Drug Discovery and Development at NIH for Rare and Neglected Diseases

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The Problem

Basic Research

Drugs

The Opportunity

Basic Research

Drugs
The best of times, the worst of times

How can we 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

**Pharmaceuticals available or in development:**
- Common diseases that affect developed world

**Human Genome**
- Neglected

**Human Diseases**
- Neglected
The Problem

• 7,000 diseases affect humankind
• Small fraction common enough to for commercial interest
• Two types of neglected diseases
  – Low prevalence
    • a.k.a., “rare”, “orphan”
    • 6000 different diseases
    • etiology can often be traced to mutations in the human genome
    • e.g., cystic fibrosis, SMA, sickle cell anemia…
  – High prevalence in developing world (might be “rare” in US)
    • Population cannot pay for medicine
    • Most are infectious diseases
    • e.g., schistosomiasis, leishmaniasis, trypanosomiasis…
The current drug development paradigm

Science

Discover “Achilles’ heel” to be targeted by drug
Develop “assay” to identify compounds that affect target
Use info about target and assays to identify “tool” compounds for the disease
Optimize compounds for activity against target and for pharmaceutical properties for testing in animals

Perform clinical testing to confirm that compounds that are safe and effective in humans
Phases: I II III
Obtain FDA approval for general use in humans

Investigational New Drug Application

Patients

Recruit patients for clinical trials, determine clinical endpoints
Clinical Trials: Steps in Making Drugs Available

Phase 1
- Short, small trial for safety and dosing; first time therapy is tested in humans, usually in healthy individuals, not CF

Phase 2
- Medium size and duration for safety, dosing and “proof of concept”: does drug candidate modulate the target?

“Pivotal” or “Registration”
- Largest, longest trials to generate primary data for FDA decision: is drug candidate safe and clinically effective?
Conventional roles of the public and private sectors in biopharma in drug development

**Public Sector Funded Basic Science**

- Indefinite
- Target identification
- 1 yr
- Assay development
- 1 yr
- Screening (HTS or otherwise)
- 1 yr
- Hit-to-Probe
- ~3 yrs
- Dedicated Chem-Biol Project Team formed

**Pharma and Biotech**

- ~3 yrs
- Compound accepted into Clinical Development
- 1 yr
- Lead Development, Optimization
- 1 yr
- Ph I
- 2 yrs
- Ph II
- ~3 yrs
- Ph III
- Clinical Trials

**FDA**

- 1.5 yrs
- Regulatory review
- Indefinite
- Ph IV-V (Additional indications, Safety monitoring)
Before the Molecular Libraries Initiative (MLI)

- Target identification: Indefinite
- Assay development: 1 yr
- Screening (HTS or otherwise): 1 yr
- Hit-to-Probe: 1 yr
- Lead Development, Optimization: ~3 yrs
- Compound accepted into Clinical Development: 1 yr
- Ph I Development, Optimization: 1 yr
- Ph II: 2 yrs
- Ph III: ~3 yrs
- Regulatory review: 1.5 yrs
- Ph IV-V (Additional indications, Safety monitoring): Indefinite

Dedicated Chem-Biol Project Team formed
MLI has expanded NIH research into early drug development

"venture philanthropy" from disease-focused foundations “de-risks” this process at early stages for hand off to pharma at later stages
How Can NIH Help....

- To increase drug discovery and development at this early stage where opportunity costs are high for industry?
  - By discovering novel drug candidates through HTS
  - By exploring re-purpose existing drugs
The NIH Chemical Genomics Center

- Founded as part of Roadmap
- 65 scientists
- Over 100 collaborations with investigators worldwide
  - 75% NIH extramural
  - 15% Foundations, Research Consortia, Pharma/Biotech
  - 10% NIH intramural
- Focus on novel targets, rare/neglected diseases
Setting the Stage at NIH for Drug Discovery and for Rare and Neglected Diseases

• NCGC Produces
  – *in vitro* tool compounds
  – new paradigms for assay development, screening, informatics, chemistry
  – Platform for screening FDA approved drugs

• NCGC sets the stage for
  – Discovery of novel drug candidates
    • Schistosomiasis as an example
  – Re-purposing approach for existing approved drugs
    • NPC and Chordoma as examples
Some of the rare/neglected diseases under study at NCGC

- Beta-thalassemia
- Charcot-Marie-Tooth
- Chordoma
- Gaucher disease
- Huntington’s disease
- Leishmaniasis
- Lymphangioleiomyomatosis
- Malaria
- Myotonic dystrophy
- Niemann-Pick C
- Progeria
- Hemolytic anemia
- Rare cancers
- Schistosomiasis
- Spinal muscular atrophy
Promising Results for Schistosomiasis

- Parasitic disease that affects 250 million people, mostly in Africa
- Dr. David Williams at Illinois State University
  - identified potential new target
  - worked together with NCGC to identify tool compounds as starting point for new drugs
Novel Compounds Identified for Further Development in Schistosomiasis

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

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\textbf{Ex vivo worm killing}

\textit{Livers of treated mice}
Sources of Approved Drugs for Repurposing

Status May 2009

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<tr>
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</tbody>
</table>

- Informatics sources for NPC
  - US FDA: Orange Book, OTC, NDC, Green Book, Drugs at FDA
  - Britain NHS
  - EMEA
  - Health Canada
  - Japan NHI

- Physical sources for NPC
  - Procurement from >20 suppliers worldwide
  - In-house purification of APIs from marketed forms
  - Synthesis
Seeking new therapeutics for chordoma (among approved drugs)

- Chordoma
  - embryonic remnants of notochord
  - Rare (1:1,000,000 prevalence)
  - Slowly growing, locally aggressive, radio/chemoresistant
- Project at NCGC
  - Chordoma Research Foundation
  - Expert group assembled by CRF/NCGC
  - Patient cell lines screened
- 2816 approved drugs screened
- Follow-up studies now in progress with chordoma expert group
  - Goal is testing of approved drugs in chordoma patients by end of 2009
  - May form the scientific basis for novel drug discovery
How can NIH help...

• To translate early findings from promising tool compounds or screening hits from approved drugs into drug candidates for clinical trials?
  – New program: Therapeutics for Rare and Neglected Diseases (TRND)
NIH News

NIH Announces New Program to Develop Therapeutics for Rare and Neglected Diseases

Bethesda, Md – Wed., May 20, 2009 – The National Institutes of Health is launching the first integrated, drug development pipeline to produce new treatments for rare and neglected diseases. The $7.5 million program jumpstarts a trans-NIH initiative called the Therapeutics for Rare and Neglected Diseases program, or TRND.

The program is unusual because TRND creates a drug development pipeline within the NIH and is specifically intended to stimulate research collaborations with academic scientists working on rare illnesses. The NIH Office of Rare Diseases Research (ORDR) will oversee the program, and TRND’s laboratory operations will be administered by the National Human Genome Research Institute (NHGRI), which also operates the NIH Chemical Genomics Center (NCGC), a principal collaborator in TRND. Other NIH components will also participate in the initiative.

A rare disease is one that affects fewer than 200,000 Americans. NIH estimates that, in total, more than 6,800 rare diseases affect more than 25 million Americans. However, effective pharmacological treatments exist for only about 200 of these illnesses. Many neglected diseases also lack treatments. Unlike rare diseases, however, neglected diseases may be quite common in some parts of the world, especially in developing countries where people cannot afford expensive treatments. Private companies seldom pursue new therapies for these types of illnesses because of high costs and failure rates and the low likelihood of recovering investments or making a profit.

"NIH is eager to begin the work to find solutions for millions of our fellow citizens faced with rare or neglected illnesses," said NIH Acting Director Raynard S. Kington, M.D., Ph.D. "The federal government may be the only institution that can take the financial risks needed to restart the development of treatments for these diseases, and NIH clearly has the scientific capability to do the work."

Developing Drugs

The drug development process is complicated and expensive. Studies suggest that it currently takes more than a dozen years and hundreds of millions of dollars to take a potential drug from discovery to the marketplace. And the failure rate is high.

"This initiative is really good news for patients with rare or neglected diseases," said ORDR Director Stephen C. Groft, Pharm.D. "While Congress has previously taken important steps to help these patients, such as providing incentives for drug companies under the Orphan Drug Act, this is the first time NIH is providing support for specific, preclinical research and product development known to be major barriers preventing potential therapeutics from entering into clinical trials for rare or neglected disorders. While we do not underestimate the difficulty of developing treatments for people with these illnesses, this program provides new hope to many people worldwide."

Typically, drug development begins when academic researchers studying the underlying cause of a disease discover a new molecular target or a chemical that may have a therapeutic effect. Too often, the process gets stuck at the point of discovery because few academic researchers can conduct all the types of studies needed to develop a new drug. If a pharmaceutical company with the resources to further the research does get involved, substantial preclinical work begins with efforts to optimize the chemistry of the potential drug. This involves an iterative series of chemical modifications and tests in progressively more complex systems - from cell cultures to animal tests - to refine the potential medicine for use in people. Only if these stages are successful can a potential treatment move to clinical trials in patients.

Unfortunately, the success rate in this preclinical process is low, with 80 to 90 percent of projects failing in the preclinical phase and never making it to clinical trials. And the costs are high: it takes 2 to 4 years of work and $10 million, on average, to move a potential medicine though this preclinical process. Drug developers colloquially call this the "Valley of Death."

TRND will work closely with disease-specific experts on selected projects, leveraging both the in-house scientific capabilities needed to carry out much of the preclinical development work, and contracting out other parts, as scientific opportunities dictate. Its strategies will be similar to approaches taken by pharmaceutical and biotechnology companies, but TRND will be working on diseases mostly ignored by the private companies. Importantly, TRND will also devote some of its efforts to improving the drug development process itself, creating new approaches to make it faster and less expensive.

If a compound does survive this preclinical stage, TRND will work to find a company willing to test the therapy in patients. There are several stages to the clinical trials process that can take several years before the safety and efficacy of a new drug is determined. FDA will only approve a drug for general use after it passes these trials. The clinical trials process is also expensive, but the failure rate is lower at this stage.

"NIH traditionally invests in basic research, which has produced important discoveries across a wide range of illnesses," said NHGRI Acting Director Alan E. Guttmacher, M.D. "Biotechnology and pharmaceutical companies have enormous strength and experience in drug development, but to maximize return-on-investment work primarily on common illnesses. TRND will develop promising treatments for rare diseases to the point that they are sufficiently "de-risked" for pharmaceutical companies, disease-oriented foundations, or others, to undertake the necessary clinical trials. NIH's goal is to get new medications to people currently without treatment, and thus without hope."
What is the Charge of the TRND Program?

**Basic Research**
- NCGC, Molecular Libraries Initiative

**TRND**
- Probe
- Lead
- Candidate
- PK/PD
- In vivo Tox
- Formulation
- GMP Manufacture
- Ph I (Safety)
- Ph II (Dose finding, initial efficacy in patient pop.)
- Ph III (Efficacy and safety in large populations)

**Biotech, Pharma**
- NIH Clinical Center
- CTSAs

**FDA**
- Ph IV-V (Additional indications, Safety monitoring)

**Indefinite**
- Target identification

**1 yr**
- Assay development
- HTS
- Hit-to-Probe

**2 yrs**
- Probe
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**1 yr**
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**~3 yrs**
- Ph III (Efficacy and safety in large populations)

**1 yr**
- Regulatory review

**Indefinite**
- Ph IV-V (Additional indications, Safety monitoring)
TRND: History

• June-July 2008: Dr. Zerhouni discusses possible new NIH initiative to develop therapies for rare and neglected diseases with members of congress

• July 2008: “jumpstart a rare and neglected diseases initiative” language in House and Senate FY09 budget report

• Oct-Nov 2008: 5-year budgets devised

• Jan 2009: Building 1 requests plan for $24M that would likely be in FY09 budget

• Mar 2009: Budget approved and Therapeutics for Rare and Neglected Disease (TRND) initiated
TRND

- Initial plan, assuming $24 M per year, is to work on approximately five projects per year
- The average project should take approximately three years
- Projects will be monitored closely for progress; those making insufficient headway will be culled quickly, to allow next project in pipeline to start as soon as possible
TRND: Governance

• Centered at Office Of Rare Diseases Research
  – To take advantage of ORDR’s inherently pan-IC nature and its long-standing relationships with the rare disease community
TRND

• Administration: NHGRI, NIH

• Scientific and clinical input
  – Trans-NIH Staff Advisory Group
    • Members nominated by ICs from among their staffs
  – Expert External Panel
  – Individuals with focus on rare and neglected diseases

• In the planning Stages
  – Staff
  – Facilities
New Opportunities to Make a Difference for Individuals with Rare & Neglected Diseases

• The majority of diseases that affect humans are not being addressed
• Efficient and effective 21\textsuperscript{st} century drug development cannot be done using the current 20\textsuperscript{th} century model
• Unprecedented opportunity to develop new therapeutics to improve human health