Catalyzing innovation - the National Center for Advancing Translational Sciences

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Disorders with Known Molecular Basis

Source: Online Mendelian Inheritance in Man, Morbid Anatomy of the Human Genome
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 on a system-wide level as a scientific and organizational problem.

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**Translational Science Spectrum**

[Diagram showing various components of translational science]
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 Scientific Initiatives

- Clinical Translational Science
  - Clinical and Translational Science Awards
  - Rare Disease Clinical Research Network
  - New Therapeutic Uses program
- Preclinical Translational Science
  - NCATS 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
Clinical and Translational Science Awards (CTSAs)

NCATS Division of Clinical Innovation

- 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 Hubs
Streamlining Multi-Site Clinical Studies

- The problem: current atomized system is inefficient, costly and often ineffective
  - Duplicative IRB reviews among sites
  - Subcontracting among institutions delays start-up
  - Duplicative investigator/site qualification
- Solutions in progress
  - Centralized IRB review (reliance agreements, IT solutions)
  - Streamlined contracting (pre-negotiated master agreements)
  - GCP training across CTSA sites

Improving Participant Recruitment

- The problem: slow or failed recruitment leads to delays, increased costs, lost efficiency
- Solution in progress
  - Building national recruitment capacity across CTSA network using data from Electronic Health Record (EHR) to identify potential trial participants who meet entry criteria

<table>
<thead>
<tr>
<th>Trial planning phase</th>
<th>Trial implementation phase</th>
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</thead>
<tbody>
<tr>
<td>Data-driven site selection</td>
<td>Privacy and IRB compliant recruitment</td>
</tr>
<tr>
<td>Feasibility analysis (n)</td>
<td>Expert staff helping with implementation</td>
</tr>
<tr>
<td>Outside firewall</td>
<td></td>
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Common Data Elements (CDEs)

Data standards for neurological research

1. "General" Core CDEs
   Relevant across neuroscience clinical research

2. Disease-specific Core CDEs
   Should be used in all studies for this disease

3. Disease-specific Supplemental CDEs
   Extended set that are "common", but supplemental, i.e. not required - Choose from a "menu"

4. Disease-specific Exploratory CDEs
   Not yet validated, or under development

Coriell Forms or links to other repositories

Outcome Measures

PROMIS

Patient Reported Outcomes Measurement Information System (PROMIS), funded by the National Institutes of Health (NIH), is a system of highly reliable, valid, flexible, precise, and responsive assessment tools that measure patient-reported health status.

NeuroQoL

Toolbox

nihtoolbox.org/
www.neuroqol.org/
www.nihpromis.org/
Office of Rare Diseases Research

- **Rare Diseases Clinical Research Network (RDCRN)**
  - 22 consortia at 250 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
  - Patients + NCATS + NIH ICs + FDA + Biopharma

- **Global Rare Disease Registry (GRDR)**
  - 15 GRDR patient registries + 19 existing registries
  - Ability to conduct cross-disease analysis and recruitment
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

- 9 projects in 8 diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Academic Partner</th>
<th>Pharma Partner</th>
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<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>Yale</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>U Rhode Island/NIAAA</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Calcific Aortic Stenosis</td>
<td>Mayo Clinic</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>Kennedy Krieger/UWash</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>Baylor</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Peripheral Artery Disease</td>
<td>U Virginia</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>VCU/Pittsburgh</td>
<td>Janssen</td>
</tr>
<tr>
<td>Schizophrenia (2)</td>
<td>Indiana U</td>
<td>Lilly</td>
</tr>
<tr>
<td></td>
<td>Yale</td>
<td>Pfizer</td>
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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?
Innovation in Preclinical Development: Therapeutics for Rare and Neglected Diseases (TRND) Program

- **Model**: Collaboration between NCATS labs with preclinical drug development expertise and external organizations with disease area/target expertise
- **Projects**:
  - Entry from Probe to IND-enabling
  - Taken to stage needed to attract external organization to adopt for completion of clinical development
  - Serve to develop new generally applicable platform technologies and paradigms
- **Eligible Applicants**:
  - Academic, Non-Profit, Government Lab, Biotech, Pharma
  - Ex-U.S. applicants accepted
- **Intellectual Property**:
  - Each partnerships is unique and 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

Tissue Chip 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

- Stress [kPa]
- Time [s]

- Film length
  - Automatic projection tracking

Data provided by Dr. Kit Parker, Wyss Institute
Personalized Body-on-a-Chip?

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

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

Program Leads at NCATS

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