The National Center for Advancing Translational Sciences

Catalyzing Translational Innovation

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DIRECTOR, NCATS

NHC VOLUNTARY HEALTH LEADERSHIP CONFERENCE
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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
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.

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

Diagram showing the connections between various NIH institutes and centers.
Catalyzing Collaborations Outside NIH

NCATS

Academia

Biotech

Pharma

FDA

Advocacy Groups

Non-Profits
Standard Model

Basic Laboratory Research

Clinical Research

Translational Research

Population Research

Improved Public Health
The Way It Should Work

- Basic Laboratory Research
- Population-based Clinical Research
- Patient-oriented Clinical Research
- Clinical Trials

Improved Public Health
Catalyzing Collaboration within NCATS Across the Translational Spectrum

• What is meant by “community” engagement?
• We really mean “communities”
  - Patients, families, disease advocacy groups, non-profits, health care providers, clinical researchers, PBRNs, geographic groupings, cultural groups, faith-based organizations, local health departments, “the public”
• Consistent involvement is critical for meaningful prioritization, focus, and outcomes
• Particular focus on “innovative methods and technologies” to address critical research questions and advance translation T1-T4
NCATS Advisory Council Subcommittees

• Patient Engagement
  - Margaret Anderson
  - Myrl Weinberg

• Medical Technologies
  - Frank L. Douglas
  - Paul Yock

• Interactions with Biotech/Pharma/VC
  - Freda Lewis-Hall
  - Ankit Mahadevia
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”

Develop
Demonstrate
Disseminate
NCATS Patient Engagement
Across the Translational Spectrum

• Observation to POC intervention (T1)
  ➢ Identify most important research questions
  ➢ Recruit best researchers
  ➢ Build partnerships
  ➢ Complementary funding for research studies
  ➢ Bridge gap between fundamental science researchers and patients

• Clinical and translational research (T2-T3)
  ➢ Help develop relevant and practicable research protocols
  ➢ Foster community participation and recruiting research participants for clinical trials
  ➢ Increase collaboration and communication among key stakeholders (e.g., academia, biopharma, patients)

• Community health and population research (T4)
  ➢ Adoption of demonstrably useful interventions (i.e., dissemination)
  ➢ Adherence
  ➢ Interface with research partners including PCORI, Collaboratory, AHRQ, etc.
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

- CTSA-funded institutions
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 and the CTSA program should ensure that patients, family members, health care providers, clinical researchers, and other community stakeholders are involved across the continuum.

NCATS and the CTSA program should...

1. Define community engagement broadly
2. Ensure active and substantive community stakeholder participation in priority setting and decision making across all phases
3. Define and clearly communicate goals and expectations and ensure the broad dissemination of best practices
4. Explore opportunities and incentives to engage a more diverse community
NCATS Advisory Council WG on the IOM CTSA Report

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

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  CREA Results
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  Third Rock Ventures, LLC

Stay tuned...
NCATS DPI: A Collaborative Pipeline

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

**DPI Program**
- Target Validation
- Assay Dev
- Probe/Lead Development
- Lead Optimization
- Preclinical Development
- Clinical Trials

- FDA approval

**Deliverables**
- Genome-wide RNAi systems biology data
- Chemical genomics systems biology data
- Leads for therapeutic development
- Approved drugs effective for new indications
- New drugs for untreatable diseases

- Small molecule and siRNA research probes
- Predictive in vitro toxicology profiles
- Drugs suitable for adoption for further development
- Novel clinical trial designs

- More efficient/faster/cheaper translation and therapeutic development
All DPI Projects are Collaborations

DPI currently has >300 collaborations with investigators all over the U.S....
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
Identification of Drug Modulators Targeting Gene-Dosage Disease CMT1A

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†National Center of Advancing Translational Sciences and #National Human Genome Research Institute, National Institutes of Health, Bethesda, †Cancer Biology & Therapy 14:7, 638–647; July 2013; © 2013 Landes Bioscience
§Department of Cell Biology, Duke University, Durham

Identification of repurposed small molecule drugs for chordoma therapy

Menghang Xia,†,* Ruili Huang,† Srilatha Sakamuru,† David Alcorta,‡ Ming-Hsung Cho,† Dae-Hee Lee,∥ Deric M Park,∥ Michael J Kelley,‡ Josh Sommer,‡ and Christopher P Austin†

∥NIH Chemical Genomics Center; National Human Genome Research Institute; National Cancer Institute; †Department of Medicine; Duke University; Durham

Keywords: chordoma, NCGC, LncRnas, small molecule drugs

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

Jessica L. Childs-Disney†,* Ewa Sztorniak-Koniczewska‡, Tuan Tran‡,# Ilyas Yildirim§, Hajeung Park†, Catherine Z. Chen‡, Jason Hoskins§, Noel Southall‡, Juan J. Marugan‡, Samarjit Patnaik§, Wei Zheng‡, Chris P. Austin‡, George C. Schatz‡, Krzysztof Sobczak‡, Charles A. Thornton§ & Matthew D. Disney†
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.
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
<table>
<thead>
<tr>
<th>Therapeutic Area / Disease</th>
<th>Collaborator(s)</th>
<th>Agent</th>
<th>Status</th>
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<tr>
<td>Sickle Cell Disease</td>
<td>Aes-Rx, NHLBI</td>
<td>NME – Small Molecule</td>
<td>Clinical</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>Leukemia &amp; Lymphoma Society, University of Kansas</td>
<td>Repurposed Drug – Small Molecule</td>
<td>Clinical</td>
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<td>Hereditary Inclusion Body Myopathy</td>
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<td>NME – Small Molecule</td>
<td>Clinical</td>
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<td>Niemann-Pick Type C1</td>
<td>Johnson &amp; Johnson, Albert Einstein College of Medicine, Univ. of Pennsylvania, Washington Univ., NICHD, NINDS, NHGRI</td>
<td>Repurposed Drug - Small Molecule</td>
<td>Clinical</td>
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<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>ReveraGen BioPharma</td>
<td>NME – Small Molecule</td>
<td>Preclinical</td>
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<tr>
<td>Cryptococcal Meningitis</td>
<td>Viamet Pharmaceuticals, Inc.</td>
<td>NME - Small Molecule</td>
<td>Preclinical</td>
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<td>Core Binding Factor Leukemia</td>
<td>NHGRI</td>
<td>Repurposed Drug - Small Molecule</td>
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<td>Schistosomiasis</td>
<td>CoNCERT Pharmaceuticals</td>
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<td>Preclinical</td>
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<tr>
<td>Creatine Transporter Defect</td>
<td>Lumos Pharma</td>
<td>NME - Small Molecule</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
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-β-cyclodextrin (HP-β-CD) selected by TRND as pre-clinical candidate
- December 2012: IND filed
- February 2013: Phase I initiated and 1st patient dosed 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

Candidate Small Molecules

Biomarkers
PK/PD/Tox
Bio-analytical Assay
Clinical Trial
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)
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
Rare Diseases Clinical Research Network

Goals

• Facilitate clinical research by
  - Creation of Consortia focused on minimum three related rare diseases
  - Making meaningful large-scale clinical studies possible
    - Longitudinal cohorts, pilot projects, and randomized trials
  - Establishing uniform protocols for data collection

• Direct community engagement of patients and their advocates as research partners

• Enhance training of new investigators
Coalition of Patient Advocacy Groups (CPAG)

- Collaborative Clinical Research
- Centralized Data Coordination and Technology Development
- Public Resources and Education
- Training

DHHS-NIH
ORDR/NCATS, NINDS, NIAMS, NICH, NHLBI, NIDDK, NIDCR, NIAID, NCI

The Data Management and Coordinating Center

Chronic Graft Versus Host Disease Consortium

North America Mitochondrial Diseases Consortium

Primary Immune Deficiency Treatment Consortium

The Data Management and Coordinating Center

Rare Kidney Stone Consortium

Nephrotic Syndrome Rare Disease Clinical Research Network

Angelman, Rett and Prader-Willi Syndromes Consortium

Brain Vascular Malformation Consortium

Urea Cycle Disorders Consortium

Inherited Neuropathies Consortium

Lysosomal Disease Network

Porphyria Rare Disease Clinical Research Consortium

Vasculitis Clinical Research Consortium

Genetic Disorders of Mucociliary Clearance Consortium

Dystonia Coalition

Autonomic Rare Diseases Clinical Research Consortium

Sterol and Isoprenoid Diseases Consortium

Salivary Gland Carcinomas Consortium
ABOUT THE GENETIC AND RARE DISEASES (GARD) INFORMATION CENTER

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.
Global Rare Diseases Patient Registry and Data Repository (GRDR)
Pilot Project Overview

- 12 GRDR patient registries + 12 existing registries
- Ability to conduct pan-disease analysis and recruitment
- Share de-identified patient data
- Develop and use rare disease Common Data Elements (CDE)
- Explore integration of Electronic Health Records (EHR) into GRDR
- Develop an accessible web-based registry template
- Establish a public/private partnership model of sustainability
- Evaluate the data mapping, data export/import processes, and data mining capabilities
Happy Retirement, Steve Groft!

Starting February 8, 2014
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 rare Diseases Research, a position he also held.

Additional Information:

- [NORD: 30th Anniversary Celebration](#)
ORDR will continue its important work...

Though its founder is riding into the sunset...
Program Leads at NCATS

- **Target-to-Lead/NCGC:** Anton Simeonov
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