What is Translation?

*Translation* is the process of turning observations in the laboratory and clinic 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.
Why is engagement so critical to translational science?

• Definition
  - Middle English: from Latin translatus 'carried across', past participle of transferre (transfer)

• Thus every scientific translational must be done with the party/community to whom the information/product/intervention is to be transferred

• Very different from much of the rest of science!
What is engagement?

• 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”

• Critical for meaningful prioritization, focus, outcomes
• NCATS is all about the SCIENCE of engagement - how to best engage - focus on “innovative methods and technologies”
Standard Model

Basic Laboratory Research

Clinical Research

Translational Research

Population Research

Improved Public Health
The Way It Should Work

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

Improved Public Health
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

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.
Patient Engagement at NCATS
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 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.
NCATS Advisory Council Subcommittees

• Medical Technologies
  - Frank L. Douglas
  - Paul Yock

• Patient Engagement
  - Margaret Anderson
  - Myrl Weinberg

• Interactions with Biotech/Pharma/VC
  - Freda Lewis-Hall
  - Ankit Mahadevia
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 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 “3D’s”

Develop
Demonstrate
Disseminate
NCATS DPI: A Collaborative Pipeline

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

**Target**
- Target Validation
- Assay Dev
- Probe/Lead Development
- Lead Optimization
- Preclinical Development
- Clinical Trials
- FDA approval

**DPI Program**
- RNAi
- Probe Devel/NCGC
- Preclinical Development/TRND
- Assay, Chemistry Technologies
- BrIDGs
- FDA Collaboration
- Systems Toxicology (Tox21)
- Repurposing
- 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
All DPI Projects are Collaborations

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

Sung-Wook Jang, Camila Lopez-Anido, Ryan MacArthur, John Swaren, and James Inglese

National Center for Advancing Translational Sciences and National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, Cancer Biology & Therapy 14:7, 638–647; July 2013; © 2013 Landes Bioscience

Identification of repurposed small molecule drugs for chordoma therapy

Menghang Xia, Ruili Huang, Srilatha Sakamuru, David Alcorta, Ming-Huang 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; Department of Medicine; Duke University; National Institutes of Health, Bethesda, Maryland

Keywords: chordoma, NCGC

ARTICLE

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

Jessica L. Childs-Disney, Ewa Stepniak-Koniczewska, Tuan Tran, Ilyas Yildirim, HaeJung Park, Catherine Z. Chen, Jason Hoskins, Noel Southall, Juan J. Marugan, Samir B Patnaik, Wei Zheng, Chris P. Austin, George C. Schatz, Krzysztof Sobczak, Charles A. Thornton & Matthew D. Disney

NIH National Center for Advancing Translational Sciences
Assay Development and Screening Technology

Two new collaborations are examples of patient foundation-initiated science:

1. The Alpha-1 Project
   Alpha-1 Antitrypsin Deficiency

2. Hannah’s Hope Fund
   Giant Axonal Neuropathy

Healthy liver on left and two damaged livers by alcohol abuse and cirrhosis. (http://alpha-1foundation.org/)

http://www.news.emory.edu/
Partnership for Drug Repurposing: 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
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-led Niemann-Pick Type C (NPC) Disease Project

The Power of Collaboration

• Rare genetic progressive neurodegenerative disease, death by teens
  ➢ No FDA approved treatment
• Project initiated 2007 via contact by disease advocacy groups
  ➢ Goal: repurpose an existing drug for NPC treatment within current patients’ lifetimes
• Drug identified in screen of NCATS drug collection
  ➢ Currently in clinical testing
• Key to success: Collaboration
  ➢ 10 different disciplines
  ➢ Team: NCATS, 3 other NIH ICs, 4 universities, 2 companies, multiple patient groups
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

- **May 12, 2014:** New FOAs released
- **May 29, 2014:** Technical Assistance webinar
- **July 15, 2014:** Pre-applications due
  - UH3 applications - directly going to Phase 2a trial
  - UH2/UH3 applications for adult indications
  - UH2/UH3 applications for pediatric indications

- Other NIH ICs and the FDA Office of Orphan Product Development are participating and providing funding
- Expands the program to include pediatric indications
- **Inclusion of relevant Patient Advocacy Groups is encouraged and part of the review criteria**
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
CPAG Model for Patient Engagement in the RDCRN

- Patient groups part of each consortium
- Substantive input into protocols
- Representatives from each Center to the Coalition of Patient Advocacy Groups (CPAG)
  - Have standing meetings of all members
  - Meeting once a year in conjunction with RDCRN Steering Committee meeting
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
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
Austin CTSA Program Sites Visited (n=28) or Upcoming (n=4) since becoming NCATS Director September 2012

[Map showing the locations of CTSA-funded institutions]
IOM Report on the CTSA Program

Recommendations

• Released June 2013
• 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 Advisory Council WG on the IOM CTSA Report

Co-Chairs
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  FARAFriedreich’s Ataxia Research Alliance
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• Fernando Pineda-Reyes
  CREA Results
• Robert I. Tepper, M.D.
  Third Rock Ventures, LLC

• Recommendations presented to NCATS Council May 16, 2014
• Find report at
  • http://www.ncats.nih.gov/about/ncats-council/wgs/ctsa-iom/ctsa-iom.html
Implementation of IOM Report Recommendations

Overview of the Process

IOM Report Recommendations
June 2013

Working Group
sets strategic
goals and
identifies
measurable
objectives

WG Report
Recommendations
May 2014

NCATS develops
implementation
strategy and
programmatic
metrics

NCATS measures
results
Strategic Goals

Working Group Recommendations

- **Workforce Development**
  - The translational science workforce has the skills and knowledge necessary to advance translation of discoveries.

- **Collaboration/Engagement**
  - Stakeholders are engaged in collaborations to advance translation.

- **Integration**
  - Translational science is integrated across its multiple phases and disciplines within complex populations and across the individual lifespan.

- **Methods and Processes**
  - The scientific study of the process of conducting translational science itself enables significant advances in translation.
WG Strategic Goal: Collaboration/Engagement

*Evolution based on CTSA WG Report*

Engage stakeholder communities across the translational spectrum

- Include patients in
  - Concept development early on to assure we answer questions that matter to them.
  - Protocol development to assure the plan is feasible in terms of participant burden.
  - Considering risk/benefit relationships and in developing consent language.
  - Considering endpoints to assure what is measured matters to them.
  - Developing communication plans to assure messages reach relevant communities.

- Include all relevant stakeholders in the health care delivery system (e.g. hospitals, office-based clinicians).
- Promote partnerships with industry and non-profit organizations.
- Identify and disseminate successful collaboration models.
Petra Kaufmann Joins NCATS as Clinical Innovation Director

Petra Kaufmann, M.D., M.Sc., will head the NCATS Division of Clinical Innovation beginning May 4, 2014. Her new role will include overseeing the Clinical and Translational Science Awards (CTSA) program with the aim of improving the effectiveness and efficiency of the process of translation from scientific discovery through clinical research to improved health outcomes. Kaufmann currently serves as director of the Office of Clinical Research at NIH’s National Institute of Neurological Disorders and Stroke (NINDS).

"Following a comprehensive national search, I am delighted that Petra is joining the NCATS leadership team," said NCATS Director Christopher P. Austin, M.D. "Her record of expertise and accomplishment across the translational sciences—from basic research to clinical studies—makes her ideally suited to lead our clinical innovation efforts."

Prior to joining NINDS in 2009, Kaufmann was a tenured associate professor of neurology at Columbia University in New York, where she worked in the neuromuscular division, electromyography laboratories and pediatric neuromuscular clinic. At Columbia, she gained experience with the CTSA program by serving on several committees within the Irving Institute for Clinical and Translational Research, including the Clinical Research Resource Advisory Committee.

At NINDS, Kaufmann recognized the need for clinical research infrastructure and established NeuroNEXT, an academic research trial network for Phase II clinical trials across a wide range of neurological diseases, as well as StrokeNET, a Phase II and III clinical trial network for stroke. These networks aim to accelerate clinical research by including a central institutional review board and pre-negotiated master trial agreements. They also foster public-private partnerships by engaging industry and patient groups. Kaufmann also led efforts at NINDS to engage patients earlier in the clinical research process by soliciting their active input in protocol development as well as in the implementation and safety oversight of clinical trials.

"I enjoyed my work in the lab and the clinic," Kaufmann said. "I'm excited for the opportunity to work in the translational sciences field that aims to bridge these disciplines for the greater good of patients in need."

Kaufmann will maintain her current adjunct academic appointment at Columbia University, privileges at the NIH Clinical Center and patient care at the Muscular Dystrophy Association Clinic at Children’s National Medical Center. She earned her M.D. from the University of Bonn in Germany and her M.Sc. in biostatistics from Columbia’s Mailman School of Public Health, and she trained in neurology at Columbia University.

Posted April 2014
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 century needs cannot be solved with 20th century structures

• NCATS has just begun to transform itself and its programs to meet these opportunities and needs for the benefit of patients and communities
Learn More About NCATS

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