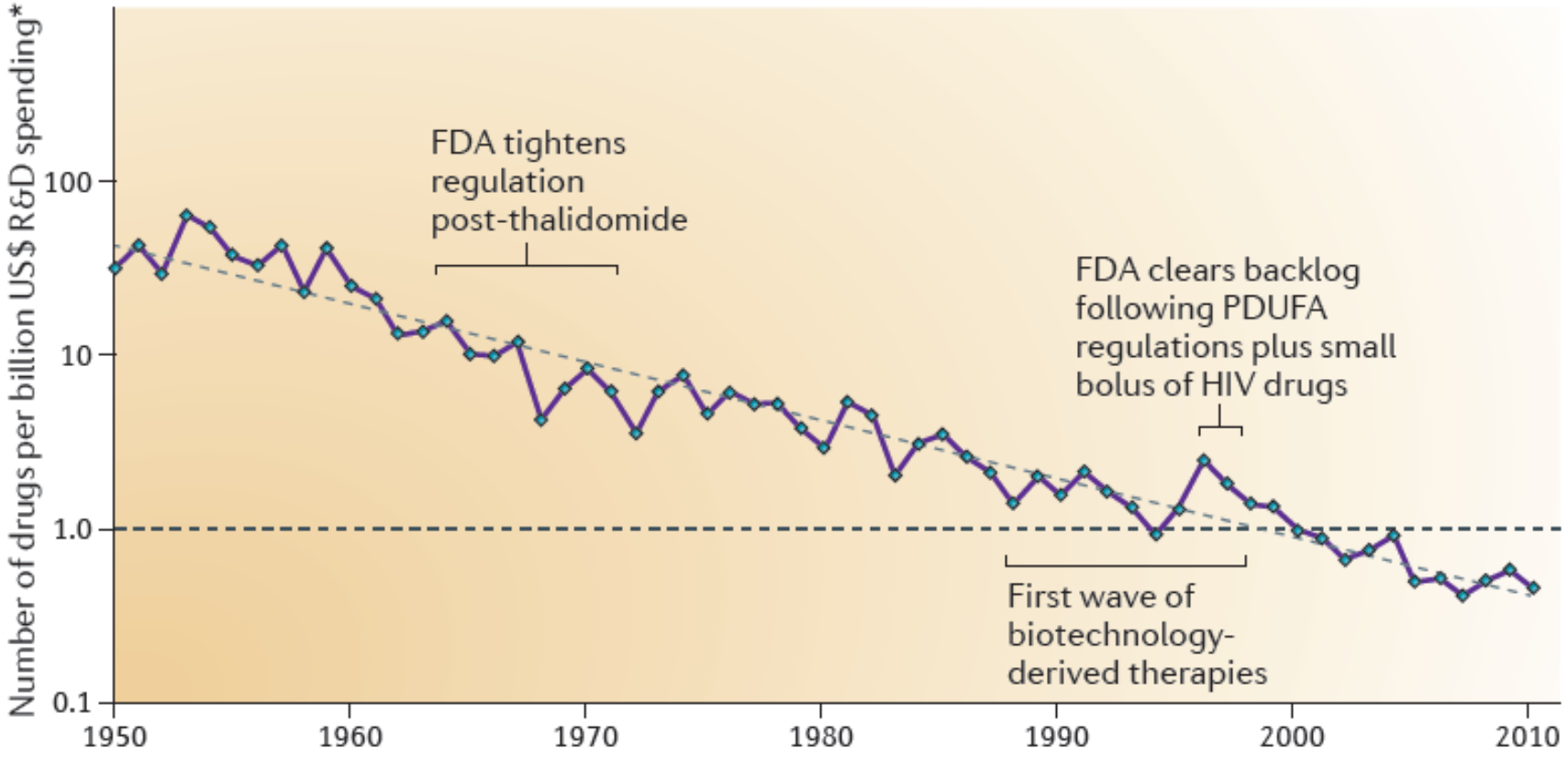
Fundamental science unprecedentedly advanced, but:

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

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.

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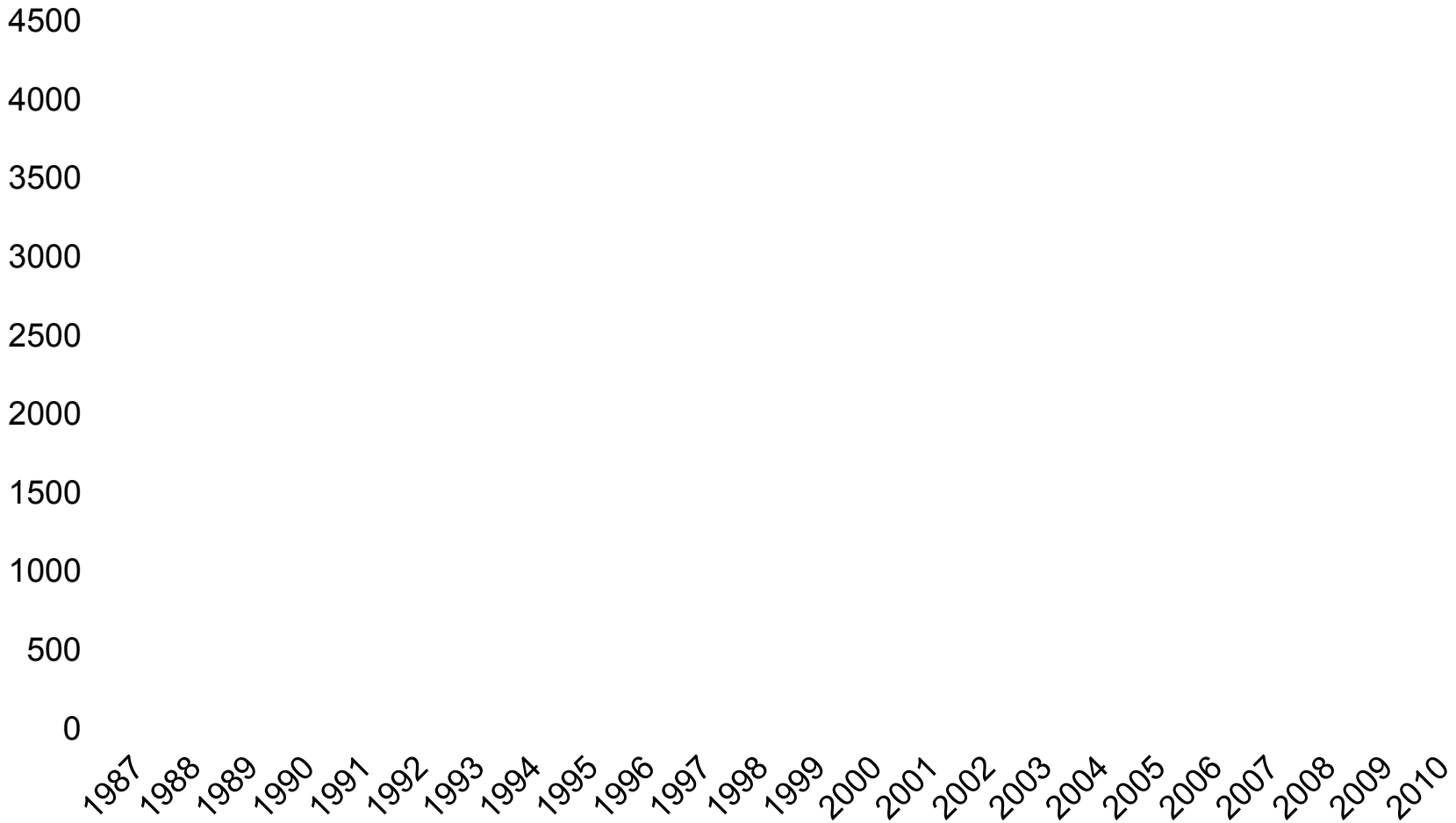
Scannell et al., *Nature Reviews Drug Discovery* 11:191, 2012

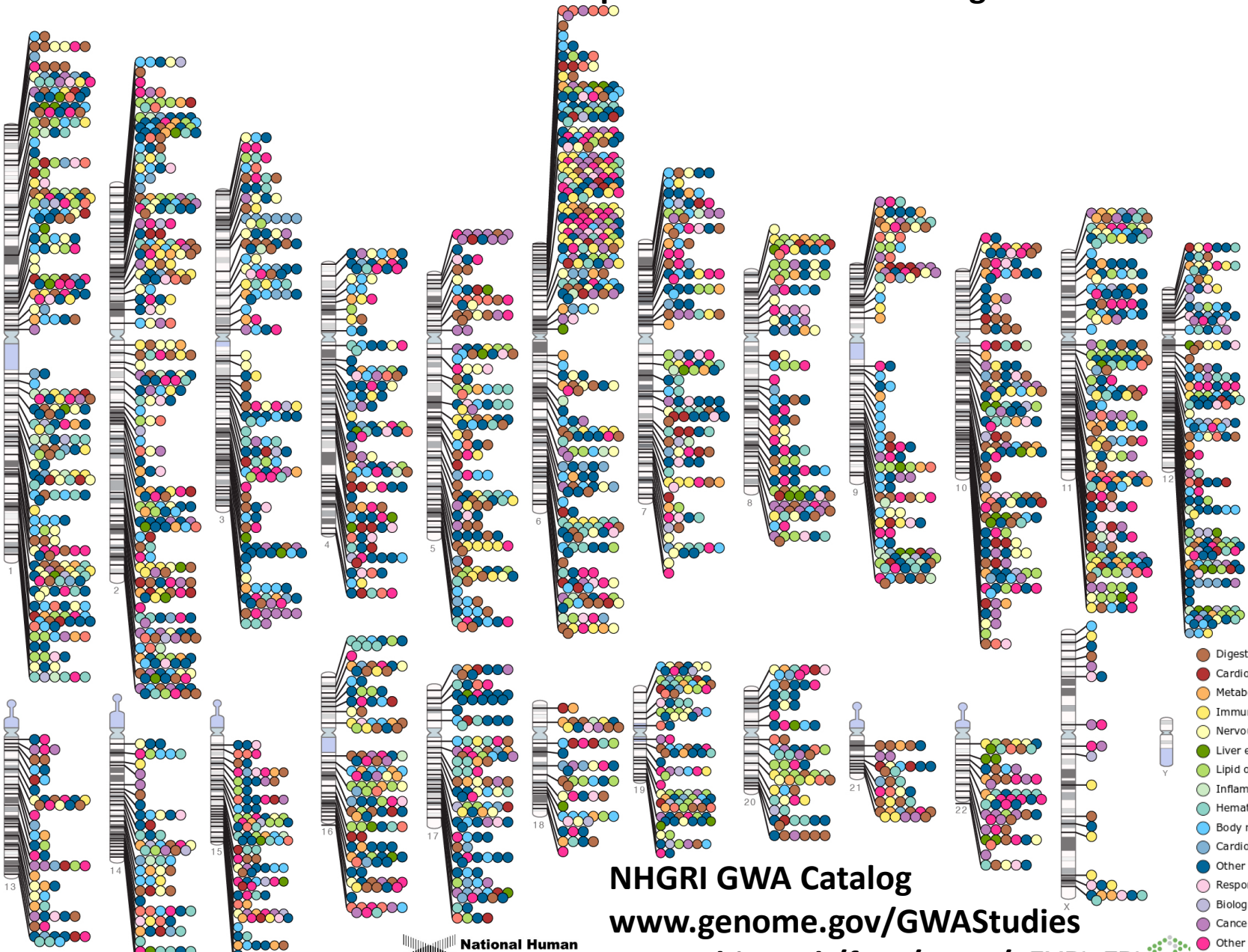
Rare Disorders with Identified Molecular Basis



Source: Online *Mendelian Inheritance in Man*

Published Genome-Wide Associations through 12/2012

Published GWA at $p \leq 5X10^{-8}$ for 17 trait categories



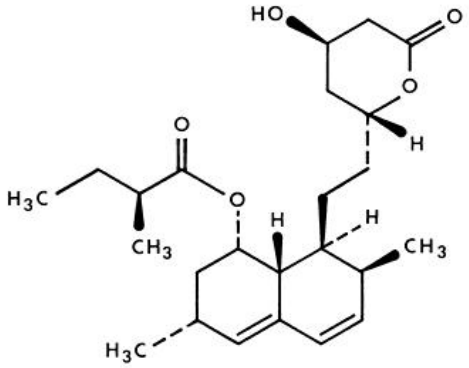
NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/

National Human Genome Research Institute

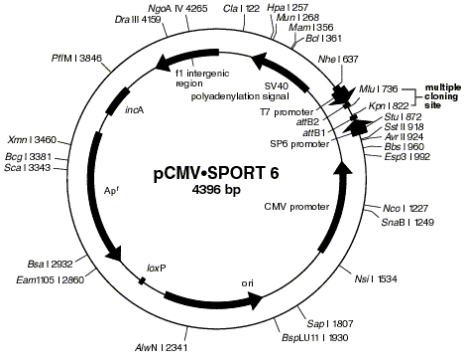
EMBL-EBI

Creating the Human Genome Translation Toolbox

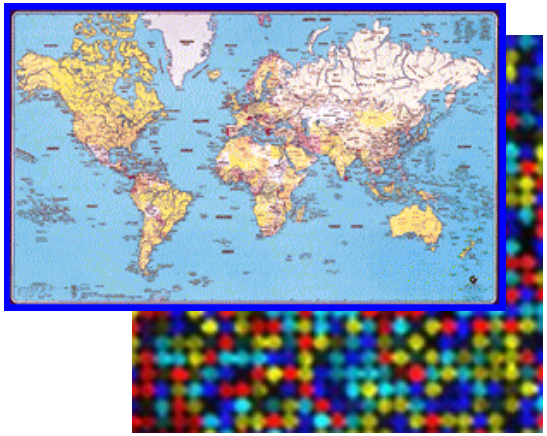
HumanBase



Small molecules



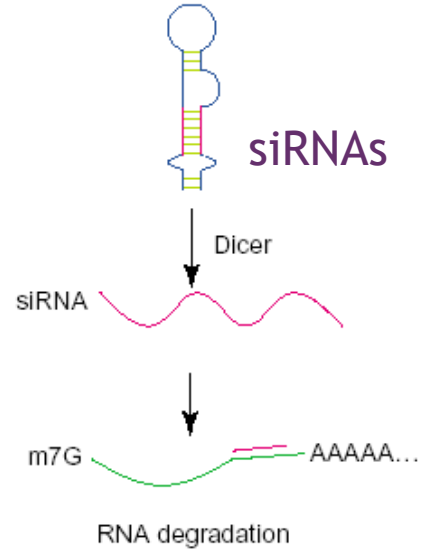
cDNA collection (MGC)



Transcriptome Reference Sets (MRT Project)

ENCyclopedia Of DNA Elements

KO mice genome-wide (KOMP)



I ♥ PCSK9

"The *PCSK9* story is a terrific example of an up-and-coming pattern of translational research."

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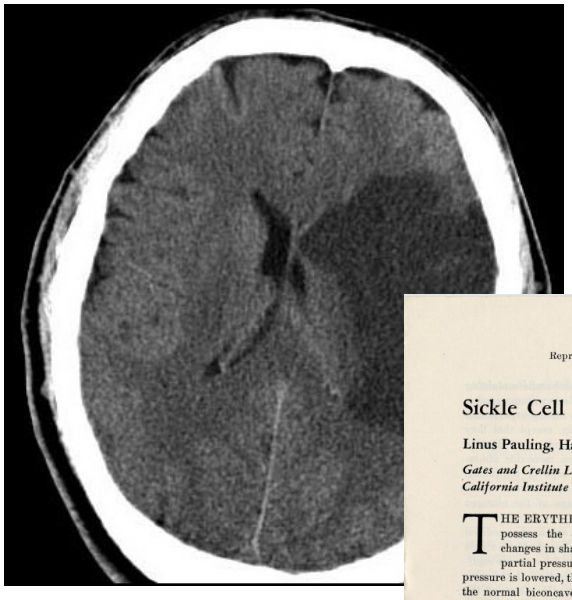
What I learned as a neurologist, and then again as a geneticist



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 promeniscocytes. The hemoglobin appears to be uniformly distributed and randomly oriented within normal cells and promeniscocytes, 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 promeniscocytes 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.

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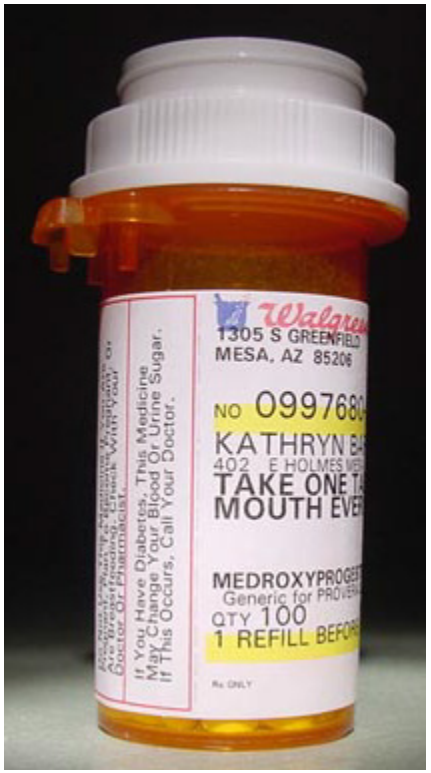

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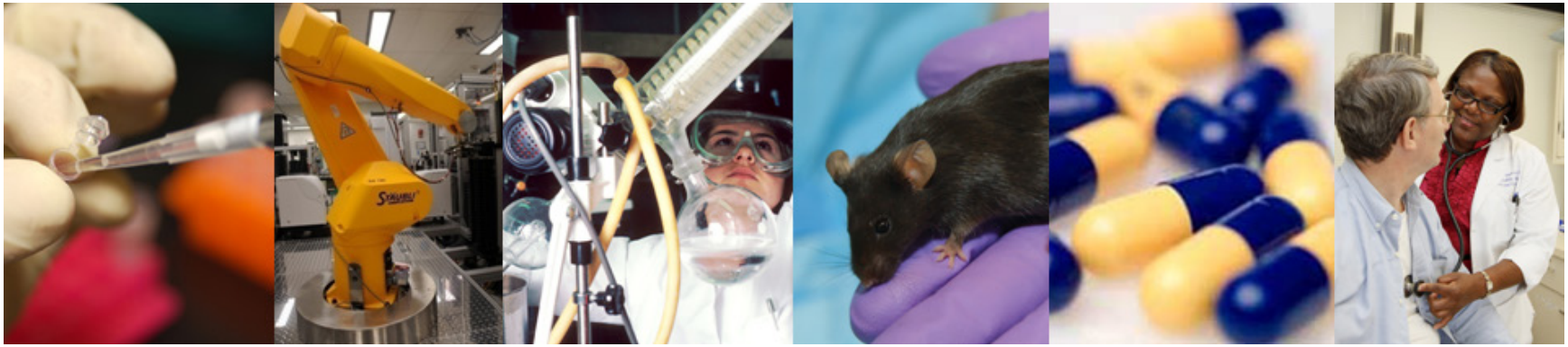
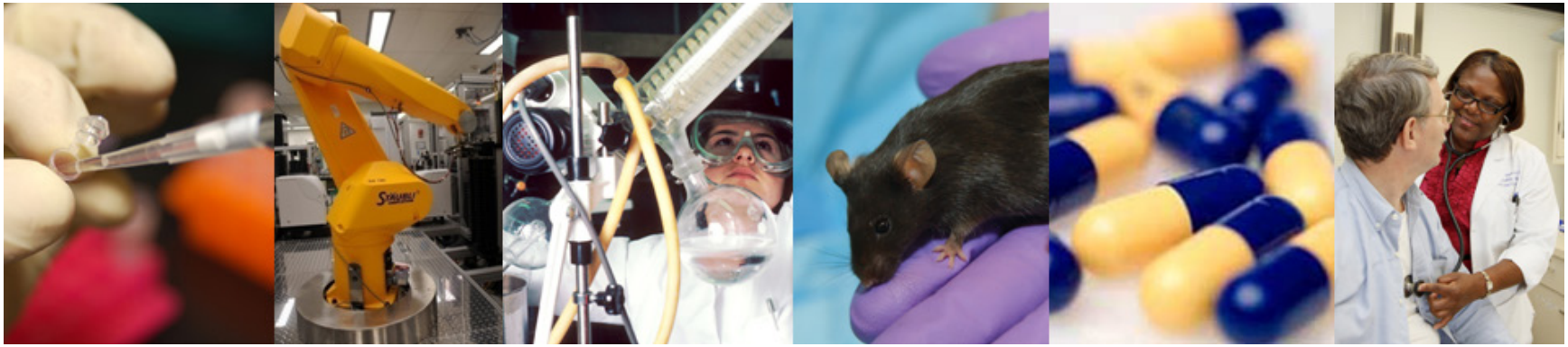
NCATS Mission



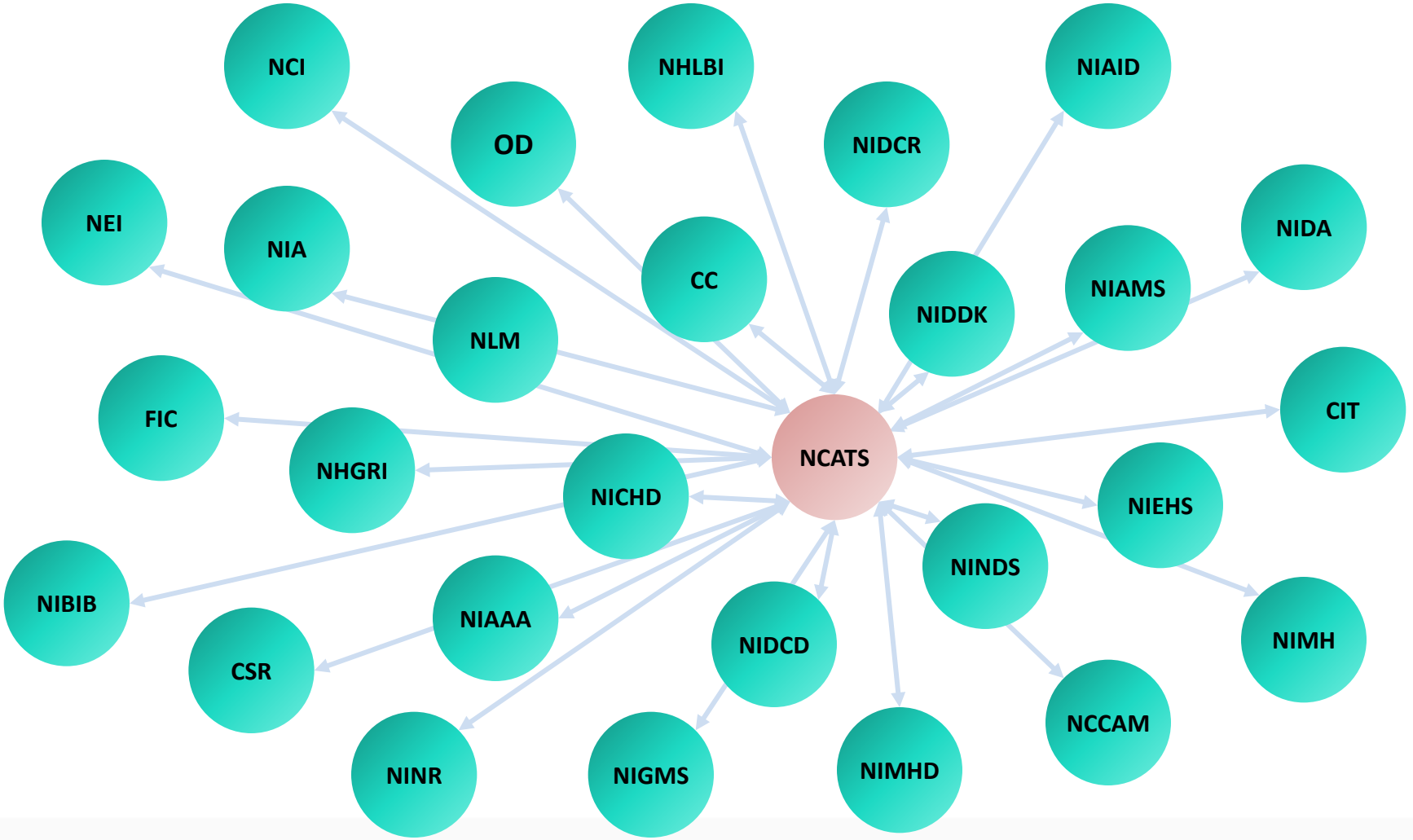
To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

NCATS Mission: an informal but important modification

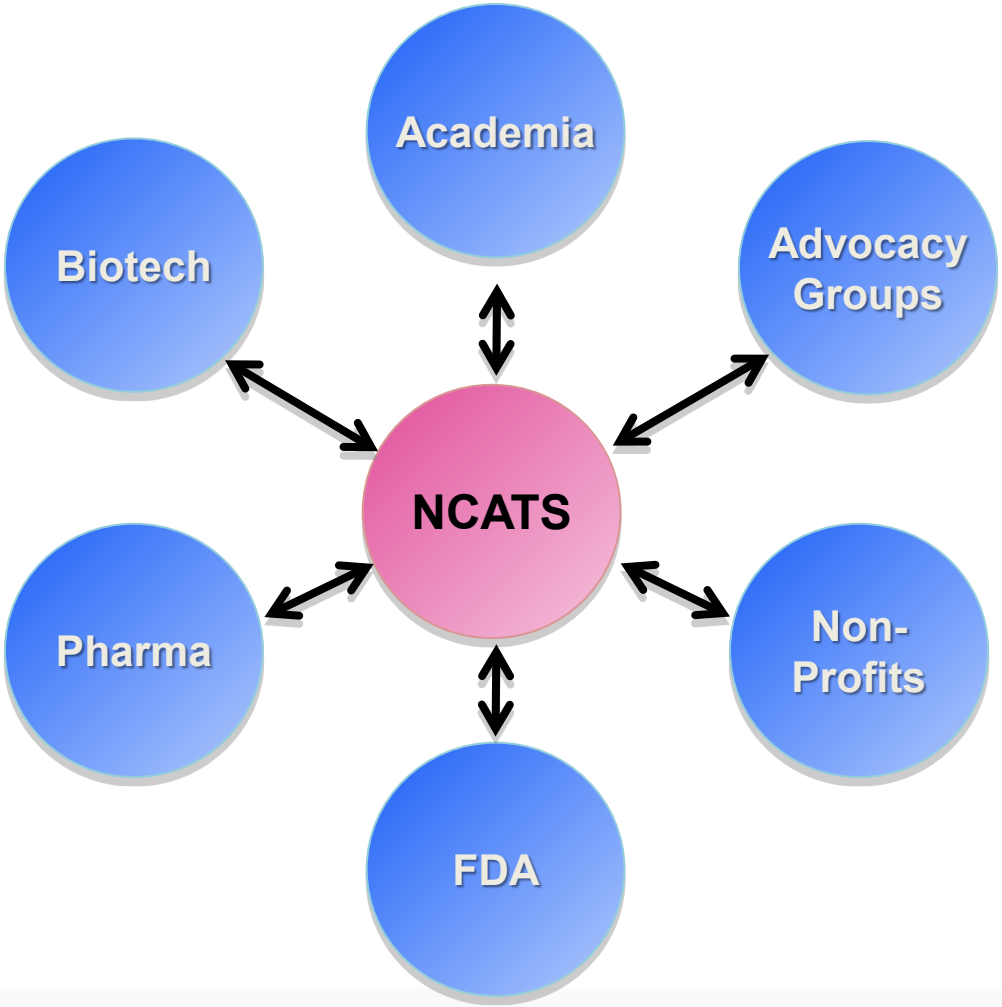


To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of interventions that tangibly improve human health across a wide range of human diseases and conditions.

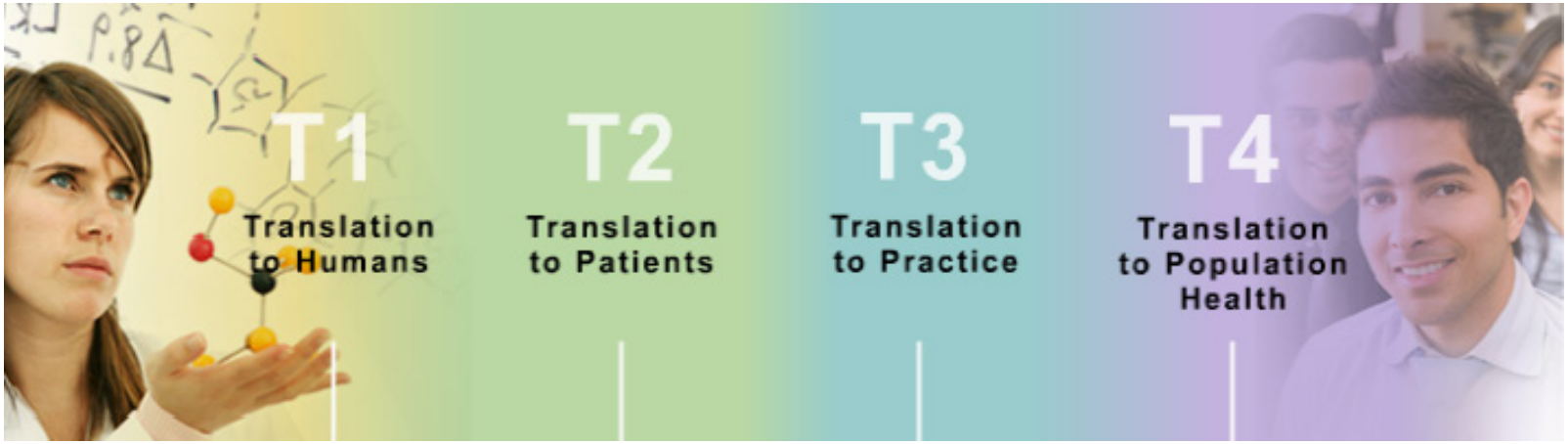
Catalyzing Collaborations Within NIH



Catalyzing Collaborations Outside NIH



Catalyzing Collaboration within NCATS Across the Translational Spectrum



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

- Predictive toxicology
- Predictive efficacy
- Derisking undruggable targets/untreatable diseases
- Data interoperability
- Biomarker qualification process, including for "personalized medicine"
- 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)

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- Clinical outcome criteria (e.g., PROs)
- Adaptive clinical trial designs
- Shortening time of intervention adoption in appropriate patients
- Methods to better measure impact on health (or lack of)

NCATS Programs and Initiatives

Clinical and Translational Science Activities

- Clinical and Translational Science Awards

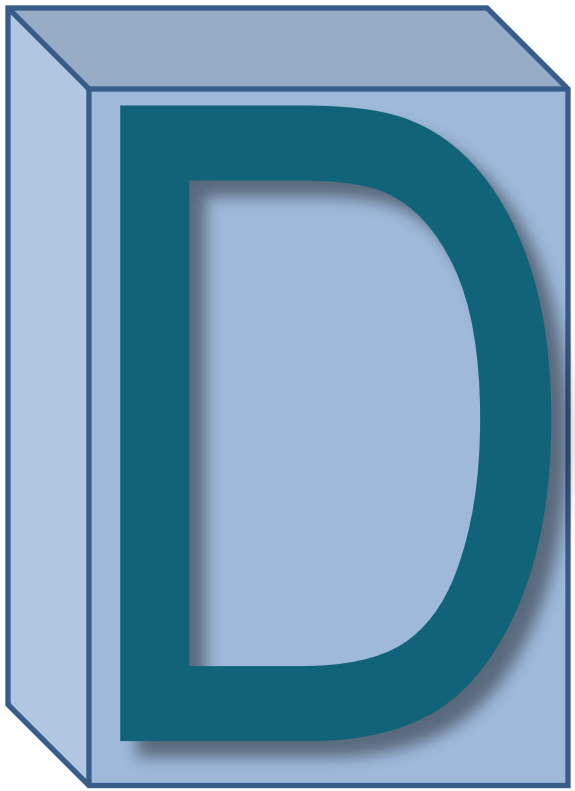
Rare Diseases Research and Therapeutics

- Therapeutics for Rare and Neglected Diseases
- Bridging Interventional Development Gaps
- Office of Rare Diseases Research

Re-engineering Translational Sciences

- NIH Chemical Genomics Center
- Toxicology in the 21st Century

NCATS "3D's"



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Division of Clinical Innovation

Vision

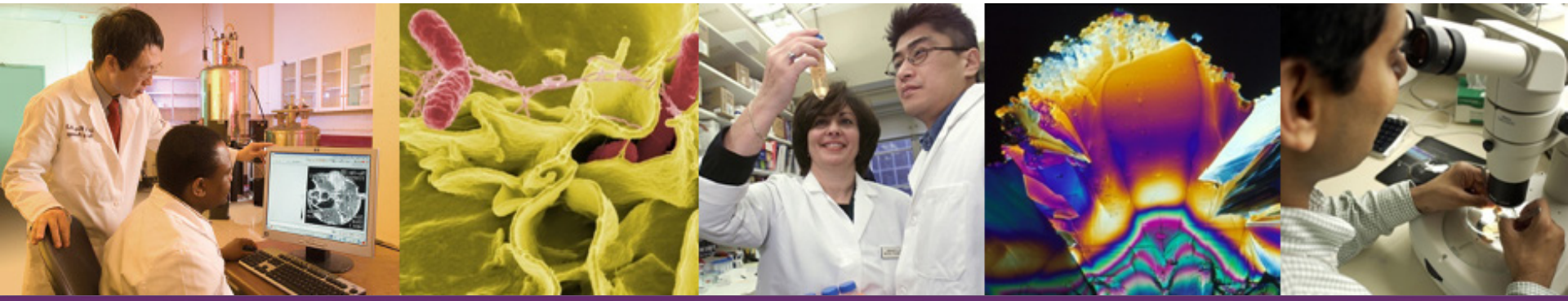
- Development, demonstration, and dissemination of methods and technologies to logarithmically improve the efficiency of clinical translational research
- Emphasis on clinical investigation/phenotyping in translation
- Innovative training programs for the research team members required for end-to-end translation
- Development of a robust academic discipline of Translational Research, with distinct characteristics
- New models for engagement, collaboration, and partnership of **communities** across clinical translation spectrum

Clinical and Translational Science Awards

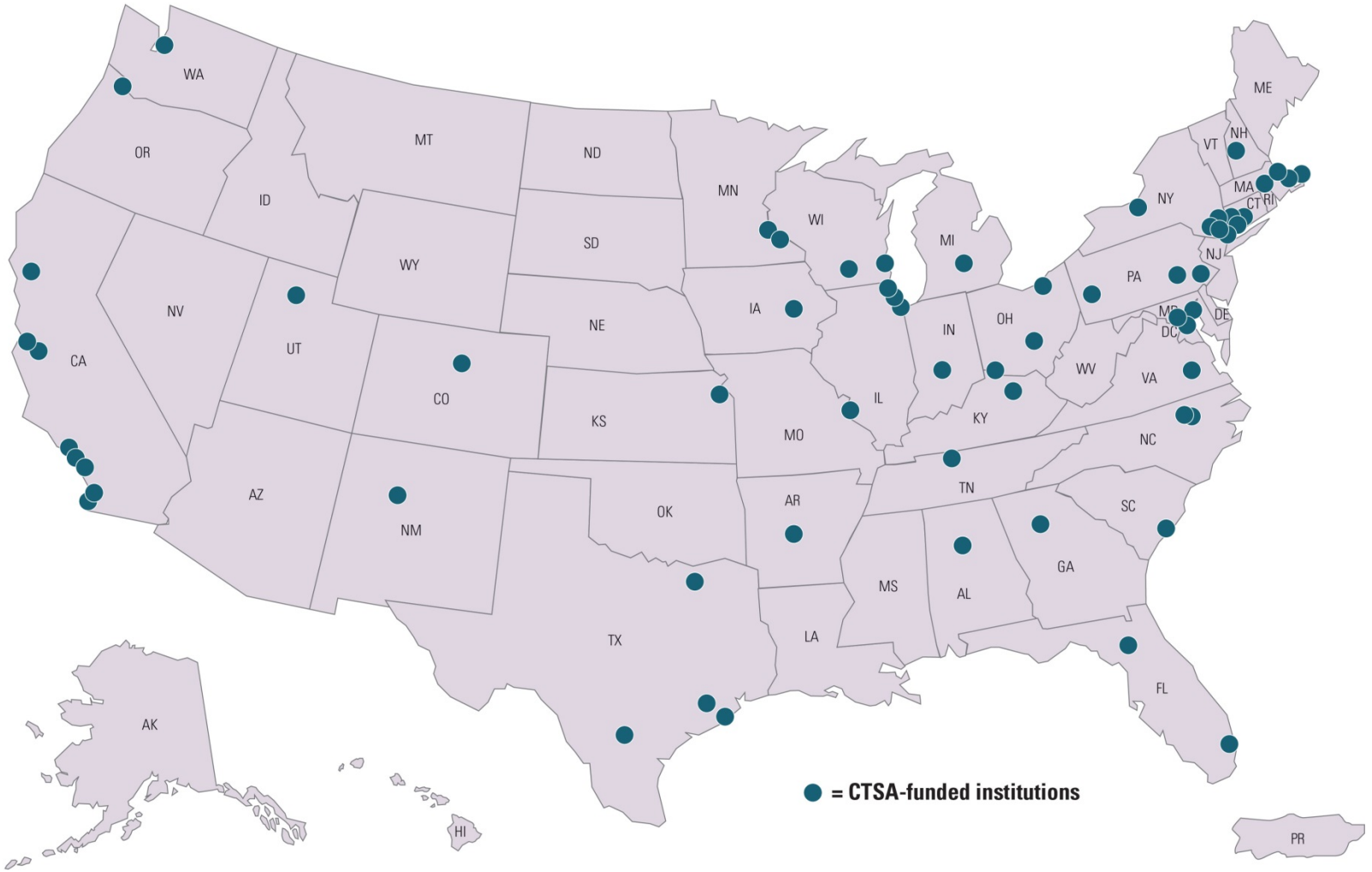
Led by NCATS Division of Clinical Innovation

CTSAs:

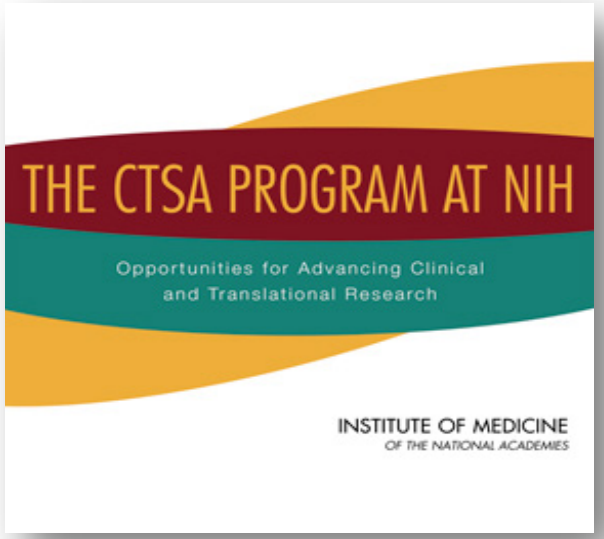
- Support a national consortium of medical research institutions
- Work together to improve the way clinical and translational research is conducted nationwide
- Accelerate the research translation process
- Provide innovative training for clinical and translation researchers



Clinical and Translational Science Awards
(CTSA) Program Sites



IOM Report on the CTSA Program
Recommendations



- IOM CTSA Report released June 2013
- Report includes 7 recommendations

1. Strengthen leadership of the CTSA program by NCATS
2. Reconfigure and streamline CTSA consortium
3. Build on the strengths of the individual CTSAs across the spectrum of research
4. Formalize and standardize clear, consistent, and novel metrics
5. Advance innovative education and training models with a focus on team science, leadership, and entrepreneurship
6. Ensure community engagement in all phases of research
7. Strengthen translational research relevant to child health

NCATS Director Statement: Institute of Medicine Report on the CTSA Program at NIH

June 25, 2013

In 2006, recognizing the need for a "new vision" for translational and clinical science, the National Institutes of Health (NIH) established the Clinical and Translational Science Awards (CTSA) program. The institutions supported by the CTSA program have been transformative to the science and culture of those academic centers across the country, providing expertise, capacities, training and collaborations to advance clinical translational science as a discipline across the translational spectrum.

NCATS Advisory Council WG on the IOM CTSA Report

- Established December 2013
- Report expected to be presented to Council in May

Co-Chairs

- **Ronald J. Bartek**
  FARA/Friedreich's Ataxia Research Alliance
- **Mary L. (Nora) Disis, M.D.**
  University of Washington School of Medicine
- **Scott J. Weir, Pharm.D., Ph.D.**
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- **Fernando Pineda-Reyes**
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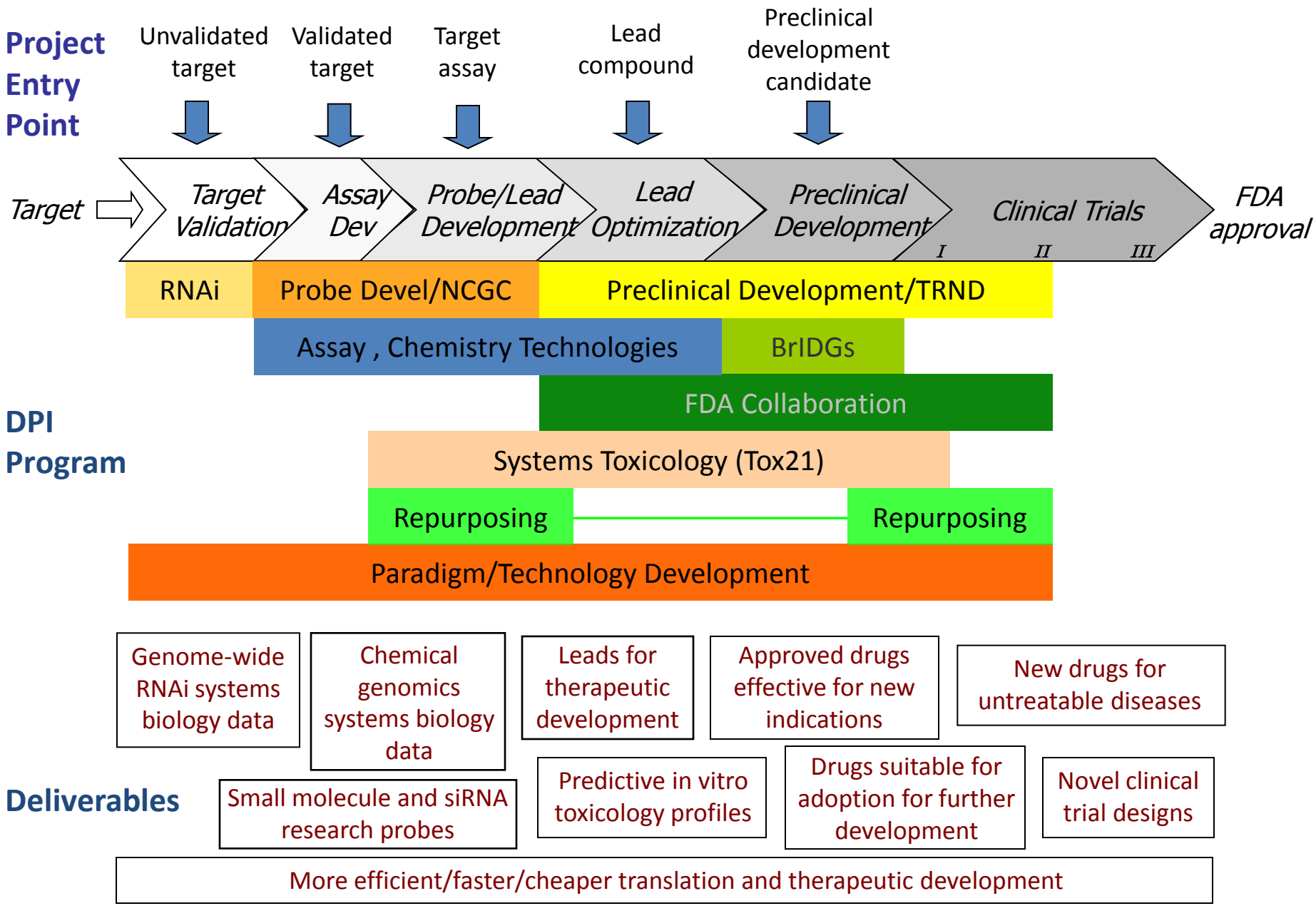
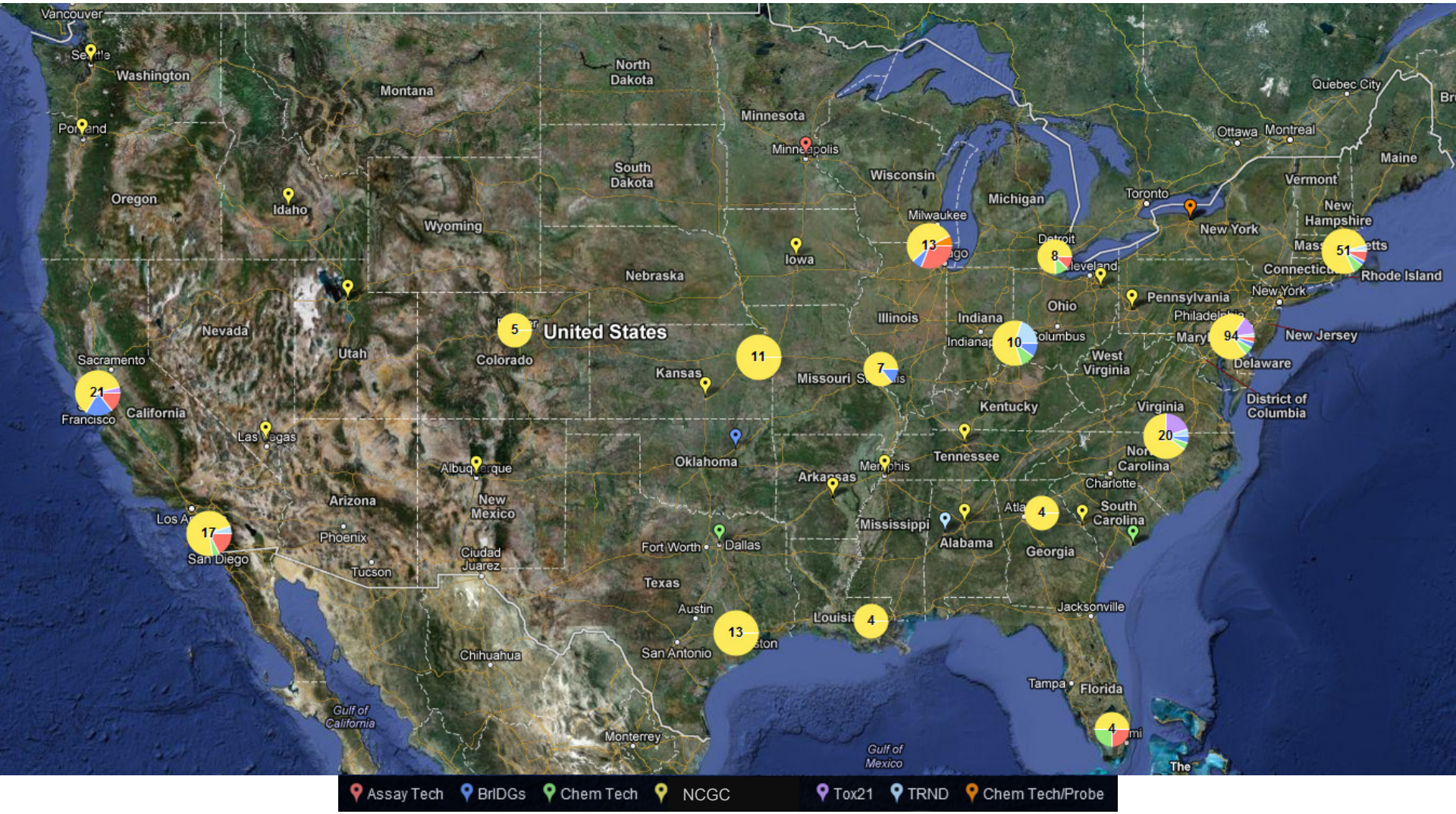
Stay tuned…

NCATS DPI: A Collaborative Pipeline



All DPI Projects are Collaborations



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

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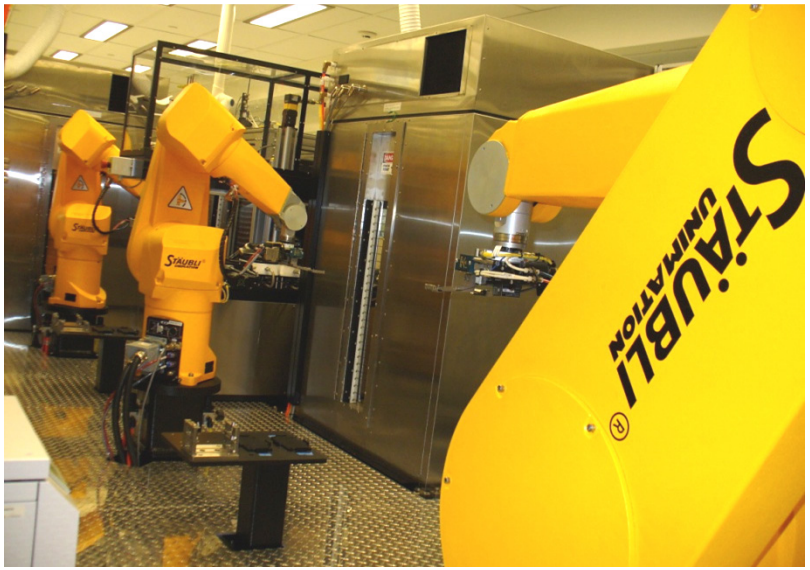
NCATS DPI Staff

NIH Chemical Genomics Center

- Obligatory collaboration model
- Currently > 200 collaborations with investigators worldwide
- Assay development, HTS, chemical informatics, medicinal chemistry: “target to lead”
- Focus is unprecedented targets, rare/neglected diseases
- Mission
  - Chemical and siRNA probes/leads
  - New technologies/paradigms to improve efficiency and success rates of target-to-lead stage of drug development
  - Chemical genomics: general principles of siRNA action, small molecule – target interactions



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DPI

RNAi Screening

Embargoed for Release: Sunday, November 24, 2013, 1 p.m. EST

Gene-silencing study finds new targets for Parkinson's disease

NIH study sheds light on treatment of related disorders

Scientists at the National Institutes of Health have used RNA interference (RNAi) technology to reveal dozens of genes which may represent new therapeutic targets for treating Parkinson's disease. The findings also may be relevant to several diseases caused by damage to mitochondria, the biological power plants found in cells throughout the body.

"We discovered a network of genes that may regulate the disposal of dysfunctional mitochondria, opening the door to new drug targets for Parkinson's disease and other disorders," said Richard Youle, Ph.D., an investigator at the National Institute of Neurological Disorders and Stroke (NINDS) and a leader of the study. The findings were published online in Nature. Dr. Youle collaborated with researchers from the National Center for Advancing Translational Sciences (NCATS).

Institute/Center

National Institute of Neurological Disorders and Stroke (NINDS)

National Center for Advancing Translational Sciences (NCATS)

Contact

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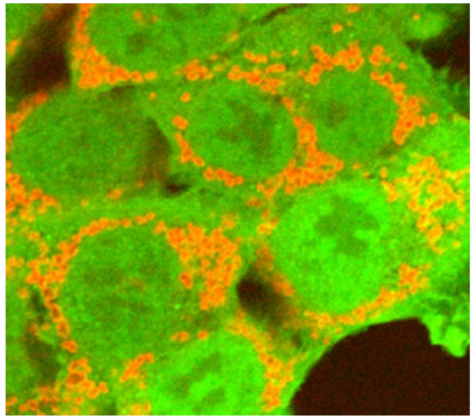

Media Coverage

genomeweb

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GEN Genetic Engineering & Biotechnology News

DRUG DISCOVERY & DEVELOPMENT

genomeweb Gene Silencing News
Probing Advances in RNAi and miRNA

NIH National Center for Advancing Translational Sciences

DPI

RNAi Screening

Embargoed for Release: Wednesday, December 11, 2013, 9 a.m. EST

Gene-silencing data now publicly available to help scientists better understand disease

NIH data-sharing collaboration with Life Technologies will advance genetic and translational research, therapeutic target discovery

For the first time, large-scale information on the biochemical makeup of small interfering RNA (siRNA) molecules is available publicly. These molecules are used in research to help scientists better understand how genes function in disease. Making these data accessible to researchers worldwide increases the potential of finding new treatments for patients.

Institute/Center

National Center for Advancing Translational Sciences (NCATS)

Contact

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301-435-0888

Mauricio Minotta
Life Technologies Corporation
760-929-2456

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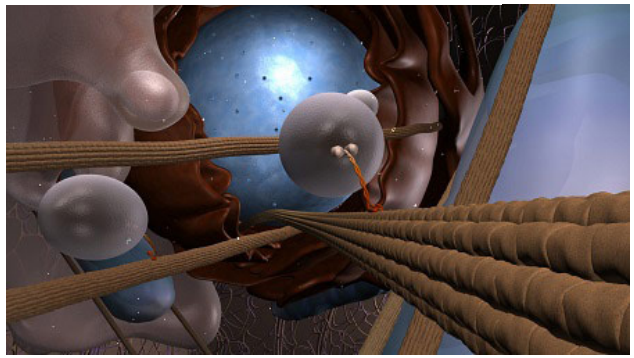
DRUG DISCOVERY & DEVELOPMENT



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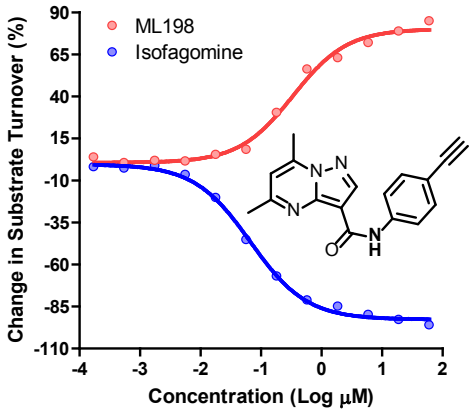
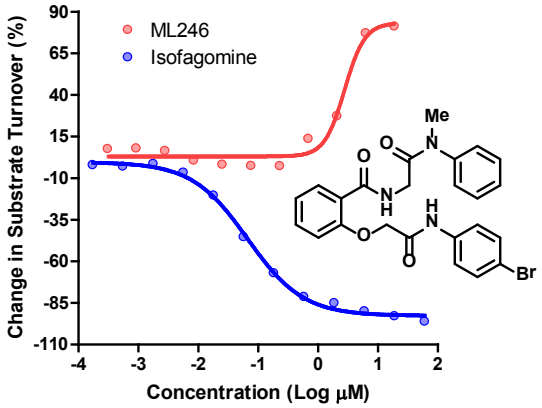
Non-inhibitory GCase Small Molecule Chaperones for Gaucher Disease

- **Collaborator:**
  - Ellen Sidransky (NHGRI)
- **Target and rationale:**
  - Gaucher disease is a lysosomal storage disorder due to dysfunction of Glucocerebrosidase. (GCase). Many GCase mutants are enzymatically active but improperly fold in the ER, where they accumulate avoiding their transport to the lysosome.

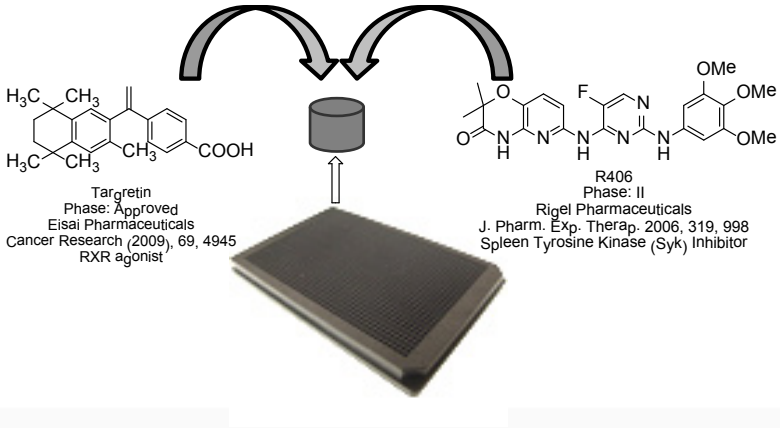


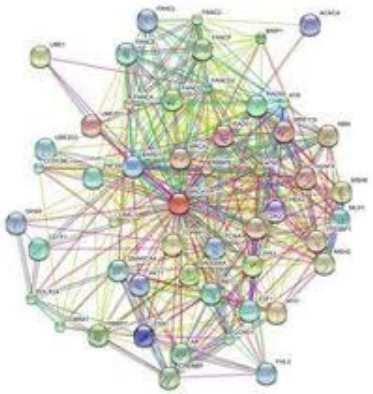


- **Results**
  - Assay development → HTS → cheminformatics → medicinal chemistry SAR
  - Optimized two series of non-inhibitory Gcase small molecule chaperones that increase WT and mutant GCase translocation to the lysosome, and clear glucosylceramide accumulated in lysosomes of Gaucher macrophages and neurons.
  - Both series have been out licensed to biotech companies (LTI and Biogen) for further development.
- **Current Studies**
  - Investigating how activity of GCase may affect alpha synuclein levels in Parkinson and Gaucher neuronal models (from iPSCs)
  - Effects of GCase small molecule chaperones on alpha synuclein levels and storage.

Screening for Novel Drug Combinations

- Drug combinations offer advantages for both efficacy and potential reduction of target related toxicities
- Combination studies also offer insight into systems level interactions





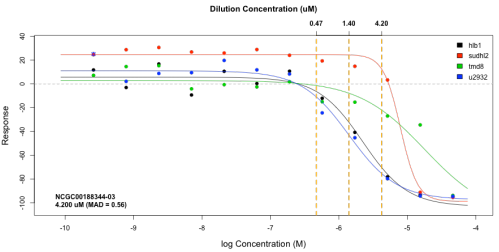
Creating a technology platform for the discovery of novel drug combinations

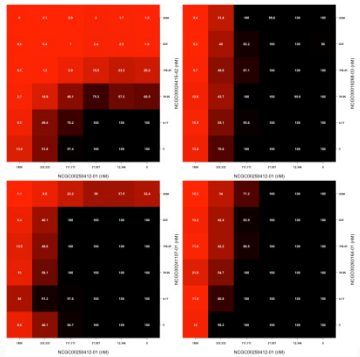
Needed: 1) a high-value library of small molecules
2) an effective plating process
3) an automated data analysis method

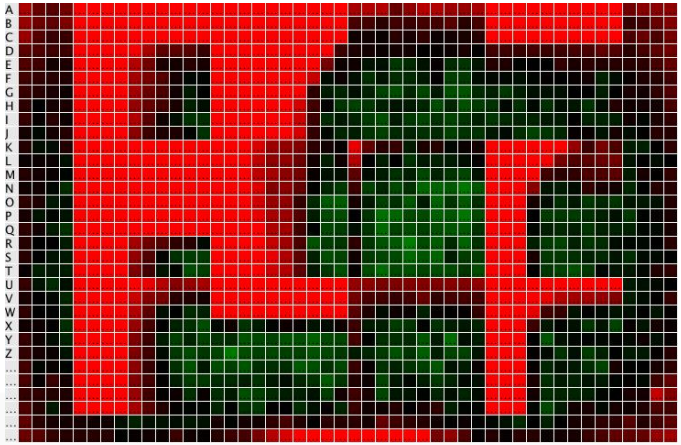
Step 1: Generate single agent results.

Step 2: Generate 6X6 matrix data to uncover potential synergies.

Step 3: Expand good combinations to 10X10 blocks to confirm synergistic combinations and perform self-crosses to provide context for activities.







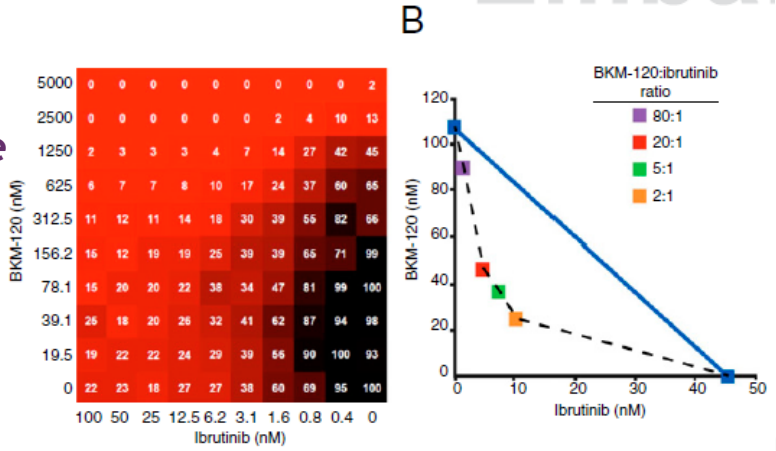
Matrix Drug Combination Screening Program

High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill ABC diffuse large B-cell lymphoma cells

Lesley A. Mathews Griner[a,1], Rajarshi Guha[a,1], Paul Shinn[a,1], Ryan M. Young[b,1], Jonathan Keller[a], Dongbo Liu[a], Ian S. Goldlust[a], Adam Yasgar[a], Crystal McKnight[a], Matthew B. Boxer[a], Damien Y. Duveau[a], Jian-Kang Jiang[a], Sam Michael[a], Tim Mierzwa[a], Wenwei Huang[a], Martin J. Walsh[a], Bryan T. Mott[a], Paresma Patel[a,c], William Leister[a], David J. Maloney[a], Christopher A. LeClair[a], Ganesha Rai[a], Ajit Jadhav[a], Brian D. Peyser[d], Christopher P. Austin[a], Scott E. Martin[a], Anton Simeonov[a], Marc Ferrer[a], Louis M. Staudt[b,2], and Craig J. Thomas[a,2]

[a]Division of Preclinical Innovation, National Institutes of Health Chemical Genomics Center, National Center for Advancing Translational Sciences, [b]Metabolism Branch, Center for Cancer Research and [d]Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892; and [c]Basic Science Program, SAIC-Frederick, Inc., Chemical Biology Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD

- NCATS-NCI collaboration
- Unbiased small-molecule combination (matrix) screening identified potential drugs to combine with ibrutinib for activated B-cell like subtype (ABC) of diffuse large B-Cell lymphoma (DLBCL)
  - PI3K pathway inhibitors
  - BCL family antagonists, navitoclax and ABT-199
  - Cytotoxic Chemotherapeutic Agents, including several components of R-CHOP and EPOCH-R regimens currently used to treat DLBCL



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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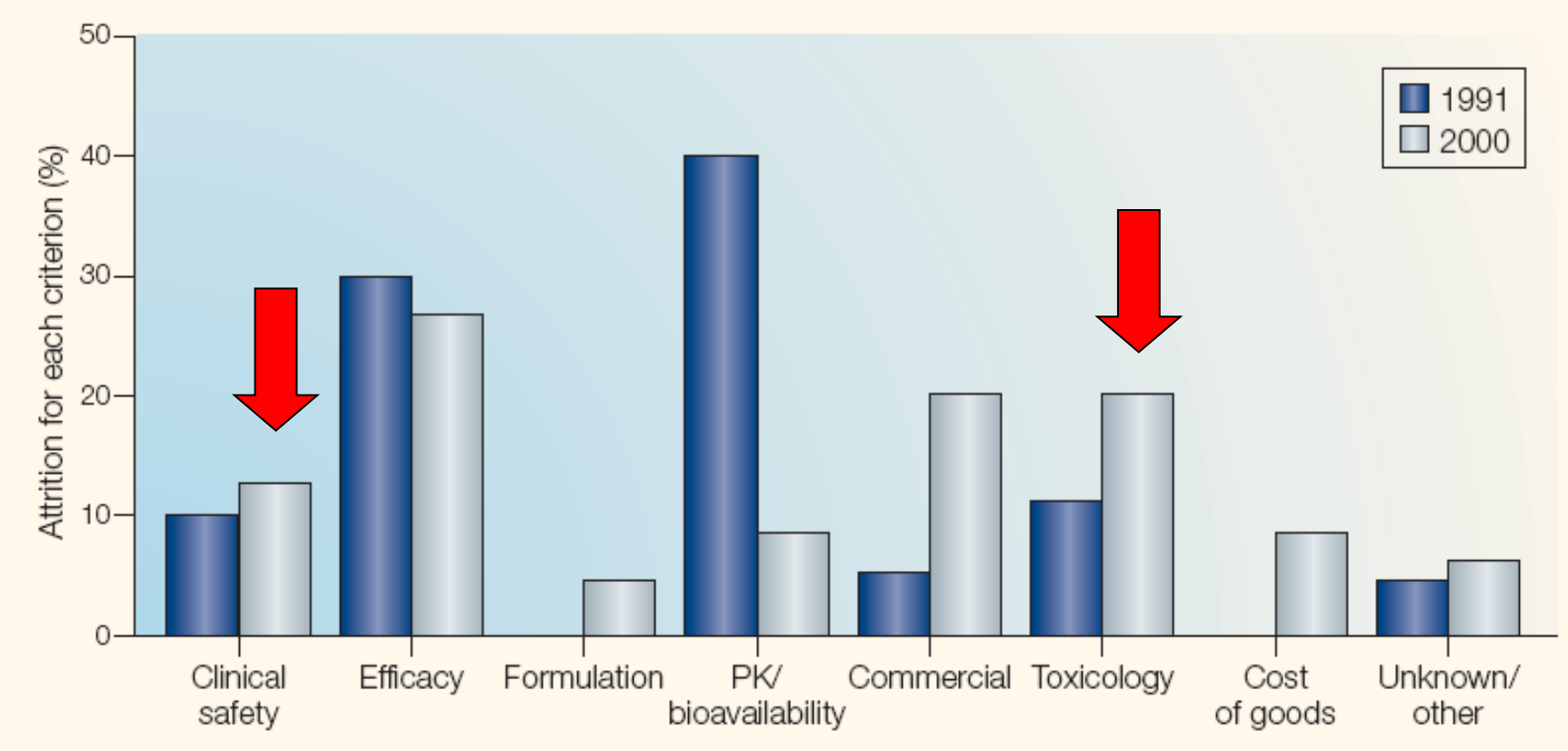
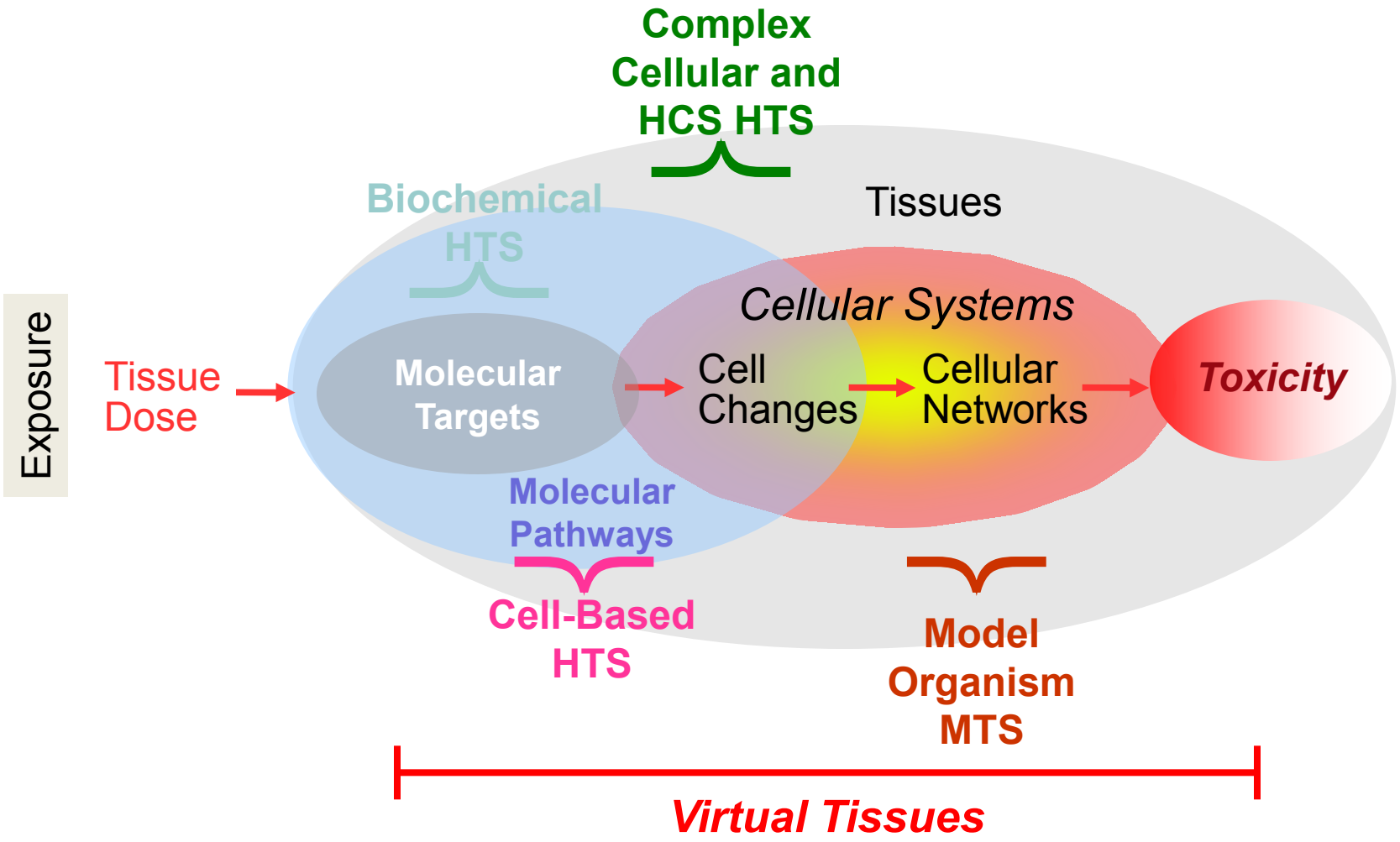
Toxicity is a common reason for drug development failure



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

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

A Grand Challenge: Predicting Toxicity

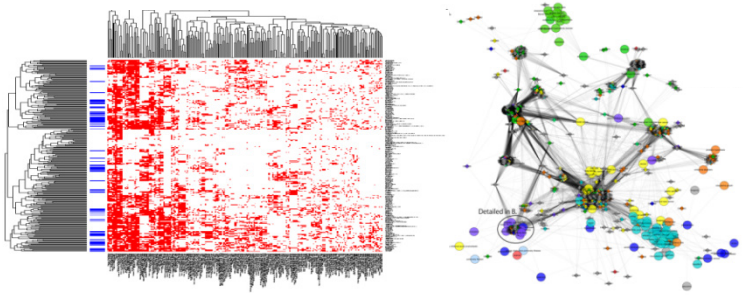


Toxicology Technology Development

The Tox21 Program

Tox21 Goals

- Identify patterns of compound-induced biological response in order to:
  - characterize toxicity/disease pathways
  - facilitate cross-species extrapolation
  - model low-dose extrapolation
- Prioritize compounds for more extensive toxicological evaluation
- Develop predictive models for biological response in humans



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DPI

Tox21: *PubChem Data Deposition*

PubChem deposition status:

-Making data publicly available

- 66 Assay IDs
- 33 million data points of Phase II data have been deposited into PubChem!

PubChem

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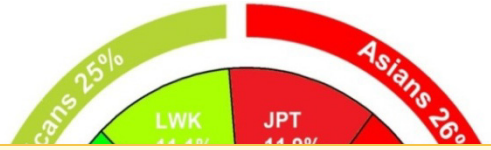
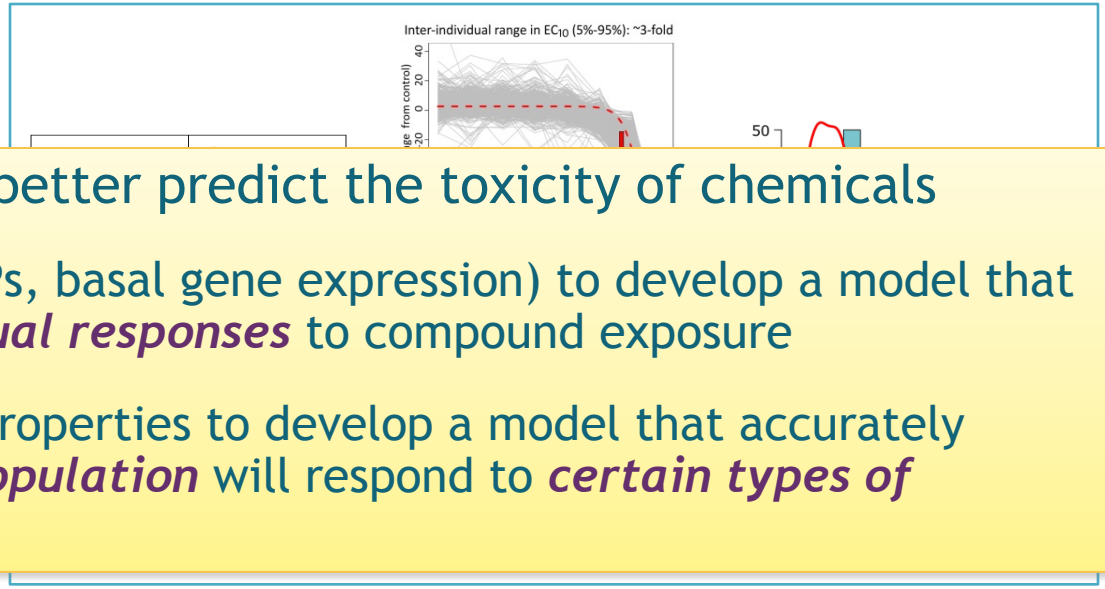
NIEHS-NCATS-UNC TOXICOgenETICS PROJECT:

qHTS for Cytotoxicity in a Population-Based *in vitro* Model

POPULATION-WIDE STUDY DESIGN:





Goal: use crowdsourcing to better predict the toxicity of chemicals

1. Use the biological data (SNPs, basal gene expression) to develop a model that accurately predicts ***individual responses*** to compound exposure
2. Use the intrinsic chemical properties to develop a model that accurately predicts how a particular ***population*** will respond to ***certain types of chemicals***

- To understand how genetic variation affects individual response to common environmental and pharmaceutical chemicals
- The largest ever population-based ex-vivo cytotoxicity study
  - 1086 cell lines
  - 179 common, pharmaceutical, or important environmental chemicals (9 duplicates)
  - 8 concentrations (0.33 nM - 92 mM)
  - 1-3 plate replicates
  - ~2,400,000 data points + 2-5x10^6 SNPs

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Sage BIONETWORKS

DREAM

DPI
Tox21: *DREAM Challenge*

- Teams from the **Quantitative Biomedical Research Center (QBRC)** at the **University of Texas Southwestern (UTSW) Medical Center** were named best performer in **both** of the sub-challenges
  - Team Yang Lab, represented in Toronto by Ph.D. student Tao Wang, took the honors for sub-challenge #1
  - Team QBRC, also represented in Toronto by Tao Wang, on behalf of assistant professor Hao Tang, Ph.D., came in first in sub-challenge #2

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

NIH National Center for Advancing Translational Sciences

NIEHS National Institute of Environmental Health Sciences

NTP National Toxicology Program U.S. Department of Health and Human Services

Sage BIONETWORKS

Toxicology Technology Development
Tissue Chips for Drug Screening

- Goal
  - Develop chip to screen for safe, effective drugs
    - Liver, heart, lung, other cell types
    - Designed for multiple different readouts
- NIH, DARPA contribute ~$70M each over 5 years
  - NCATS and DARPA independently manage, fund separate 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

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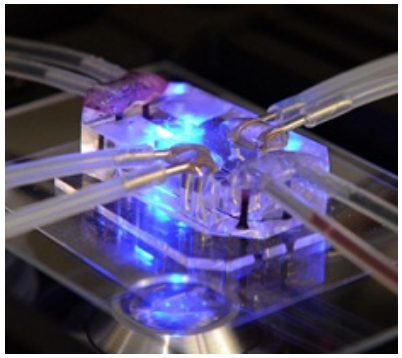
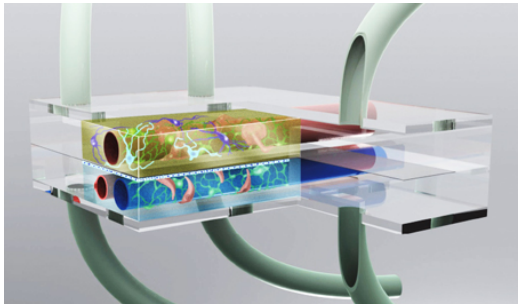
Tissue Chip Program
Project Awards

- Nineteen research project awards
  - Twelve to develop 3-D cellular microsystems representing human organ systems that will…
    - Be functionally relevant
    - Accurately reflect complexity of tissue of origin
  - Seven to explore potential of stem, progenitor cells to differentiate into multiple cell types
    - Representing cellular architecture within organ systems
    - Cells could populate tissue chips



Lung chip
Wyss Institute



Blood-brain barrier chip
J. Wikswo, Vanderbilt

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

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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

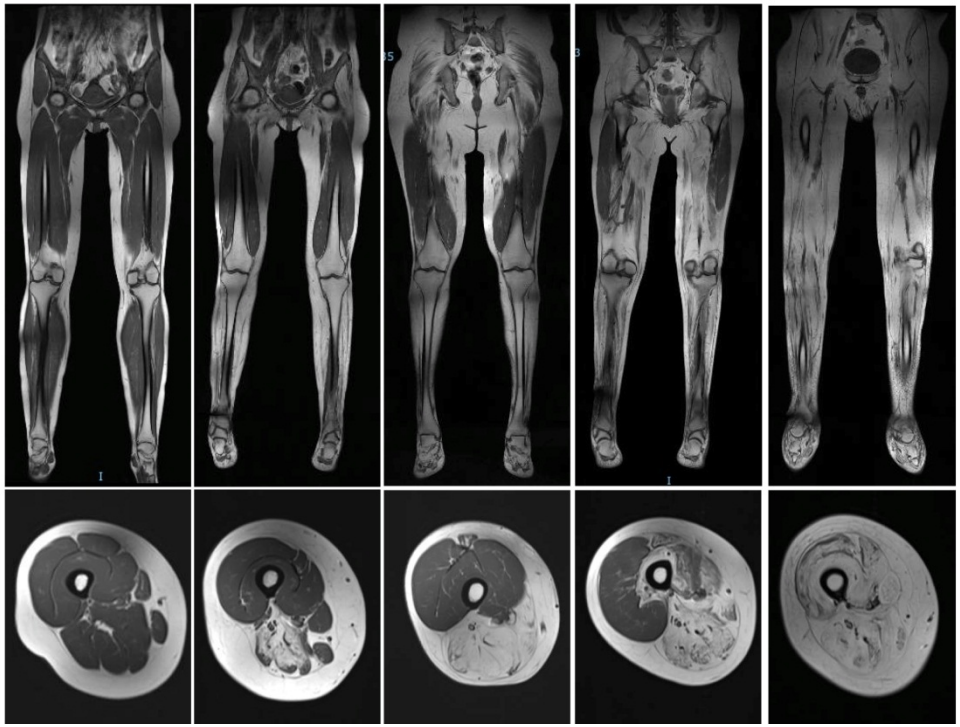
TRND Portfolio

Therapeutic Area / Disease	Collaborator(s)	Agent	Status
Sickle Cell Disease	Aes-Rx, NHLBI	NME – Small Molecule	Clinical
Chronic Lymphocytic Leukemia	Leukemia & Lymphoma Society, University of Kansas	Repurposed Drug – Small Molecule	Clinical
Hereditary Inclusion Body Myopathy	New Zealand Pharmaceuticals, **NHGRI**	NME – Small Molecule	Clinical
Niemann-Pick Type C1	Johnson & Johnson, Albert Einstein College of Medicine, Univ. of Pennsylvania, Washington Univ., NICHD , NINDS , **NHGRI**	Repurposed Drug - Small Molecule	Clinical
Duchenne Muscular Dystrophy	ReveraGen BioPharma	NME – Small Molecule	Preclinical
Cryptococcal Meningitis	Viamet Pharmaceuticals, Inc.	NME - Small Molecule	Preclinical
Core Binding Factor Leukemia	**NHGRI**	Repurposed Drug - Small Molecule	Preclinical
Neonatal Herpes Simplex	University of Alabama, NIAID	NME – Small Molecule	Preclinical
Autoimmune Pulmonary Alveolar Proteinosis	Cincinnati Children's Hospital	Repurposed Drug - Biologic	Preclinical
Fibrodysplasia Ossificans Progressiva	Massachusetts General Hospital	NME - Small Molecule	Preclinical
Schistosomiasis	CoNCERT Pharmaceuticals	NME – Small Molecule	Preclinical
Creatine Transporter Defect	Lumos Pharma	NME - Small Molecule	Preclinical

TRND

Hereditary Inclusion Body Myopathy (HIBM)

- Collaborator: New Zealand Pharmaceuticals & NHGRI
- The problem: HIBM is a rare genetic skeletal muscle wasting disorder
  - » Estimated 1:1,000,000 in the US
  - » No current therapeutic intervention
  - » Caused by a single genetic mutation of the *GNE* gene. GNE is a key enzyme in the sialic acid metabolic pathway.
- The solution: Development of ManNAc – a naturally occurring key intermediate in sialic acid pathway
  - » Patients lack sialic acid due to the dysfunction of the GNE enzyme. Sialic acid can be replenished by providing its precursor ManNAc
  - » Application of ManNAc to treat more common renal diseases



- Current Status:
  - » Tox studies - completed
  - » Phase 1a trial – completed at NIH CC
  - » Natural history study – ongoing at NIH CC
  - » R&D for kidney glomerular disease – ongoing at NIH (NHGRI & NIDDK)

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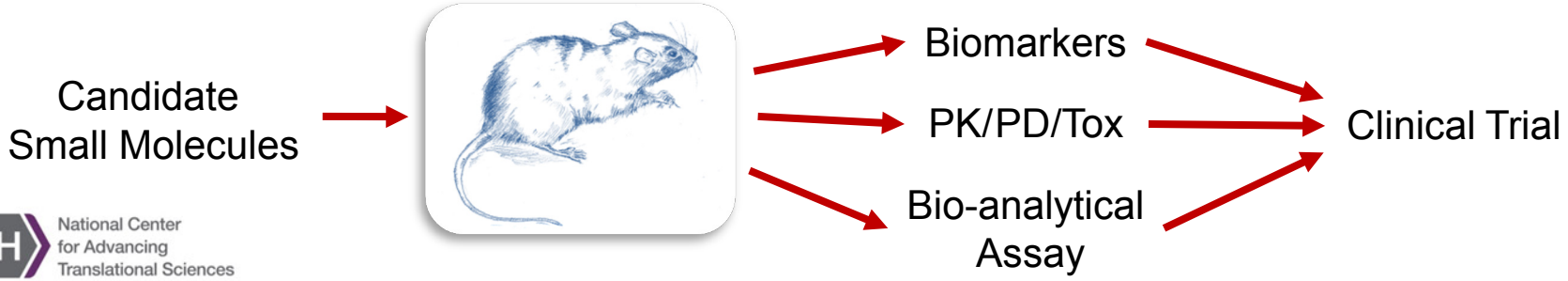
TRND
Niemann Pick Type C Collaboration

- 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



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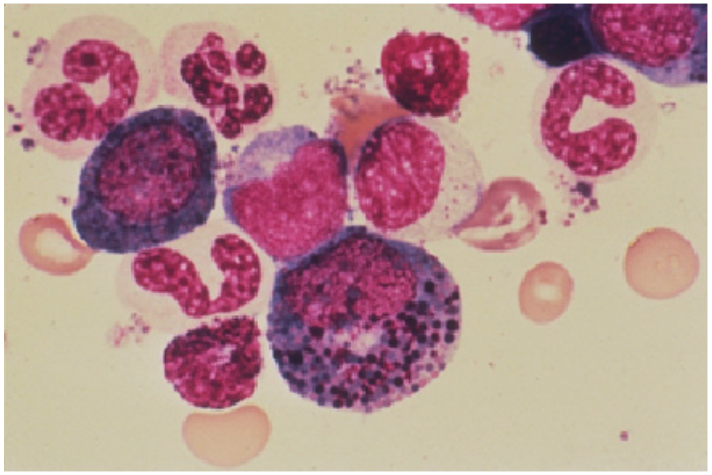
TRND
CBF Leukemia

- **Collaborator**
  - Paul Liu (NHGRI)
- **Background**
  - Core binding factor (CBF) leukemias, those with translocations or inversions involving RUNX1 or CBFb account for ~24% of adult AML and 25% of pediatric ALL
  - 5 year survival rate of CBF leukemias is 50%
  - Hypothesis: interaction between RUNX1 and CBFb is critical for CBF leukemia
- **Strategy**
  - Ro5-3335 identified as inhibitor of CBF leukemia (NHGRI/NCATS collaboration)
  - Efficacy of Ro5-3335 confirmed *in vivo* by TRND – robust in vivo procedures developed, suitable for translation
  - Further study of Ro5-3335 and related molecule Ro24-7429 planned to support selection of a compound for development



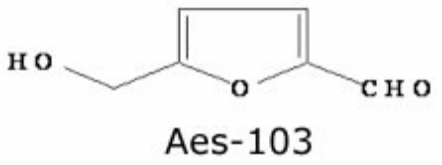
Core binding factor (CBF) is a group of heterodimeric transcription factors consisting of a non-DNA-binding CBFβ chain and a DNA-binding CBFα chain (RUNX1, RUNX2, RUNX3)

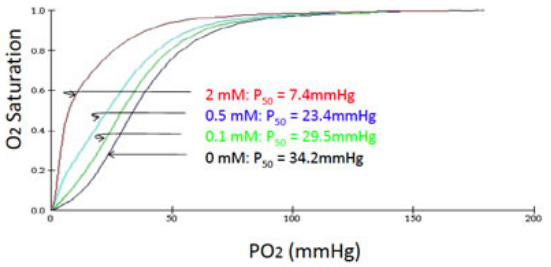
Identification of benzodiazepine Ro5-3335 as an inhibitor of CBF leukemia through quantitative high throughput screen against RUNX1–CBFβ interaction

Lea Cunningham[a], Steven Finckbeiner[a], R. Katherine Hyde[a], Noel Southall[b], Juan Marugan[b], Venkat R. K. Yedavalli[c], Seameen Jean Dehdashti[b], William C. Reinhold[d], Lemlem Alemu[a], Ling Zhao[a], Jing-Ruey Joanna Yeh[e], Raman Sood[a,f], Yves Pommier[d], Christopher P. Austin[b], Kuan-Teh Jeang[c], Wei Zheng[b,1], and Paul Liu[a,1]

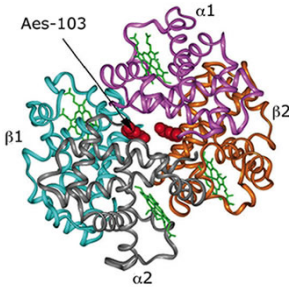
14592–14597 | PNAS | September 4, 2012 | vol. 109 | no. 36

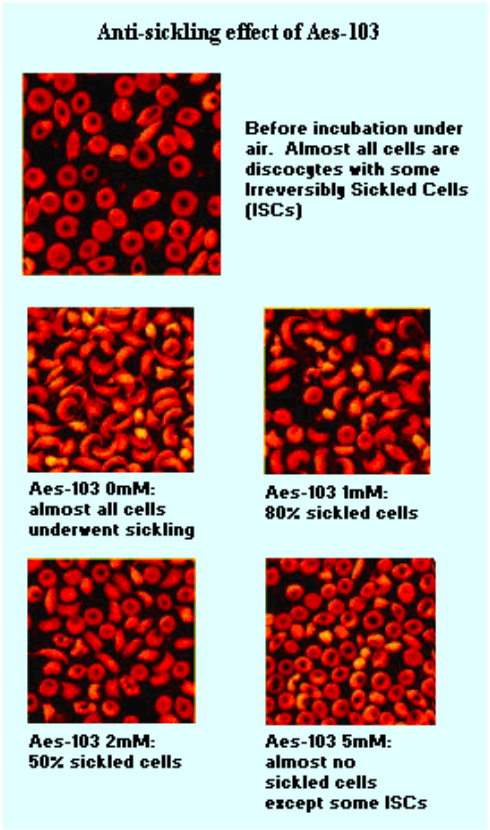
TRND
Sickle Cell Disease





- Collaborator: AesRx, LLC
- Compound: Aes-103 (5-hydroxymethyl-2-furfural)
  - Binds to sickle hemoglobin, increases O_2 affinity
- Roadblocks in drug development
  - 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, CMC
  - Project initiation to patients in <12 mos
  - IND filed Oct. 14th 2011
  - Ph I (normal volunteers) began 4Q 2011
  - Ph IIa (clinical proof-of-concept) began 2Q 2012
- Phase I-II clinical trials at NIH Clinical Center (Greg Kato, NHLBI) and CRU





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Bridging Interventional Development Gaps (BrIDGs) Program

- Model: In-kind, government contract-based services provided to overcome obstacles in later-stage preclinical development

- Projects:
  - May address any disease or disorder, regardless of prevalence or incidence
  - May require only one or two key development steps

- Eligible Applicants:
  - Academic, Nonprofit, NIH Intramural, or *SBIR Eligible* Small Business
  - Ex-U.S. applicants accepted, but businesses must satisfy SBIR criteria

- Intellectual Property:
  - Products and information return to the originating investigator in support of additional studies or IND filing
  - Investigators retain intellectual property

BrIDGs Scope
Contract Access

- Project-specific activities facilitated
  - Production / bulk supply
  - GMP manufacturing
  - Formulation
  - PK testing
  - Animal toxicology
  - Manufacture of clinical trial supplies
  - Product development planning and advice in IND preparation

TRND

Fibrodysplasia Ossificans Progressiva (FOP)

- Collaborator: Ken Bloch, Massachusetts General Hospital
- The problem: FOP is a rare inherited bone disease without targeted therapies
  - » Autosomal dominant; ~0.5 affected individuals per million
  - » *Acvr1* gene mutations encoding a constitutively-active bone morphogenetic protein (BMP) type I receptor ALK2
- The solution: Development of novel small molecules that inhibit BMP type 1 receptor activity
  - » Novel treatment of a rare disease
  - » Application of BMP inhibitors to treat more common disorders including anemia of inflammation, ankylosing spondylitis, and neoplasia
- Current Status:
  - » Toxicology of the lead compound, LDN-193189
  - » Generation of back-up compounds

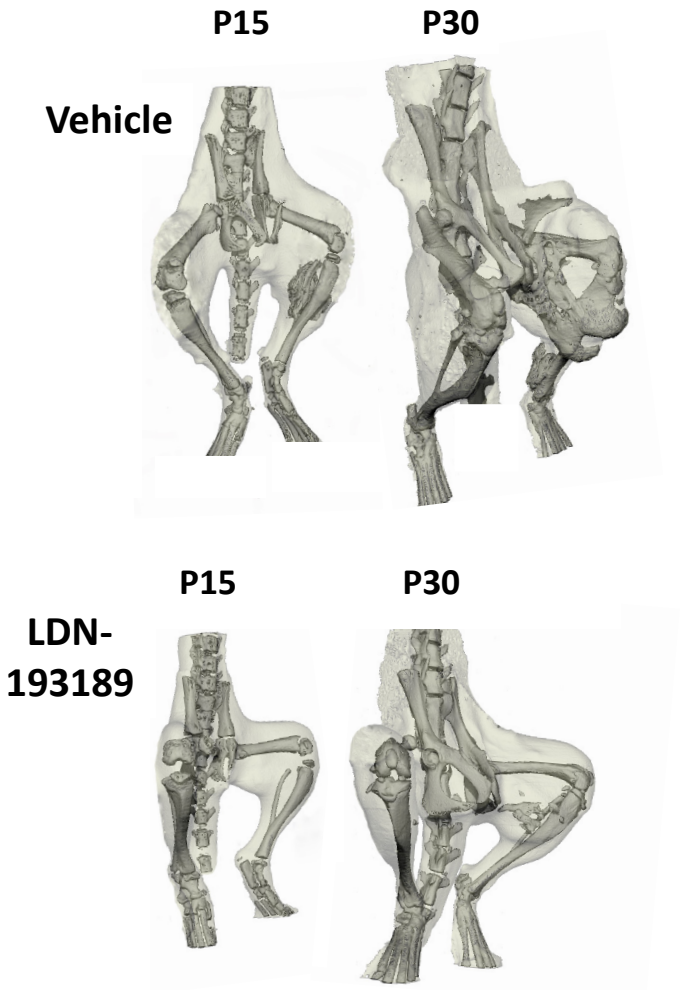

Figure 1. Treatment of mouse FOP model

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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

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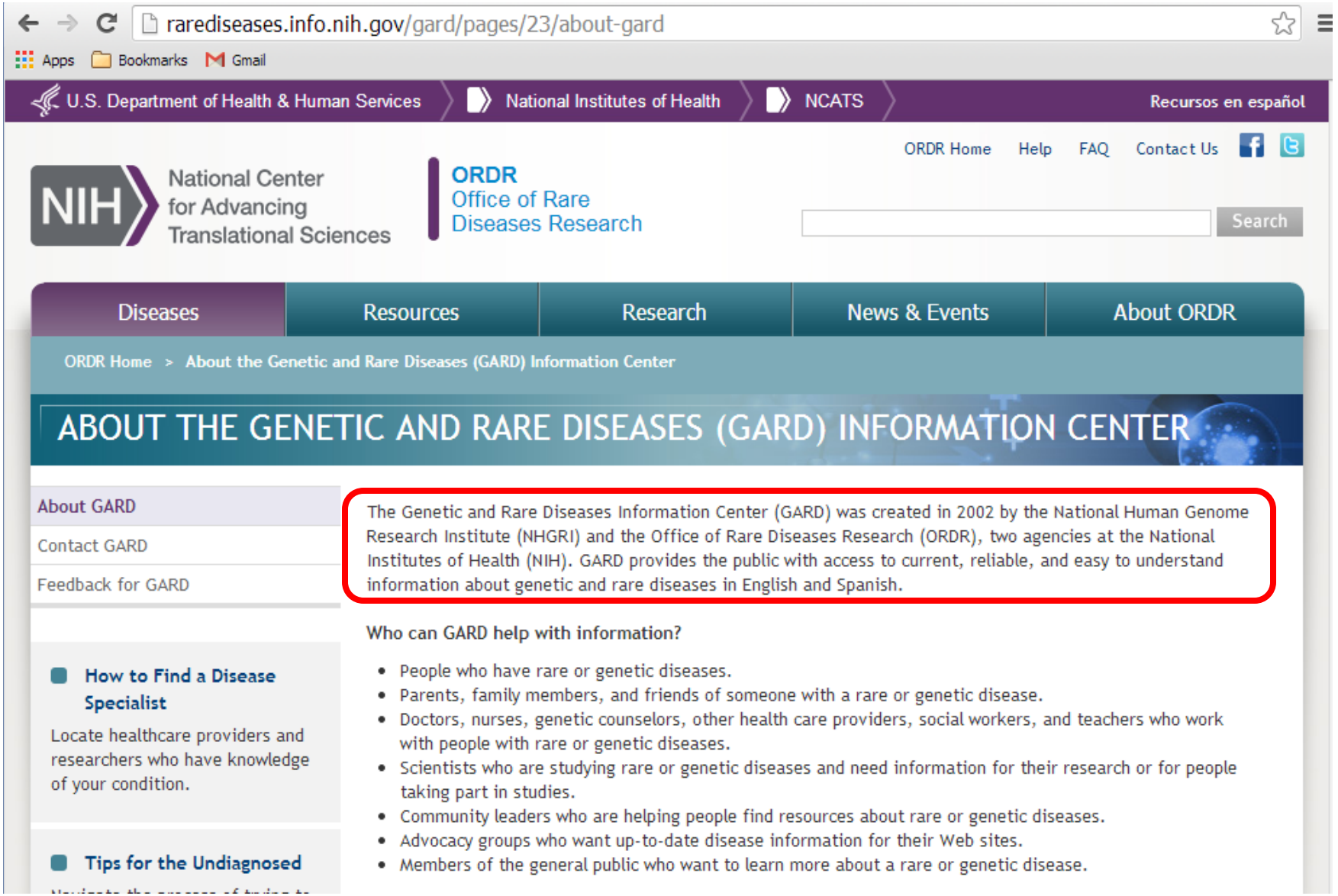
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U.S. Department of Health & Human Services
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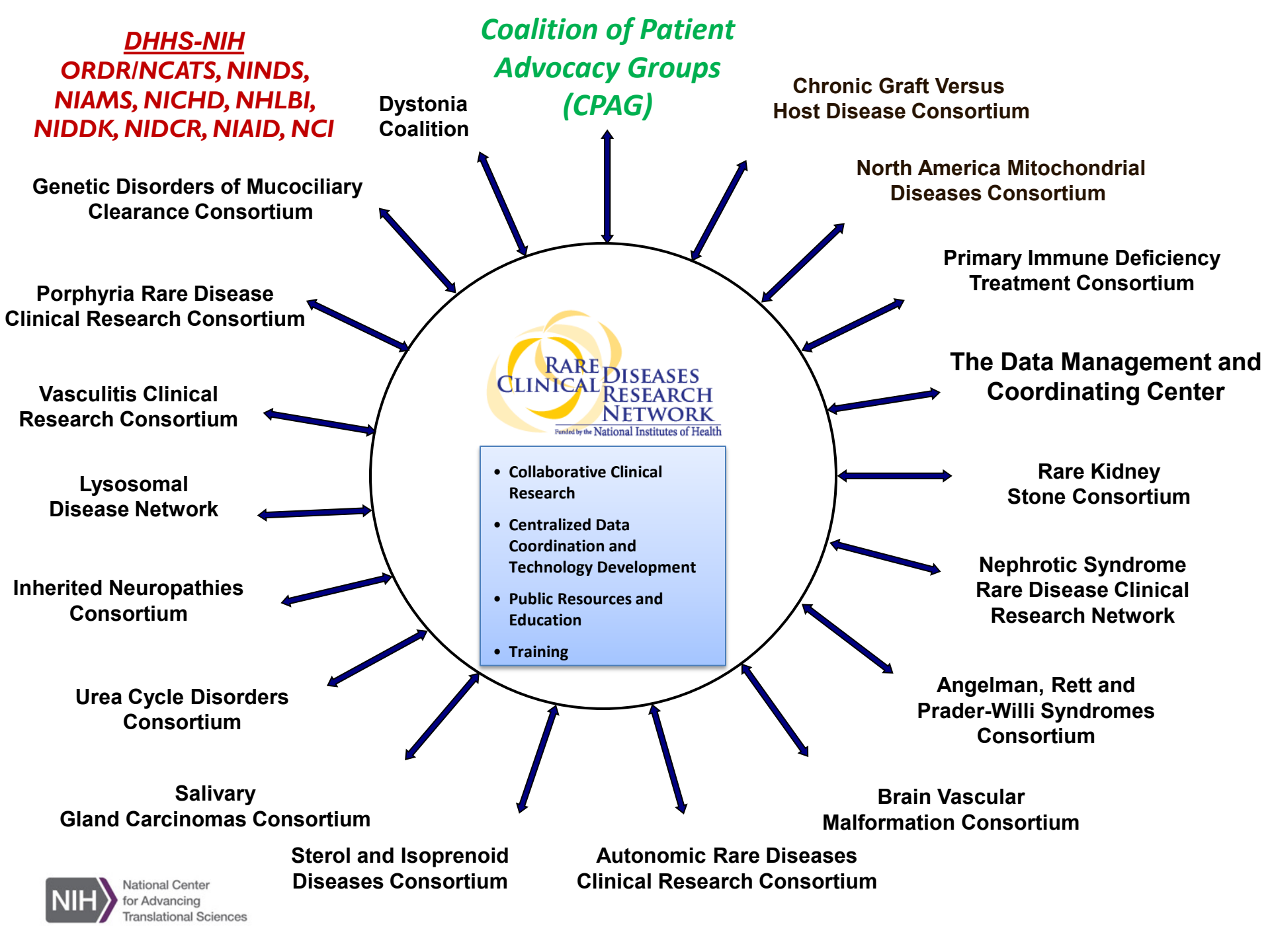
ABOUT THE GENETIC AND RARE DISEASES (GARD) INFORMATION CENTER
About GARD
Contact GARD
Feedback for GARD
How to Find a Disease Specialist
Locate healthcare providers and researchers who have knowledge of your condition.
Tips for the Undiagnosed
The Genetic and Rare Diseases Information Center (GARD) was created in 2002 by the National Human Genome Research Institute (NHGRI) and the Office of Rare Diseases Research (ORDR), two agencies at the National Institutes of Health (NIH). GARD provides the public with access to current, reliable, and easy to understand information about genetic and rare diseases in English and Spanish.
Who can GARD help with information?
People who have rare or genetic diseases.
Parents, family members, and friends of someone with a rare or genetic disease.
Doctors, nurses, genetic counselors, other health care providers, social workers, and teachers who work with people with rare or genetic diseases.
Scientists who are studying rare or genetic diseases and need information for their research or for people taking part in studies.
Community leaders who are helping people find resources about rare or genetic diseases.
Advocacy groups who want up-to-date disease information for their Web sites.
Members of the general public who want to learn more about a rare or genetic disease.


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
Genetic Disorders of Mucociliary Clearance Consortium
North America Mitochondrial Diseases Consortium
Porphyria Rare Disease Clinical Research Consortium
Primary Immune Deficiency Treatment Consortium
Vasculitis Clinical Research Consortium
The Data Management and Coordinating Center
Lysosomal Disease Network
Rare Kidney Stone Consortium
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
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

Happy Retirement, Steve Groft!

Starting February 2014

NIH
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The Orphan Drug Act and National Organization for Rare Disorders Celebrate 30th Anniversary

Steve Groft Honored for his Work in Rare Diseases

On May 14th, at the Mellon Auditorium in Washington DC, more than 500 people celebrated the 30th anniversary of The Orphan Drug Act as well as the founding of the National Organization for Rare Disorders (NORD), a national federation of rare diseases patient advocacy groups.

In a moving ceremony, Stephen C. Groft , Pharm D, the Director of the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences (NCATS), received NORD's Medal of Honor for "Vision and Pioneering Guidance" in rare diseases and research. He was lauded for "providing guidance and encouragement to rare disease patient advocates since the very beginning of this movement. Peter Saltonstall, NORD's President and CEO, commented that Dr. Groft "was honored as one of those individuals who have played an important and continuing role in the evolution of both [the Orphan Drug Act and NORD]."

Originally at the FDA, Dr. Groft worked under Marion Finkel, MD, the first Director of the FDA's Office of

Stephen C. Groft, Pharm D

Additional Information:

- NORD: 30th Anniversary Celebration

ORDR will continue its important work…

Though its founder is riding into the sunset…

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