Bridging the Gap: Defining and Understanding the Necessary NIH Capabilities and Infrastructure

NIH Chemical Genomics Center and Therapeutics for Rare and Neglected Diseases

Susan E. Old, Ph.D.
Special Advisor
Acting Deputy Director
NIH Center for Translational Therapeutics
National Institutes of Health

Science and Management Review Board
September 14, 2010
Therapeutic Development Pipeline

Discovery
- Assay development
- HTS
- Hit-to-Probe
- Probe
- Lead
- Candidate

Development
- Probes
- 2 yrs
- Lead
- 2 yrs
- Candidate
- PK/PD
- Non-GLP Tox
- Formulation
- GMP Manufacture

IND-Enabling Studies and CMC
- IND
- Toxicology, Safety Pharm
- Process Chemistry

Clinical Trials
- Ph I
  (Safety)
- Ph II
  (Dose finding, initial efficacy in patient pop.)
- Ph III
  (Efficacy and safety in large populations)
- Clinical Trials
- Drug Target and Drug MOA Validation,
  Biology Efficacy, Off-Target Safety Testing
  in Animal Models
- Clinical Translation Assessments
- Regulatory Planning
- 1 yr
- 2 yrs
- ~3 yrs
- 1 yr

NDA filing
NIH Chemical Genomics Center

- Founded as part of Roadmap – *Molecular Libraries Program*
- 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
Only a small % of genome-encoded targets and diseases are being addressed for drug development.

Current drug targets:
Well understood proteins

Current targeted diseases:
Prevalent diseases that affect developed world

Human Genome
20,000 genes

Human Diseases
7000 diseases
Disease areas of NCGC assays

- Basic Research: 36%
- Cancer: 23%
- Infectious Diseases: 11%
- Neuroscience: 8%
- Toxicology: 7%
- Metabolic Diseases: 5%
- Genetic Diseases: 5%
- Other: 5%

- Total: 100%
The NCGC: Facilitating Drug Discovery

- Molecular Libraries Program
- NCI CMC
- NIEHS, EPA (Tox21 Program)
- RNAi
- NIH Intramural
- Disease Foundations
- Biotechnology, Pharmaceutical Companies

- Chemical Probes for basic research
- Chemical Profiles of biological activity for toxicology, drug development
- Chemical Probes for new drug development
- Discovery with Genomic (RNAi) approaches
The long pathway to drug development

- **Basic and Clinical Research**
  - Indefinite
  - Identify Target

- **NCGC, Molecular Libraries Initiative**
  - 3 yrs
  - Identify chemical starting point for drug

- **“Valley of Death”**
  - 4 yrs
  - Make many chemical modifications to give drug beneficial effect without side effects

- **Pharmas, Biotechs NIH Clinical Center, Academic Clinical Centers**
  - Ph I: 1 yr
  - Ph II: 2 yrs
  - Ph III: ~3 yrs

- **FDA**
  - Review: 1 yr
  - Patient Use
NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

Creating a Drug Development Pipeline at NIH

- Congressionally-mandated effort to speed development of new drugs for rare and neglected diseases
- Administration and governance at NIH
  - Governance/oversight by Office of Rare Diseases Research
  - Administered by NHGRI
- Operations: collaboration between intramural and extramural labs with appropriate expertise
- Projects will:
  - Enter TRND at a variety of stages of development
  - Be taken to phase needed for external organization to adopt for clinical development
NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

Distinguishing features
- Collaboration / Partnerships (not service center)
  - Government, Academics, Non-Profit, For-Profit collaborations
- Building the laboratory and expertise infrastructure at NIH
- Disease agnostic, take advantage of cross-cutting mechanisms
- Science of preclinical drug development
- Technology/paradigm development (20% of effort, toward improving success rates)
- Large-scale systematic repurposing

Project-specific activities
- Medicinal chemistry, efficacy, pharmacology, absorption, distribution, metabolism, and excretion (ADME), toxicology, pharmacokinetics/pharmacodynamics (PK/PD)
- Chemical Manufacturing and Controls (CMC), Compound scale-up, formulation
- First in Human or Proof of Concept clinical trials as needed for project
NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

- **FY09:** infrastructure (May 2009)
- **FY10:** infrastructure and pilot projects (June 2009)
  - Budget $24M
  - Focus: governance, hiring, research community outreach, pilot projects
- **FY11:** infrastructure and project solicitation
  - **President’s budget recommends $50M**
  - **Solicitation of projects in Sept 2010 to begin in April 2011; 3-5 projects**
- **FY12:** fully operational
  - Laboratories completed Early 2012
  - Work on several new projects per year
  - Average project should take ~3 years
  - Projects will be monitored closely for progress
### TRND Pilot Projects

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>
</tr>
<tr>
<td>Niemann Pick C</td>
<td>Rare</td>
<td>CNS, liver/spleen</td>
<td>Disease Find, Extramural, Intramural</td>
<td>Repurposed approved drug</td>
<td>Mid-stage</td>
</tr>
<tr>
<td>HIBM</td>
<td>Rare</td>
<td>Muscle</td>
<td>Biotech, Intramural</td>
<td>Intermediate replacement</td>
<td>Pre-IND</td>
</tr>
<tr>
<td>Sickle Cell Disease</td>
<td>Rare</td>
<td>Blood</td>
<td>Nonprofit, Intramural, Extramural</td>
<td>NME</td>
<td>Mid-stage</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>Rare</td>
<td>Cancer</td>
<td>Disease Find, Extramural</td>
<td>Repurposed approved drug</td>
<td>Pre-IND</td>
</tr>
</tbody>
</table>
NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

*Pilot Program Discoveries*

- Funding Collaborators
- Collaboration Agreements
- Intellectual Property
- Project Management
- Expert Advice: inside and outside
- Excitement and Anticipation
Filling the Gaps Between Discovery and Product

Partnerships and Collaborations
Therapeutic Development Pipeline

Molecular Libraries — TRND — Licensing Partners

- **Discovery**
  - 1 yr Assay development
  - 1 yr HTS
  - 1 yr Hit-to-Probe
  - 2 yrs Probe → Lead → Candidate

- **Development**
  - 2 yrs PK/PD
  - 2 yrs Non-GLP Tox
  - 2 yrs Formulation
  - 2 yrs GMP Manufacture

- **Clinical Trials**
  - IND-Enabling Studies and CMC
  - Clinical Translation Assessments
  - Ph I (Safety)
  - Ph II (Dose finding, initial efficacy in patient pop.)
  - Ph III (Efficacy and safety in large populations)

- **Regulatory Planning**
  - TOX
  - Clinical Trials

- **IND**
  - NDA filing

**Drug Target and Drug MOA Validation, Biology Efficacy, Off-Target Safety Testing in Animal Models**

**IND-Enabling Studies and CMC**

**Clinical Translation Assessments**

**Regulatory Planning**

**NDA filing**