The NIH Translational Therapeutics Pipeline

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NHGRI Science Reporters Workshop
June 7, 2010
The best of times, the worst of times

How to translate the genome into biological insights and therapeutics?
Only a small % of diseases and genome-encoded targets are being addressed for drug development.

**Current drug targets:**
Well understood proteins

**Current diseases:**
Prevalent diseases that affect developed world
Acronyms

- **NCGC**: NIH Chemical Genomics Center
- **MLI**: Molecular Libraries Roadmap Initiative
- **TRND**: Therapeutics for Rare and Neglected Diseases program
- **RAID**: Rapid Access to Intervention Development
- **CAN**: Cures Acceleration Network
Trans-NIH programs to translate genes into drugs

- Identify target (a.k.a., "assay")
- Create testing system
- Test >300,000 chemicals for activity on target
- Make modifications to active chemicals to make suitable for human use
- Test in animals for safety, effectiveness
- Test in humans for safety, effectiveness

NIH basic research
Roadmap Molecular Libraries Program
NIH Chemical Genomics Center (NCGC)
Therapeutics for Rare and Neglected Diseases (TRND) Program
Biotech, Pharma
NIH Clinical Center
NIH Chemical Genomics Center

- Founded as part of Roadmap
- 75 scientists
- > 100 collaborations with investigators worldwide
  - 75% NIH extramural
  - 15% Foundations, Research Consortia, Pharma/Biotech
  - 10% NIH intramural
- Focus on novel targets, rare/neglected diseases
- Produces
  - chemical probes/leads
  - new paradigms for assay development, screening, informatics, chemistry
Two approaches to therapeutics for rare and neglected diseases

- >400,000 compounds, 10 yrs
- 3000 drugs
- FDA approval
- 1-2 years?
- Target → Screen → Hit → Lead → Lead Optimization → Preclinical Development → Clinical Trials

3000 drugs
Repurposing a Drug for Niemann-Pick Disease Type C

NCGC – Dan Ory (Washington Univ) – Steve Walkley (Einstein) – Denny Porter and Bill Pavan (NIH)

- Autosomal recessive
  - Gene ID’ed 1998
- Prevalence: 1:150,000
- Progressive neurodegeneration, death by teens
- NCGC, university investigators, and patient groups are collaborating to repurpose an existing drug for NPC treatment
- Drug identified is entering clinical testing this fall
Developing drugs for Schistosomiasis

• Parasitic disease that affects 250 million people, mostly in Africa
• Dr. David Williams at Rush University identified potential new gene drug target
• NCGC and Dr. Williams worked together to
  – Screen 100,000 chemicals
  – Perform chemistry optimization
  – Successfully identify targeted chemicals that provide proof of principle and a starting point for new drugs
Livers of treated mice

Ex vivo killing of S. mansoni worms by NCGC1597

Identification of oxadiazoles as new drug leads for the control of schistosomiasis

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NIH’s new programs to translate genes into drugs

- **NIH basic research**
- **Roadmap Molecular Libraries Program**
- **NIH Chemical Genomics Center (NCGC)**
- **Therapeutics for Rare and Neglected Diseases (TRND) Program**
- **Biotech, Pharma**
- **NIH Clinical Center**

**Identify target** → **Create testing system (a.k.a., “assay”)** → **Test >300,000 chemicals for activity on target** → **Make modifications to active chemicals to make suitable for human use** → **Test in animals for safety, effectiveness** → **Test in humans for safety, effectiveness**
The New NIH Center for Translational Therapeutics: An Integrated Pipeline

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

Target Validation
- RNAi
- Probe Development
- Preclinical Development/TRAID

Assay Development
- NCTT Branch

FDA Collaboration

Toxicology
- Repurposing
- Repurposing

Paradigm/Technology Development
- Genome-wide RNAi systems biology data
- Chemical genomics systems biology data
- Leads for therapeutic development
- New drugs for untreatable diseases
- Approved drugs effective for new indications

Deliverables
- 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
BACKUPS
TRND Operational Model

• Analogous to NCGC
• In-house laboratories with expertise in preclinical drug development will collaborate with external laboratories with expertise in disease/target
• Projects will be taken to phase needed for external organization to adopt for clinical development
• Projects will enter TRND at a variety of stages of development
• Distinguishing features
  – Disease agnostic, take advantage of cross-cutting mechanisms
    • “Diseaseome” approach
  – Science of preclinical drug development
    • Reasons for successes and failures will be investigated and published
  – Technology Development
    • Efficacy models (iPS), Toxicity models (Tox21), BBB penetration
  – Large-scale systematic repurposing
    • What % of all rare diseases are treatable by entire current pharmacopeia
TRND Pilot Projects Ongoing

* Chosen to establish processes in advance of solicitation, with diversity of project stage, type of disease and collaborators

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type</th>
<th>Pathology</th>
<th>Collaborators</th>
<th>Compound type</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosomiasis, Hookworm</td>
<td>Neglected</td>
<td>Infectious parasite</td>
<td>Extramural</td>
<td>NME</td>
<td>Early (lead optimization)</td>
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<tr>
<td>NPC</td>
<td>Rare</td>
<td>CNS, liver/spleen</td>
<td>Disease Fnd, Extramural, Intramural</td>
<td>Repurposed approved drug</td>
<td>Mid-stage</td>
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<tr>
<td>HIBM</td>
<td>Rare</td>
<td>Muscle</td>
<td>Biotech, Intramural</td>
<td>Intermediate replacement</td>
<td>Pre-IND</td>
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