TB Alliance Drug Discovery and Development: Harnessing Global Resources to Address a Global Disease

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TB Pandemic

Tuberculosis is one of the leading global killers

• TB kills 1 person nearly every 25 seconds
  – 1.4 million deaths each year
• Nearly 9 million new cases annually
• Leading killer of people with AIDS
• 3rd leading cause of death among women ages 15-44
• TB is a leading cause of death among children worldwide
  – Children are susceptible to the most severe and fatal forms of the disease
Global TB Pandemic

- 12 million active TB cases; 650,000 MDR-TB
- 98% of TB deaths occur in the developing world
- India and China have the highest TB burdens
- Africa has highest rates of TB, TB/HIV and death
- Europe has the highest rates of MDR/XDR-TB
Though TB cases are disproportionately clustered in the developing world, TB is transmitted through the air.

One need not “fail” TB treatment to develop MDR-TB/XDR-TB – it can be transmitted directly.

It routinely takes several years and millions of dollars to cure XDR-TB in the US.
Current TB Therapy and Unmet Needs

<table>
<thead>
<tr>
<th>Current Therapy</th>
<th>Unmet Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Sensitive TB</td>
<td>4 drugs taken for 6 or more months</td>
</tr>
<tr>
<td>M(XDR)-TB</td>
<td>Injections and drugs taken for more than 2 years, poorly tolerated</td>
</tr>
<tr>
<td>TB/HIV co-infection</td>
<td>Drug-drug interactions with ARVs</td>
</tr>
<tr>
<td>Latent TB Infection</td>
<td>9 months of isoniazid</td>
</tr>
<tr>
<td>Pediatric TB</td>
<td>No adequate dosing formulations</td>
</tr>
</tbody>
</table>

Rapid, accurate, affordable point of care diagnostic

TB Alliance discovery/development programs seek to help all TB patient populations
About TB Alliance

Catalyzing and advancing new TB cures

- Founded in 2000 as a not-for-profit product development partnership (PDP) dedicated to discovering and developing better, faster TB drugs for all in need

- Offices in New York, USA; Pretoria, South Africa; Brussels, Belgium (total staff: 48)

- Developing new TB drugs—and redefining the way TB drugs are developed
  - Virtual business model promotes innovation and efficient, rapid progress
  - Leverage global pipeline of drugs to find the most promising TB regimens
  - Transform TB treatment with new regimens that treat drug-sensitive and drug-resistant TB
  - Ensure beneficial new TB regimens are quickly and widely adopted

- Largest TB drug pipeline in history
A Global Network of Partners
Leveraging the best science from around the world
TB Alliance Vision

- Shorter, simpler regimens
- No pre-existing drug resistance ("universal")
- Success requires novel drug combinations
### Discovery

<table>
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<tr>
<th>Lead Identification</th>
<th>Lead Optimization</th>
<th>Preclinical Development</th>
<th>Phase 1</th>
<th>Phase 2A</th>
<th>Phase 2B</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
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<tbody>
<tr>
<td>ATP Synthesis Inhibitors</td>
<td>Calibr</td>
<td>Macrolides Sanofi</td>
<td>Preclinical TB Regimen Development JHU</td>
<td>TBA-354</td>
<td>Linezolid Dose-Ranging Study</td>
<td>Pretomanid/Bedaquiline/Pyrazinamide (BPaZ)</td>
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### Early Development

- DprE1 Inhibitors
- Ureas Sanofi
- Diarylquinolines Janssen/University of Auckland/UIC
- InhA Inhibitors
- Cyclopeptides Sanofi
- Oxazolidinones IMM
- Squaramides
- Pyrimidines GSK
- PKS-13 Dundee/TAMU
- Indazoles GSK

### Late Development

- NC-005
- NC-005
- STAND
- Pretomanid/Moxifloxacin/Pyrazinamide (PaMZ)
- Pretomanid/Moxifloxacin
- Pretomanid/Moxifloxacin/L线扎腺
- Pretomanid/Moxifloxacin/L线扎腺

### TB Alliance R&D Partners:

- AstraZeneca
- Beijing Tuberculosis and Thoracic Tumor Research Institute (BTTRI)
- Calibr
- Cornell University
- Daiichi Sankyo
- GlaxoSmithKline (GSK)
- Institute of Materia Medica (IMM)
- IMPAACT
- Janssen [Johnson & Johnson]
- Johns Hopkins University (JHU)
- Medical Research Council (MRC) at UCL (US) National Institutes of Health (NIH)
- OP-BIO
- Roche Pharmaceuticals
- Rutgers University
- Sanofi
- Schrödinger
- Shionogi
- Stellenbosch University
- Takeda Pharmaceuticals
- Takeda Pharmaceuticals
- Texas A&M University (TAMU)
- University College London (UCL)
- University of Auckland
- University of Dundee (Dundee)
- University of Illinois at Chicago (UIC)
- University of Pennsylvania School of Medicine (UPenn)
- Yonsei University
1,4-azaindoles: novel, non-covalent inhibitors of DprE1

Target: DprE1 subunit of Decaprenylphosphoryl-β-D-ribose 2’-epimerase

- DPA - only known donor of D-arabinose in bacteria
- DprE1 involved in DPA synthesis
- Essential gene in *M. tuberculosis:

Kolly et. al., *Mol Microbiology*, 2014, 92, 194-211


**BTZ043**

DPR : decaprenylphosphoryl-β-D-ribose
DPA : decaprenylphosphoryl-β-D-arabinose

arabinogalactan
lipoarabinomannan


**Compound 1**
(TBA-7371)

**DPR**

**DPA**

**DPX**

**DprE1**

**DprE2**

FAD  FADH₂  NADH  NAD⁺
1,4-azaindole: Potential Drug Candidate for Treatment of Tuberculosis


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<td><strong>Compound 1</strong></td>
<td><strong>Compound 2</strong></td>
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<td>TBA-7371</td>
<td>TBA-8140</td>
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<th><strong>Parameter</strong></th>
<th><strong>Value</strong></th>
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<tr>
<td><em>Mtb</em> DprE1 IC$_{50}$ (nM)</td>
<td>10.2</td>
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<tr>
<td><em>Mtb</em> MIC (µM)</td>
<td>0.78-3.12</td>
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<tr>
<td><em>Mtb</em> MBC (µM)</td>
<td>1.56</td>
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<tr>
<td><em>Mtb</em> LORA (µM)</td>
<td>≥32</td>
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<tr>
<td>Drug sensitive clinical isolates MIC (µM)</td>
<td>0.4-6.25</td>
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<tr>
<td>INH$^R$, RIF$^R$ clinical isolates (µM)</td>
<td>0.78-3.12</td>
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<tr>
<td><em>Mtb</em> DprE1 over-expression strain MIC (µM)</td>
<td>50-200</td>
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<tr>
<td><em>Mtb</em> DprE1 C387S/G (BTZ043$^R$) MIC (µM)</td>
<td>0.78-1.56</td>
</tr>
<tr>
<td>Intracellular THP1 (log$_{10}$CFU reduction)</td>
<td>~1.5</td>
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<tr>
<td>Cytotoxicity (µM) THP-1</td>
<td>&gt;100</td>
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<tr>
<td>Ames</td>
<td>Negative</td>
</tr>
<tr>
<td>hERG IC$_{50}$ (µM)</td>
<td>&gt;33</td>
</tr>
<tr>
<td>PDE6 IC$_{50}$ (µM)</td>
<td>4 (only sec. pharm. hit)</td>
</tr>
</tbody>
</table>
TBA-7371 demonstrates dose-responsive bactericidal efficacy in mice

- Estimated MED: 100 mg/kg with AUC$_{0-24h}$ in mice = ~30 h*ug/mL (25-40 h*ug/mL)

Low dose aerosol model of acute infection
Erdman, BALB/c mice, 3 wks Rx

High dose aerosol model of acute infection
H37Rv, BALB/c mice, 4 wks Rx
**TBA-7371** demonstrates a substantial safety margin in rats, and reasonable projected human dose

Non-GLP 14 day rat toxicity/TK study: 100, 300, and 1000 mpk:

- NOAEL in Rats (14 day): \(\geq 1000\) mg/kg; \(\text{AUC}_{0-24h} = \frac{643}{1163}\) hr\(\times\)ug/mL (M/F)
- MED in Mice: \(100\) mg/kg; \(\text{AUC}_{0-24h} = \sim 30\) h\(\times\)ug/mL
- Safety margin: \(~21/39X\) (M/F)

Projected preliminary efficacious human dose: \(~500\) mg QD

Initiated 14 day dog non-GLP safety study

- Data expected mid-May, 2016
### Discovery

- **Lead Identification**
  - ATP Synthesis Inhibitors: Calibr
  - Whole-Cell Hit-to-Lead Program: Sanofi
  - RNA Polymerase Inhibitors: Rutgers University
  - Whole-Cell Hit-to-Lead Program: GSK
  - Energy Metabolism Inhibitors: Unv. Auckland
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- **Lead Optimization**
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  - Ureas: Sanofi
  - Diarylquinolines: Janssen/University of Auckland/UIC
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  - MmpL3 Inhibitors: Rutgers University
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  - Squaramides: IMM
  - Pyrimidines: GSK
  - PKS-13: Dundee/TAMU
  - Indazoles: GSK

### Early Development

- **Preclinical Development**
  - Preclinical TB Regimen Development: JHU

- **Phase 1**
  - TBA-354

- **Phase 2A**
  - Pharmacokinetics of first-line drugs in children < 5kg
  - Stellenbosch University

- **Phase 2B**
  - Pretomanid/
  - Bedaquiline/
  - Pyrazinamide (BPaz)

- **Phase 3**
  - NC-005
  - Pretomanid/
  - Bedaquiline/
  - Linezolid
  - STAND
  - Pretomanid/
  - Moxifloxacin/
  - Pyrazinamide (PaMZ)
  - Pretomanid/
  - Bedaquiline/
  - Linezolid

### Late Development

- **Optimized Pediatric Formulations**
  - Ethambutol/Rifampicin/Pyrazinamide for children > 5kg
  - Ethambutol for children > 5kg
  - Isoniazid for children > 5kg
  - Pyrazinamide for children > 5kg

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Takeda Pharmaceuticals
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TB Drug Accelerator (TBDA)
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University College London (UCL)
University of Auckland
University of Dundee (Dundee)
University of Illinois at Chicago (UIC)
University of Pennsylvania School of Medicine (UPenn)
Yonsei University
Accelerating Progress: From Drugs to Regimens

TB Alliance is searching for the best combinations of novel drugs

- TB must be treated with multi-drug combinations to prevent the development of resistance
- Today’s pipeline of TB drugs can be tested together, speeding development of novel TB regimens and reducing R&D from decades to years

Combination approach reduces time to market by 75%
TB Drug/Regimen

Discovery and Development Process

Discovery

Drug Candidate Pool

Single Compound Preclinical Development → Phase I → EBA

Phase II → Phase III

Regimen Identification in Mice

Regimen Identification in Mice

Identification of New Drug Candidates

Selection of Potential New Regimens

Compounds:
- Compound 1
- Compound 2
- Compound 3
- Compound 4
- Compound 5

Regimens:
- Regimen A
- Regimen B
- Regimen C
Treatment (44-90 days) d1
3 mice
Day 0
M1
M2
M3
M4
M5
(15) mice held for (3) months without treatment and then sacrificed to determine permanent cure without relapse

(15) mice held for (3) months without treatment and then sacrificed to determine permanent cure without relapse

Scheme for Relapse Experiments
<table>
<thead>
<tr>
<th></th>
<th>Mean lung CFU count (proportion of mice relapsing)</th>
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<tbody>
<tr>
<td></td>
<td>D-17</td>
<td>D0</td>
<td>M1</td>
<td>M1.5 (+3)</td>
<td>M2 (+3)</td>
<td>M3 (+3)</td>
<td>M4 (+3)</td>
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<tr>
<td>RHZ</td>
<td>4.16±0.24</td>
<td>2.47±0.26</td>
<td>(10/15)</td>
<td>(2/15)</td>
<td></td>
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<tr>
<td>PaMZ</td>
<td>3.50±0.06</td>
<td>1.39±0.54</td>
<td>(10/14)</td>
<td>(3/15)</td>
<td></td>
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<tr>
<td>JPaM</td>
<td>3.61±0.15</td>
<td>2.33±0.18</td>
<td>(2/15)</td>
<td>(0/14)</td>
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<tr>
<td>JPaZ</td>
<td>1.71±0.11</td>
<td>(13/14)</td>
<td>(0/15)</td>
<td>(0/15)</td>
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<tr>
<td>JPaZM</td>
<td>1.74±0.03</td>
<td>(3/15)</td>
<td>(0/15)</td>
<td>(0/15)</td>
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<tr>
<td>JPaZ</td>
<td>2.89±0.35</td>
<td>(9/15)</td>
<td>(1/15)</td>
<td></td>
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<tr>
<td>1JPaZL100/1JPaZ</td>
<td>0.07*</td>
<td>(0/15)</td>
<td>(0/15)</td>
<td></td>
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<tr>
<td>2JPaZL100</td>
<td></td>
<td>(0/15)</td>
<td>(1/15)</td>
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<tr>
<td>JPa</td>
<td>4.48±0.20</td>
<td>2.34±0.34</td>
<td>(3/14)</td>
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<tr>
<td>JPaU</td>
<td>1.88±0.22</td>
<td>(1/14)</td>
<td>(0/14)</td>
<td></td>
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<tr>
<td>3JPaL100</td>
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<td>(0/15)</td>
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<tr>
<td>2JPaL100/1JPaL50</td>
<td></td>
<td></td>
<td></td>
<td>(1/12)</td>
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<tr>
<td>2JPaL100/1JPa</td>
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<td>(6/15)</td>
<td>(0/15)</td>
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<tr>
<td>1JPaL100/2JPa</td>
<td>2.45±0.16</td>
<td>(9/15)</td>
<td>(0/15)</td>
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- Bedaquiline (J) reduces the relapse rate of PaMZ by a factor of at least 2 months
- JPaZL is **4.5 months better** than the standard of care, RHZ (M6, data not shown)
- Addition of L (linezolid) to JPaZ for only 4 or 6 weeks significantly reduces the relapse rate of JPaZ
- JPa(pretomanid)L: currently in NiX Phase 2B XDR TB clinical trial
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<th>Late Development</th>
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<td>Oxazolidinones</td>
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**Phase 1**
- Pretomanid/Bedaquiline/Linezolid
- Pharmacokinetics of first-line drugs in children < 5kg
- Stellenbosch University

**Phase 2A**
- Linezolid Dose-Ranging Study

**Phase 2B**
- Pretomanid/Bedaquiline/Linezolid
- NC-005

**Phase 3**
- Pretomanid/Bedaquiline/Pyrazinamide (BPaZ)
- STAND

**Phase 4**
- Pretomanid/Bedaquiline/Linezolid
- Nix-TB
- Ethambutol for children > 5kg
- Ethambutol for children > 5kg
- Isoniazid for children > 5kg
- Pyrazinamide for children > 5kg

**Preclinical TB Regimen Development**
- JHU
- Ethambutol for children > 5kg
- Pyrazinamide for children > 5kg
- Isoniazid for children > 5kg
- Isoniazid/Rifampicin for children > 5kg
- Ethambutol/Rifampicin/Pyrazinamide for children > 5kg

**Optimized Pediatric Formulations**
- Ethambutol/Rifampicin/Pyrazinamide for children > 5kg
- Ethambutol/Rifampicin for children > 5kg
- Isoniazid for children > 5kg
- Pyrazinamide for children > 5kg

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Launched in May 2015, Nix is the first clinical trial for a novel XDR-TB regimen with minimal pre-existing resistance; all pills, no injections.

- Regimen includes bedaquiline, pretomanid, and linezolid
- Potential to be a 6-9 month simple, effective treatment for XDR-TB
- Regimen could be first “universal” treatment; if safe and effective the study will expand to include people with MDR-TB and drug-sensitive TB

Novel treatments to fight XDR-TB are urgently needed. In a recent review in South Africa, only 16% of people with XDR-TB were cured.
Nix-TB Clinical Trial

- Sponsor: TB Alliance
- Investigators: Dr. Conradie, Sizwe Tropical Diseases Hospital and Dr. Diacon, Brooklyn Chest Hospital in South Africa
- Other Partners: Janssen
- Trial may be expanded to include additional investigators, sites, and countries and new patient populations
Conclusions/Observations

• Currently advancing a broad range of novel chemical series into advanced lead optimization and preclinical evaluations.

• Virtual R&D organization -> capable of enlisting superb drug discovery/development talent from around the world.

• Increased use of distributed secure data environments (i.e. SharePoint portals, CDD, and BIOVIA [Science Cloud] chemoinformatic db’s) combined with high-speed communication tools (TC’s, internet, Skype/WebEx) allows for more rapid decision-making, and broader level of consensus across project teams.
Conclusions/Observations (continued)

• Agnostic approach to TB drug discovery projects:
  – Biochemical targets/chemical series are evaluated purely on their likelihood to reduce TB treatment time.
  – No “pet” or “legacy” projects -> all programs are milestone driven.
  – Diverse chemical series against common TB targets are routinely evaluated head-to-head to avoid unnecessary, duplicative efforts on a “weak” or less promising series.

• Willingness/eagerness to learn – embracing a culture of scientific humility!
  – Explore new, higher-risk, poorly validated *Mtb* targets as warranted.
  – Explore “ugly” chemotypes to achieve proof-of-concept.

• Overarching and shared mission to address a critical, unmet medical need -> greater sense of purpose and drive to achieve success.
Acknowledgements

• TB Alliance
  – Nader Fotouhi
  – Anna Upton
  – Takushi Kaneko
  – Manisha Lotlikar
  – Khisi Mdluli
  – Rajneesh Taneja
  – Tian Yang

• Janssen
  – Koen Andries
  – Jerome Guillemont
  – Walter Van den Broeck
  – Ron Gilissen

• UIC
  – Scott Franzblau
  – Yuehong Wang
  – Rui Ma
  – Baojie Wan
  – Sanghyun Cho
  – Akie Matsumura

• CSU
  – Anne Lenaerts
  – Janet Gilliland
  – Roni Gruppo
  – Lisa Woolhisser
  – Mary Jackson
  – Wei Li

• BioDuro
  – JP Shaw
  – Jianglin Liu
  – Frank Ruebsam
  – Zicheng Wu
  – Huili Wang

• JHU
  – Eric Nuermberger
  – Si-Yang Li
  – Fabrice Betoudji

• AstraZeneca
  – Monalisa Chatterji
  – Radha Shandil
  – Claire Sadler
  – Pravin Shirude

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  – Roni Gruppo
  – Lisa Woolhisser
  – Mary Jackson
  – Wei Li

• NITD
  – Ujjini Manjunatha

• TBDA
TB Alliance Supporters

Thanks to all those who support our mission to identify better, faster TB drugs
Thank you!