National Center for Advancing Translational Sciences:

*Catalyzing Translational Innovation*

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DIRECTOR, NCATS

NIH COUNCIL OF COUNCILS
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“Houston, we have a problem.”

Fundamental science unprecedentedly advanced, but:

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

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

To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.
NCATS: Established December 23, 2011

CTSAs (NCRR)

NCTT (NHGRI)

ORDR (OD)

CAN

NIH Institutes & Centers

NCATS
Catalyzing Collaborations Within NIH
Catalyzing Collaborations Outside NIH

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

- Therapeutic target validation
- Chemistry
- Virtual drug design
- Preclinical toxicology
- Biomarkers
- Imaging
- Efficacy testing
- Rescuing and repurposing
- Adaptive clinical trial designs
- Post-marketing research
NCATS “3D’s”

Develop
demonstrate
isseminate
NCATS DPI: A Collaborative Pipeline

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

**Target Validation**
- RNAi
- Probe Dev/NCGC
- Preclinical Development/TRND
- Assay, Chemistry Technologies
- BrIDGs
- FDA Collaboration
- Systems Toxicology (Tox21)
- Repurposing
- Paradigm/Technology Development

**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

FDA Approval
DPI Is Different in Science and Operation

- DPI is administratively intramural
  - No independent PIs, no tenure system
  - All projects are collaborations, (n = 300 currently), 90% of which are with extramural investigators/foundations/companies
  - Projects are selected via solicitation/review

- Science is intermediary between mechanistic research and commercialization
  - “Adaptor” function
  - Each project has tangible deliverable and technology/paradigm development components

- DPI is disease agnostic, works across disease spectrum
  - Common mechanisms and principles to make translation better/faster/cheaper for all

- Focuses on new technologies, enabling tools, dissemination
NCATS NIH Chemical Genomics Center

- Founded 2004
- 85 scientists
- > 200 collaborations with investigators worldwide
- Assay development, high-throughput screening (HTS), chemical informatics, medicinal chemistry: “target to lead”
- Focus is unprecedented targets, rare/neglected diseases
- Mission
  - Chemical probes/leads
  - New technologies/paradigms to improve efficiency and success rates of target-to-lead stage of drug development
  - Chemical genomics: general principles of small molecule – target interactions
Originally developed as quantitative biology manual for HTS and lead optimization at Eli Lilly & Co.

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

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Two approaches to therapeutics at NCATS

1–2 years?

> 400,000 compounds, 15 years

3,500 drugs
Development of Human Pyruvate Kinase Activators as Anti-Cancer Agents

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

Hee-Won Park
U. of Toronto, SGC

Lew Cantley, Harvard
Matt Vander Heiden, MIT
Heather Christofk, UCLA
Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis


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

Figure 6 | PKM2 activators impair xenograft growth.
Two approaches to therapeutics at NCATS

1–2 years?

> 400,000 compounds, 15 years

Target

Screen → Hit → Lead

Lead Optimization → Preclinical Development → Clinical Trials

FDA Approval

3,500 drugs
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.
**Repurposing Case Study: Refractory CLL**

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

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

Auranofin

Kill CLL but not normal donor B cells
The Learning Collaborative: Capitalizing on Strengths

- 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
Discovering New Therapeutic Uses for Existing Molecules Program

• Pilot program matching NIH researchers with compounds deprioritized by pharma for efficacy/business reasons
• Creation of template agreements to streamline negotiations between researchers and pharmaceutical companies
• 58 compounds from eight companies
  • Abbott
  • AstraZeneca
  • Bristol-Myers Squibb Company
  • Eli Lilly and Co.
  • GlaxoSmithKline
  • Janssen Pharmaceutical Research & Development, L.L.C.
  • Pfizer Inc.
  • Sanofi
Therapeutics Discovery Pilot: Timeline

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

- **Model:** Comprehensive drug development collaboration between DPI and extramural labs with disease-area/target expertise

- **Projects**
  - May enter at various stages of preclinical development
  - Disease must meet FDA orphan or WHO neglected tropical disease criteria
  - Taken to stage needed to attract external organization to adopt to complete clinical development/registration, max 2a
  - Milestone driven
  - Therapeutic modalities: small molecules, proteins
  - Serve to develop new generally applicable platform technologies and paradigms

- **Eligible applicants**
  - Academic, non-profit, government lab, biotech/pharma
  - Ex-U.S. applicants accepted
## TRND Portfolio

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<th>Collaborator</th>
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<th>Partner Type(s)</th>
<th>Agent</th>
<th>Therapeutic Area / Disease</th>
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<td>Oligo (PMO)</td>
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</tr>
</tbody>
</table>
Collaborator: AesRx, Boston-based biotech

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

Roadblocks in drug development encountered by collaborator
- Animal toxicology studies
- CMC (Chemistry, Manufacturing, and Quality Control)
- Regulatory: interactions with FDA, IND filing

TRND collaborating with AesRx on
- IND-enabling pre-clinical animal toxicology studies
- API manufacturing and impurity characterization
- Preparing and filing of IND
- Proof-of-concept clinical trials

API (Aes-103) manufactured: CROs supported by RAID program and TRND

Phase I-II clinical trials performed at CRO and NIH Clinical Center

Anti-sickling effect of Aes-103
Before incubation under air. Almost all cells are discoegotes with some irreversibly Sickled Cells (ISCs)
Toxicology Technology Development:
The Tox21 Program

NIH
National Institutes of Health
Turning Discovery Into Health

NIEHS
National Institute of Environmental Health Sciences

National Toxicology Program
Department of Health and Human Services

United States Environmental Protection Agency
Computational Toxicology

NIH
National Center for Advancing Translational Sciences

NIH Chemical Genomics Center

NCATS
National Center for Advancing Translational Sciences
Tox21: Predicting Toxicity

- Complex Cellular and HCS HTS
- Tissues
- Cellular Systems
- Cell Changes
- Cellular Networks
- Toxicity

Biochemical HTS

Molecular Targets

Molecular Pathways

Cell-Based HTS

Model Organism MTS

Virtual Tissues
Tissue Chip for Drug Screening: Microsystems Initiative

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

• NIH investment (funded through CAN + Common Fund) = $70M/5 years
  » (CAN = Cures Acceleration Network)
• DARPA investment = $75M/5 years
• FDA investment = regulatory and toxicology expertise
• NCATS and DARPA independently manage and fund separate but highly coordinated programs
GOAL: Develop an *in vitro* platform that uses human tissues that will be predictive of efficacy, pharmacokinetics, safety and toxicity of promising therapies in humans and suitable for regulatory science use.

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

Clinical and Translational Science Awards (CTSAs)

- Support a national consortium of medical research institutions
- Work together to improve the way clinical and translational research is conducted nationwide
- Aim to accelerate the research translation process
“The CTSAs will advance the assembly of institutional academic ‘homes’ that can provide integrated intellectual and physical resources for the conduct of original clinical and translational science.”
Evolving CTSA Vision

- National leadership to enhance quality, safety and efficiency in translational research
- Innovation in translational research methods, resources and services that catalyze the spectrum of translational research
- Facilitate training and career development of robust translational workforce for interdisciplinary team research
- Flexible academic, community and industry collaboration and partnership models built on shared commitment to translation
- *A national network for translational medicine*
Published in December 2012; current paper in press
Brain-computer-interface (BCI) technology enables a quadriplegic to use only her thoughts to move a robotic arm
Collaborative support from NIH, DARPA, VA and FDA
University of Pittsburgh’s CTSI provided:
  » Critical mass needed for the team to work together early in the research process
  » Help with protocol development
  » Regulatory reporting and compliance expertise
  » Early pilot work and KL2 mentored career development
Office of Rare Diseases Research (ORDR)

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

Who Are We?

The Rare Diseases Clinical Research Network (RDCRN) is made up of distinctive consortia that are working in concert to improve availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community. The RDCRN also aims to provide up-to-date information for patients and to assist in connecting patients with advocacy groups, expert doctors, and clinical research opportunities.

Click on the Consortium Name to view the diseases or disorders studied by each consortium. Clicking on a disease or disorder name will take you directly to a description of that disease or disorder.

- Angelman, Rett, And Prader-Willi Syndromes Consortium
- Autonomic Rare Diseases Clinical Research Consortium
- Brain Vascular Malformation Consortium
- Chronic Graft Versus Host Disease Consortium (CGVHD)
- Dystonia Coalition
- NEPTUNE: Nephrotic Syndrome Study Network
- North American Mitochondrial Disease Consortium
- Porphyrias Consortium
- Primary Immune Deficiency Treatment Consortium
- Rare Kidney Stone Consortium
New NCATS Initiatives

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