What is Translation?

Translation is the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public - from diagnostics and therapeutics to medical procedures and behavioral changes.
What is Translational Science?

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

NCATS studies translation as a scientific and organizational problem.
The Best of Times, the Worst of Times

Fundamental science unprecedentedly advanced, but:

- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Drug/device/diagnostic development system in crisis
- Clinical trials system in crisis
- Poor adoption of demonstrably useful interventions

People unhealthier and funders of biomedical research enterprise (public and private) impatient
Moore’s Law

curve shows transistor count doubling every two years
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.

Disorders with Known Molecular Basis

Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome
Disorders with Known Molecular Basis

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

250 with therapy
Published Genome-Wide Associations through 12/2012
Published GWA at p≤5×10^{-8} for 17 trait categories
What I learned as a neurologist, and then again as a geneticist

Sickle Cell Anemia, a Molecular Disease

Lumis Pilling, Harvey A. Isaac, S. J. Singer, and Ben C. Wells

Gates and Crellin Laboratory of Chemistry, California Institute of Technology, Pasadena, California

THE ERYTHROCYTES of certain individuals appear 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 form from the normal biconcave disk to somewhat biconcave, biconvex, and other forms. This process is known as sickling. About 8 percent of Americans Negroes possess this characteristic; rarely they exhibit no pathologic consequences attributable to it. These people are said to have sickle cells, or sickle cell trait. However, about 1 in 100 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 chief 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 (1). Tests have been devised that between 30 and 40 percent of the erythrocytes in the venous circulation of sickle cell anemia individuals, but less than 1 percent of those in the venous circulation of sickle trait individuals, are normally sickled. Reported in vitro indicates that under normally low oxygen pressure, however, all cells of both types assume the sickled form.

The evidence available at this point that our investiga-
tion is begun to indicate that the process of sickling might be intimately associated with the rate of the rate of the hemoglobin within the erythrocytes. Sickled erythrocytes in which the hemoglobin is combined with oxygen or carbon monoxide have the biconcave disk contour and are refringent in red light. The investigation was carried out with the aim of a grant from the American Health Foundation in the assistant of the American Hemoglobin Society.

The author is grateful to Professor B. J. Ewing, of the Whipple Institute for his supervision, and to Dr. K. Wood, of the Whipple Institute, for his hospitality. The research was carried out in the Laboratory of the National Institute of Health in Bethesda, Md.

Standard Model

Basic Laboratory Research

Clinical Research

Translational Research

Population Research

Improved Public Health

NIH National Center for Advancing Translational Sciences
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: 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

NCATS

NIH
National Center for Advancing Translational Sciences

NCATS
Catalyzing Collaborations Outside NIH

NCATS

Biotech

Academia

Advocacy Groups

Pharma

Non-Profits

FDA
Catalyzing Collaboration within NCATS Across the Translational Spectrum
Some of the *scientific* translational problems on NCATS’ to-do list...

- Predictive toxicology
- Predictive efficacy
- Derisking undruggable targets/untreatable diseases
- Data interoperability
- Biomarker qualification process
- Clinical trial networks
- Patient recruitment
- Electronic Health Records for research
- Harmonized IRBs
- Clinical diagnostic criteria
- Clinical outcome criteria (e.g., PROs)
- Adaptive clinical trial designs
- Shortening time of intervention adoption
- Methods to better measure impact on health (or lack of)
Some of the operational translational problems on NCATS’ to-do list…

- Data transparency/release
- IP management
- Integration of project management
- Incentives/credit for team science
- Incentives/credit for health improvements
- Education/Training (scientific and cultural)
- Collaborative structures
  - Public-private partnership models
NCATS “3D’s”

Develop
demonstrate
isseminate
Translation is a team sport

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

• **Clinical Translational Science**
  - Clinical and Translational Science Awards
  - Rare Disease Clinical Research Network
  - New Therapeutic Uses program

• **Preclinical Translational Science**
  - NIH Chemical Genomics Center
  - Therapeutics for Rare and Neglected Diseases program
  - Bridging Interventional Development Gaps program

• **Re-engineering Translational Sciences**
  - Toxicology in the 21st Century
  - Microphysiological Systems (Tissue Chip) program
  - Office of Rare Diseases Research
NCATS Division of Clinical Innovation

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

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

WG Focus Areas → Strategic Goal Recommendations

IOM Report Recommendations

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

WG Focus Areas

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

Strategic Goal Recommendations

- Workforce Development
- Collaboration and Engagement
- Integration
- Methods, and Processes
New Funding Opportunity Announcement

CTSA Program Funding Opportunity Now Available

On Sept. 12, 2014, NCATS released a new funding opportunity for the Clinical and Translational Science Awards (CTSA) program, a national network of medical research institutions collaborating to transform how clinical and translational science is conducted nationwide. Applications are due Dec. 16, 2014.

CTSA hubs — the medical research centers that make up the CTSA network — support high-quality clinical and translational research locally, regionally and nationally, fostering innovation in training, collaboration and new methodologies. NCATS is continuing to develop the CTSA program to meet the evolving needs of clinical and translational investigators and the communities they serve.

*The CTSA program is a unique national resource through which we have the capability to transform the translational landscape to get more...
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
Lysosomal Disease Network
RDCRN at the University of Minnesota

- PI: Chester Whitley, M.D.
- Partnership between NCATS, NINDS and NIDDK
- Focused on eleven of the lysosomal diseases
- Goal is to solve the major challenges in diagnosis, disease management, and therapy for these complex, rare disorders
Discovering *New Therapeutic Uses for Existing Molecules Program (NTU)*

- **Problem:** 80% of drugs that enter clinic never approved

- **Opportunity:** potential for new treatments via ID of new indications for deprioritized investigational drugs

- **Program:** matches investigational agents from pharma deprioritized for lack of efficacy or business reasons with new indication ideas from academia

  - NIH provided: template Collaborative Research Agreements (CRAs) and Confidential Disclosure Agreements (CDAs), FOAs, review, funding, oversight
  
  - Pharmaceutical partners provided: compounds, biologics, in kind support, pertinent data
  
  - Academic researchers provided: deep understanding of disease biology, new concepts to test, access to appropriate patient populations
### New Therapeutic Uses Program

**Pilot Program Awards Issued June 2013**

- **9 projects in 8 diseases**

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### Translational Innovation Success Measures

- Does use of template agreements speed negotiation time?
- Does crowdsourcing of indications generate new ideas?
- Do studies result in new indications/approvals?
New Therapeutic Uses Program

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

**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

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

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

![Conversion diagram: AA → 12-LO → 12-HpETE → GPO → 12-HETE → Signalling]

- NCGC collaboration with Ted Holman (UCSC) developed assay, HTS, cheminformatics, medchem optimization, leading to first potent, enantiomer selective 12-LO inhibitor (ML127)
- The ML127 pharmacological probe has allowed dissection of 12-LO functions in vitro and in vivo
- Therapeutic development for diabetes and thrombosis

  - **Collaborators:**
    - Ted Holman (UCSC)
    - Jerry Nadler (EVMS)
    - Michael Holinstat (TJU)
  - Developed the most potent, selective and drug-like inhibitors for 12-LOX to date
  - Signed Research Collaboration Agreement with Sanofi to further characterize our inhibitors
Enabling Comprehensive Drug Repurposing

The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin

Small-molecule compounds approved for use as drugs may be “repurposed” for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.

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

<table>
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<tr>
<th>Compound</th>
<th>Activity</th>
</tr>
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<tbody>
<tr>
<td>Auranofin</td>
<td>Active</td>
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**Kill CLL but not normal donor B cells**
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
TRND
Scope

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

- Drug: IT Cyclodextrin
- Collaborators
  - NIH: (Denny Porter, NICHD - Clinical, Bill Pavan, NHGRI - Genetics)
  - Washington University (Dan Ory - Biochemistry)
  - Albert Einstein and UPenn (Steve Walkley and Charles Vite - Animal models)
  - Johnson & Johnson Pharmaceuticals
- NPC disease foundations involved and facilitating
- Milestones
  - February 2011: 2-hydroxypropyl-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)
Toxicity is a common reason for drug development failure

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

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

- **Goal**
  - Develop organoids on chips to screen for compound toxicity, efficacy
    - Liver, heart, lung, other cell types
    - Integrate platform systems
    - Designed for multiple different readouts

- **NIH, DARPA contributing ~$70M each over 5 years**
  - NCATS and DARPA independently manage, fund separately but highly coordinated program
  - FDA provides regulatory science guidance

- **Awards announced in 2012**
  - Supporting the best ideas in engineering, biology, and toxicology
Microphysiological Systems Program

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

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

Scaffold
- purified ECM
- synthetic polymers
- composites

Cells
- stem/progenitor
- differentiated
- mixed cell types

Structure
- porosity
- topography
- stiffness

Spatial/Temporal Patterning
- cytokine gradients
- controlled release

Perfusion
- embedded channels
- vascularization

Bioreactors
- optimized culture conditions
- biomechanical properties
- blood mimetics

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

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

Host Response
- generalized inflammation
- specific immunity

Innervation
- signal propagation
- coordinated response
Engineered Cardiac Muscular Thin Films

(A) Fabricate Substrate and Seed myocytes
(B) Cut out shapes
(C) Dissolve sacrificial layer peel off unwanted film
(D) Film bends up as myocytes contract

Data provided by Dr. Kit Parker, Wyss Institute

Science 2007;317:1366
Biomaterials 2010;31:3613
Lab Chip 2011;11:4165
J Pharm Tox Methods 2012;65:126

NIH National Center for Advancing Translational Sciences

Film length
Automatic projection tracking
Body-on-a-Chip?

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

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

Pre-Clinical Innovation
Take-home messages

• The opportunities (and needs) in translational science are huge and systematic, so require systematic solutions

• The scale of the opportunities/needs requires transformational change to deliver logarithmic improvements
  » 21st c. needs cannot be solved with 20th c. structures

• NCATS has just begun to transform itself and its programs to meet these opportunities and needs for the benefit of patients
Program Leads at NCATS

- **Preclinical Innovation: Anton Simeonov**
  - anton.simeonov@nih.gov

- **Clinical Innovation: Petra Kaufmann**
  - petra.kaufman@nih.gov

- **Office of Rare Diseases: Pamela McInnes**
  - pmcinnes@mail.nih.gov

- **Tissue Chip: Dan Tagle**
  - tagled@mail.nih.gov

- **New Therapeutic Uses: Christine Colvis**
  - ccolvis@mail.nih.gov

- **Strategic Alliances: Lili Portilla**
  - portilll@mail.nih.gov
Learn More About NCATS

Website: www.ncats.nih.gov

Facebook: facebook.com/ncats.nih.gov

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