DISTRIBUTED DRUG DISCOVERY FOR NEGLECTED TROPICAL DISEASES.

TRANSLATING PHARMA APPROACHES TO AN ACADEMIC ENVIRONMENT.
### Neglected diseases

**An abysmal pipeline**

<table>
<thead>
<tr>
<th>Disease</th>
<th>DALY¹ (millions)</th>
<th>Infectious Agent Class</th>
<th>Disease</th>
<th>New Drug needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>34.7</td>
<td>Protozoan</td>
<td>Malaria</td>
<td>✓</td>
</tr>
<tr>
<td>Malaria</td>
<td>34.6</td>
<td></td>
<td>African trypanosomiasis</td>
<td>✓</td>
</tr>
<tr>
<td>Lung cancer³</td>
<td>11.2</td>
<td></td>
<td>Viceral leishmaniasis</td>
<td>✓</td>
</tr>
<tr>
<td>Leishmaniasis</td>
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<td>Chagas disease</td>
<td>✓</td>
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<tr>
<td>Schistosomiasis</td>
<td>2.1</td>
<td></td>
<td>Nemotode</td>
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<tr>
<td>Prostate cancer³</td>
<td>1.6</td>
<td>Bacterial</td>
<td>Schistosomiasis</td>
<td>✓</td>
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<tr>
<td>African trypanosomiasis</td>
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<td>Lymphatic filariasis</td>
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<tr>
<td>Chagas disease</td>
<td>0.7</td>
<td>Bacterial</td>
<td>River blindness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dracunculiasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bacterial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Leprosy</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trachoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Buruli ulcer</td>
<td>✓</td>
</tr>
</tbody>
</table>

1. DALY = Disability-adjusted life years (years of healthy life lost) from WHO Global Burden of Disease 2004 Update
2. PCD = Preclinical Development
3. Candidate numbers for cancers only include projects with lung or prostate as primary indication.
Neglected diseases

• 10/90 disequilibrium in health research spending
• 1975-1999: 1,393 new chemical entities marketed
  – 68.7% registered products represented incremental improvement
  – 13 (1%) registered products for parasitic diseases
• The historical “Blockbuster model” in pharma doesn’t apply to diseases typically found in poor regions.
  – Unique niche for not-for-profit and academic drug discovery efforts

Trouiller et al 2002 Lancet 359:2188-2194
Neglected diseases

Undermine global health and well-being

• Contribute to extreme poverty and hunger.
• Impede universal primary education.
• Impede gender equality and empower women.
• Major cause of child mortality.
• Diminish maternal health.
• Complicate HIV/AIDS, malaria, & other diseases.
• Impede environmental sustainability.
• Impede beneficial development

Repurposing drug discovery

*Parachute drug discovery*

- Identify parasite targets homologous to human targets
- Bias for human targets with historical drug discovery pursuits
- Evaluate compounds selective for these human targets against parasite
- Optimize for potency at parasite target versus human target
Advantages of repurposing

• Known to be “druggable” targets
  – Fewer dry holes, potentially more productive discovery efforts
• Lead matter available without HTS
  – Cost: At $0.03 per well, a single point HTS on 1MM compounds in triplicate costs about $90k in supplies alone
  – Consider radio/chemical/consumable waste required for HTS
• A great deal of data can be repurposed
  – Structural biology (enables homology modeling)
  – Structure-activity relationships
• Potential to engage development collaborations

In sum...repurposing should be faster and cheaper.
Industrial drug discovery

An expensive process

• Resource-intensive:
  – Average of 8 med/synth chemists per project for pursuit of multiple chemotypes
  – Pharmacologists (in vitro, in vivo)
  – Scale-up & formulation chemists
  – Toxicologists

• Expensive
  – $10-20 million USD per project
  – $2-4 million per year in preclinical lead optimization

• Frequent failure
  – < 0.1% of hits can be optimized into drugs

Conventional versus repurposing

**Timeline comparison**

**Standard paradigm**

- Target ID
- Target Validation
- Assay Development
- Compd Screen
- Compd Optimization
- Clinical Trials

- 2 years
- 6-8 mo
- 4-5 years
- 6-8 years

**Repurposing paradigm**

- Target ID
- Target Validation
- Assay adaptation
- Compound ID
- Compound Optimiz.
- Clinical Trials

- <1 year
- 3 mo
- 3-4 years
- 4-5 years

**Staffing and timeline requirements reduced by repurposing**

- **Assays**
  - Can apply parasite growth assays directly
  - Assay protocols can often be readily adapted

- **Medicinal chemistry**
  - Chemotype behavior well understood for rapid evolution (SAR, solubility, toxicity, etc)
  - Homology models can be based on established crystal structures

Proof-of concept for repurposing HIV protease

- Repositioned from renin and other aspartyl proteases
  - 1985 HIV genome sequenced
  - 1988 Protease validated as target
  - 1990 first clinical candidates (and eventual drugs)

Some more recent examples in NTDs:
- N-myristoyl transferase inhibitors for sleeping sickness: Nature 2010 464, 728-732 (Dundee University: led by Paul Wyatt)
Typical project workflow

Goal: identify targets and pathways that can be repurposed, not just for one parasite, but for multiple pathogens
Iterative optimization process

**Design**
- Propose next question to test hypothesis

**Synthesis**
- Prepare, purify & characterize analog

**Screening**
- Potency/selectivity
- Efficacy
- Physical property/ADME

**Analysis**
- Form versus function
- Computational experiments
- Inform next design step
Multidisciplinary research

A change in the tide

• Drug discovery is, by definition, multidisciplinary.
• Such efforts are only recently being embraced by the academic world.
  – Multi-PI Proposals to NIH established in 2006, but still frequently perceived as a complication to review
  – Independent investigators rewarded with tenure and large grants for “soup-to-nuts” drug discovery
The stereotypical academic model

- **Advantages**
  - Independence
  - High level of recognition upon success

- **Disadvantages**
  - Difficult to have sufficient expertise in all areas
  - Difficult to broadly explore each area (resource limiting)
  - Top-level decision making (by PI) may miss opportunities

All in one lab
A typical industrial model

- **Advantages**
  - Team approach brings high levels of expertise to each aspect
  - Project workload is scalable and flexible
  - Common goal is clear and singular.

- **Disadvantages**
  - Projects often involve groups in broad, discipline-based org charts
  - Success depends on appropriate skills all being under this one roof.

\[
\begin{align*}
\text{Chemistry} & \quad \text{Comp Chem} \\
\text{Group 1} & \quad \text{Group 2} \\
\text{Biology (target)} & \quad \text{Biology (screening)} \\
\text{Group 3} & \quad \\
\text{Biology (in vivo)} & \quad \text{Toxicology} \\
\text{Group 4} & \quad \text{Group 5} \\
\end{align*}
\]
The distributed model

- **Advantages**
  - Each group within the team selected for specific knowledge
  - Network is expanded far beyond project team.
  - Other opportunities for cross-fertilization become apparent

- **Disadvantages**
  - Project logistics complicated (data, compound, IP)
  - Priorities within different groups may vary
The distributed model in action

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Target</th>
<th>Molecular Modeling</th>
<th>Target Biology</th>
<th>Parasite Biology</th>
<th>Animal Models</th>
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</table>
Trypanosomial phosphodiesterase inhibitors

REPURPOsing CASE STUDY
Outreach components

*Proselytizing the “distributed” model*

**Consulting**
- Advice in target prioritization
- Suggestions for project next steps (hit-to-lead, lead optimiz.)

**Synthesis**
- “Excess capacity” directed to support killer experiments to achieve target validation and proof-of-concept

**Collaboration**
- Develop programs and proposals for pursuit of new pathogen targets

**Products**
- Enhanced early stage pipeline for NTDs
- New collaborations
- New proposal opportunities
- Joint publications

This is all ongoing at Northeastern University and we’re looking to:
- *Create a consortium of NTD-focused med chemists who are interested in the model,*
- *Attract funding to support these “enabling” efforts.*
Summary

• Target repurposing is a proven approach to streamline drug discovery

• Neglected disease drug discovery is particularly sensitive to speed (ie cost).

• A distributed model of drug discovery has advantages that can further enhance programs

• Further innovation is needed to find the best model(s) for seeding early-stage collaborations
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