Overview of Anticipated Drug Discovery Pipeline for Clinical Development

CRITICAL PATH TO TB DRUG REGIMENS
2016 WORKSHOP
April 5th, 2016

Nader Fotouhi, PhD
TB Alliance
The burden of tuberculosis

• TB is the world’s second-leading infectious killer, disproportionately affecting developing countries:
  • 1.3 million deaths in 2012
  • 8.6 million new infections in 2012
  • 450 thousand drug-resistant TB cases in 2012

• First-line therapies for TB are antiquated and inadequate, taking six months to cure patients

The current six-month regimen contributes to high treatment default rates that can lead to increased transmission, drug resistance, and death

The world needs a shorter, safer, universal TB drug regimen
Evolution of TB Therapy – From Drugs to Regimens

1946 – First randomized trial: S Monotherapy led to S resistance

1952 – First regimen: S/PAS/H 24 months of therapy

1960s – PAS replaced by E: S/H/E 18 months of therapy

1970s – Addition of R: S/H/R/E 9-12 months of therapy

1980s – S replaced by Z: H/R/Z/E 6-8 months, oral therapy

Discovery of TB Drugs

1943 Streptomycin (S)
1948 PAS
1952 Isoniazid (H)
1954 Pyrazinamide (Z)
1955 Cycloserine
1957 Kanamycin
1960 Ethionamide
1961 Ethambutol (E)
1963 Capreomycin
1963 Rifampicin (R)
1968 Bedaquiline
2014 Delaminid

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Over the last few decades

Limited investment in TB biology and drug discovery

Lack of understanding of how to improve therapy

- Few well validated targets
- Safety of newer drugs limit use

Poor assays to screen for drugs

- Resistance to only true sterilizing and treatment shortening agent

Limited Candidates
What should we focus on?

Need to create a balanced portfolio

- Novel mechanisms
- Sequestered sites (granulomas, cavities)
- Tolerant sub-populations
- Safety
- Resistance

To generate multiple, mechanistically distinct TB candidates sufficient to advance a drug regimen to a one month clinical POC
What has happened over the last decade

• Some Pharmaceutical companies exiting the TB field
  – However, key assets not lost

• Significant investment of resources

• Significant enhancement in academic research and progress
  – New targets and chemotypes

• Enhancement and prioritization of the PDP portfolio

• Creation of the TBDA (TB Drug Accelerator)
TB Drug Accelerator launched in 2012 to accelerate the discovery of new drugs.

Comprises Pharma companies, PDP, and Research Institutes.

Work within a ‘cooperation and sharing’ agreement, pooling resources and data.

Novel phenotypic screening approach.
TBDA Membership and Capabilities

**Disease**
- Veronique Dartois
- Tanya Parish
- Kyu Rhee
- Carl Nathan
- Dirk Schnappinger
- Jim Sacchettini

**Animal Models**
- NIH
- GlaxoSmithKline

**Screening Capabilities**
- NIH
- IDRI
- Calibr

**Target ID MOA**
- Rutgers Biomedical and Health Sciences
- IDRI

**Chemical Matter Drug Hunting Expertise**
- AstraZeneca
- Eisai
- MSD Be well
- Calibr
- Lilly
- AbbVie
- SANOFI
- TB Alliance

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More predictive in vitro Phenotypic screens

Precise environmental conditions?
Replication status of the organism?
Target vulnerability?

Screen under conditions that mimic host, e.g.
- Vary carbon source
- Hypoxia
- NO

Each column is one compound

Blue: inactive  Red: Active

C. Barry, NIH
TBDA High throughput screening

- Screening libraries include...
  - Pharmaceutical company compounds
  - Compounds collected by research institutes
  - Fragments, purified natural products

- Statistics
  - Approximately 2.9M distinct compounds screened
  - Hit rates typically in the 0.5% to 2% range

- 200 Series (3,400 hits) disclosed within TBDA since April 2012

<table>
<thead>
<tr>
<th>Screening Conditions</th>
<th>Approximate Number of Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replicating Glucose</td>
<td>1,929,800</td>
</tr>
<tr>
<td>Replicating Cholesterol (± DPPC)</td>
<td>1,230,000</td>
</tr>
<tr>
<td>Replicating Butyrate (± DPPC)</td>
<td>761,800</td>
</tr>
<tr>
<td>Slow Replicating, Low pH (+ Nitrite)</td>
<td>1,842,704</td>
</tr>
<tr>
<td>Other (WC Targeted, Permeability)</td>
<td>240,000</td>
</tr>
</tbody>
</table>
Generation of high quality Drug candidates

- World class TB biology assessment
- Hit to lead (Pharma quality)
- Optimization (Pharma Quality)

Company Compound Libraries

State of the art chemistry evaluation

TB in vivo models

2018
- new preclinical candidates

2024
- 1 month, 3-drug regimen POC

2018
- 1 month, 3-drug regimen POC
CHEMISTRY AND BIOLOGY – PROFILING OF HIT COMPOUNDS

Initial Hit Profiling

- MIC
  Inc. Host relevant conditions
- Cytotoxicity
- In-vitro ADME
- Physicochemical Properties

Mechanistic studies

- Cell wall reporter assays
- Respiratory mutants
- Knockdown mutants
- Resistant mutants

Transcriptional profiling
Macromolecular incorporation
Metabolomics

In vivo Evaluation

- Pharmacokinetics
- Lesion penetration
- In vivo model mouse
- In vivo model Marmoset

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Target identification & validation

Macromolecular Incorporation
(Effect of compound on DNA, RNA, cell wall...)

Macromolecular Incorporation
(Effect of compound on DNA, RNA, cell wall...)

Metabolomics
Resistant mutant profiling
Transcriptional profiling
Chemical proteomics

MIC heat mapping
(chemo-genomic profiling)

ATP Synthase Knockdown (KD)

Isoniazid
DCCD
Nigericin
Rotenone
Bedaquiline

PI: Clif Barry, NIH
PI: Dirk Schnappinger, Cornell Weill

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Drug penetration: from lesion to caseum to bacteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>cLogP</th>
<th>PI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>-0.7</td>
<td>Veronique Dartois, Rutgers</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>&gt;7</td>
<td>Kyu Rhee, Cornell Weill</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>&gt;7</td>
<td></td>
</tr>
</tbody>
</table>

- Pyrazinamide: cLogP = -0.7
- Clofazimine: cLogP > 7
- Bedaquiline: cLogP > 7

Acid-fast bacteria are challenging to treat due to their protective capsule and thick cell wall. Here, we explore the drug penetration into the bacterial cell and into the caseum.

- Capsule (10-20 nm)
- Mycomembrane (8.3 nm)
- Periplasmic space (20 nm)
- Arabinogalactan
- Peptidoglycan
- Plasma membrane (7 nm)
- Cytoplasm

Drug delivery is crucial for effective treatment. Understanding drug penetration is essential for developing new therapies.

- Ethambutol

Ethambutol is an important drug in treating tuberculosis, but its penetration into the bacterial cell remains a challenge.

PI: Veronique Dartois, Rutgers
PI: Kyu Rhee, Cornell Weill

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Distribution of Targets Identified From Screening

- Intensive ongoing studies to elucidate unknown mechanisms
- Supplementing phenotypic hits with target based screens
TB Drug Accelerator – Lessons learned

Strengths
• Expertise – Academia and Pharma
• Unprecedented access to chemical diversity
• Pooled scientific capabilities and platforms
• Leveraged resources

Challenges
• Complex disease – many have failed
• Organizational complexity

Actions
• Create focused, integrated drug discovery teams
• Increase MOA and biology understanding
• Enhance animal models and capacity
## Discovery Portfolio – Preclinical Development

### PRECLINICAL DEVELOPMENT

<table>
<thead>
<tr>
<th>Project</th>
<th>Developer(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azaindoles DprE1 inhibitor</td>
<td>TB Alliance/TBDA</td>
</tr>
<tr>
<td>LeuRS</td>
<td>GSK/Anacor</td>
</tr>
<tr>
<td>BTZ-043</td>
<td>DZIF/LMU/HKI</td>
</tr>
</tbody>
</table>
# Discovery Portfolio – Lead Optimization

## LEAD OPTIMIZATION

<table>
<thead>
<tr>
<th>Compound Type</th>
<th>Description</th>
<th>Source(s)</th>
</tr>
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<tbody>
<tr>
<td>DARQ ATP synthase</td>
<td>(GATB/janssen/AUC/TBDA)</td>
<td>beta lactam (WCMC(TBRU)/UNC)</td>
</tr>
<tr>
<td>Oxazolidinone</td>
<td>(GATB/IMM/TBDA)</td>
<td></td>
</tr>
<tr>
<td>InhA Inhibitor</td>
<td>(GATB, GSK/TBDA)</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>(GATB/Sanofi/TBDA)</td>
<td></td>
</tr>
<tr>
<td>Ureas Mmpl3</td>
<td>(GATB/Sanofi/TBDA)</td>
<td></td>
</tr>
<tr>
<td>Cyclopeptide</td>
<td>(GATB/Sanofi)</td>
<td></td>
</tr>
<tr>
<td>Mmpl3 Indole carboxamide</td>
<td>(GATB/TBDA)</td>
<td></td>
</tr>
<tr>
<td>Pyrimidines DprE1</td>
<td>(GATB/GSK/TBDA)</td>
<td></td>
</tr>
<tr>
<td>Aryl Sulfonamides</td>
<td>(GATB/GSK/TBDA)</td>
<td></td>
</tr>
<tr>
<td>DprE1 Inhibitor</td>
<td>(Calibr/TBDA)</td>
<td></td>
</tr>
<tr>
<td>PKS13</td>
<td>(GATB/DDU/TAMU/GSK/TBDA)</td>
<td></td>
</tr>
<tr>
<td>Squaramides</td>
<td>(GATB/TBDA)</td>
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<tr>
<td>SQ609</td>
<td>(Sequella)</td>
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<tr>
<td>Spectinamide</td>
<td>(St. Jude/U Tenn/CSU/UZ/Microbiotix)</td>
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<td>CPZEN-45</td>
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<tr>
<td>LO program</td>
<td>(TBDA)</td>
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<tr>
<td>Clp</td>
<td>(SPRINT TB/ A*Star)</td>
<td></td>
</tr>
<tr>
<td>Ru(II)phosphine picolinate complex</td>
<td></td>
<td></td>
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<tr>
<td>TBI-166</td>
<td>(IMM)</td>
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</tbody>
</table>

Novel Target known Pathway

Unknown

Address Safety of known drug class

Address resistance against known target

Novel Pathway

Known target

Novel environment

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## Discovery Portfolio – Lead Identification

### LEAD IDENTIFICATION

<table>
<thead>
<tr>
<th>Project</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>RNA Polymerase (GATB/Rutgers U/TBDA)</td>
<td>Hit ID Program (GATB/OpBio)</td>
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<tr>
<td>POA Prodrugs TB Alliance/Yonsei</td>
<td>Hit ID Program (GATB/Mitsubishi-Tanabe)</td>
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<tr>
<td>ClpC/P1P2 (GATB)</td>
<td>Hit ID Program (GATB/Sumitomo)</td>
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<tr>
<td>PEPCK (GATB/ Roche/TAMU)</td>
<td>Hit to Lead (TBDA)</td>
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<tr>
<td>Hit to Lead (TBDA)</td>
<td>Hit to Lead (TBDA)</td>
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<tr>
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<td>Hit to Lead (TBDA)</td>
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<td>Proteasome (WCMC(TBRU)/GATB/TDI)</td>
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<tr>
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<tr>
<td>Hit to Lead (TBDA)</td>
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<tr>
<td>Energy Metabolism Inh. (GATB/Upenn/TBDA)</td>
<td>Hit to Lead (TBDA)</td>
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<td>Hit to Lead (TBDA)</td>
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<tr>
<td>Hit to Lead (TBDA)</td>
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<td>Procatase (WCMI(TBRU)/GATB/TDI)</td>
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<tr>
<td>Hit to Lead (TBDA)</td>
<td>Hit to Lead (TBDA)</td>
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<tr>
<td>Hit-to-Lead Program (GATB/Sanofi/TBDA)</td>
<td>Hit to Lead (TBDA)</td>
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<tr>
<td>Hit-to-Lead Program (GATB/GSK/TBDA)</td>
<td>Hit to Lead (TBDA)</td>
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<td>Hit to Lead (GATB/Daiichi Sankyo)</td>
<td>Hit to Lead (TBDA)</td>
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<td>Hit to Lead (GATB/Shionogi)</td>
<td>Hit to Lead (TBDA)</td>
</tr>
<tr>
<td>Hit ID Program (GATB/Takeda)</td>
<td>Hit to Lead (TBDA)</td>
</tr>
</tbody>
</table>

### Projects in Formal Hit Assessment

- 18 Projects in Formal Hit Assessment

### Target and Pathway Classification

- **Novel Target known Pathway**
- **Unknown**
- **Address Safety of known drug class**
- **Address resistance against known target**
- **Novel Pathway**
- **Known target**
- **Different state**
# Discovery Portfolio – Preclinical Development

<table>
<thead>
<tr>
<th>LEAD IDENTIFICATION</th>
<th>LEAD OPTIMIZATION</th>
<th>PRECLINICAL DEVELOPMENT</th>
</tr>
</thead>
</table>

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• There is an urgency to progress more NMEs into preclinical development and clinical trials

• The early portfolio is rich and has the ability to deliver over the next 5 years

• The global Discovery Portfolio needs to be carefully managed and prioritized to ensure success