Discovering and developing new treatments for tuberculosis

Guest speaker: Nader Fotouhi
Moderator: Lydia Nakiyingi
Host: Astrid Pentz-Murr (GARDP)

24 March 2021

In collaboration with:
This webinar was collaboratively organized by GARDP and the TB Alliance
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How to submit your questions

The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.
Today’s speakers

Discovering and developing new treatments for tuberculosis

Nader Fotouhi  
*Chief Scientific Officer*  
TB Alliance (US)

Moderator:  
Lydia Nakiyingi  
*Infectious diseases physician, research scientist and senior lecturer*  
Makerere University College of Health Sciences, Kampala (Uganda)
As Chief Scientific Officer for the TB Alliance, Dr. Nader Fotouhi guides and oversees the organization’s research and preclinical development activities.

Nader has 24 years of experience in the pharmaceutical industry, with significant research and early development expertise in a variety of therapeutic areas. Prior to joining the TB Alliance, Nader held various leadership positions at Hoffmann-La Roche, including the head of the Discovery Chemistry group at the Nutley New Jersey site, the global head of Discovery Technologies, and served as the Nutley New Jersey Pharma Research and Early Development Site Leader.

Nader holds a Ph.D. and post-doctoral fellowship in Organic Chemistry from the Massachusetts Institute of Technology. Nader has authored or co-authored more than 50 articles and presentations and holds 20 patents.
Discovering and developing new treatments for tuberculosis

Nader Fotouhi, SVP, Chief Scientific Officer, TB Alliance
March 24, 2021
TB Alliance is a not-for-profit organization dedicated to the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those in need.
20 Years of Impact

FEBRUARY 2000

Declaration of Cape Town calls for TB ALLIANCE

a public-private partnership dedicated to developing new TB treatments.
TB is a Pandemic

TB is the **LEADING** infectious disease killer

and a **TOP 10** killer worldwide

killing one person every **22 SECONDS**

1 MILLION children become ill with TB

1.4 MILLION people die from TB

10 MILLION new TB cases develop

Leading killer of people with HIV/AIDS

Drug-resistance is on the rise with about half a million cases annually
TB Therapy

Obsolete
Arsenal of drugs developed mostly in 1960s

Long
TB treatment today takes 6-18+ months

Complicated
Can exceed 14,000 pills for drug-resistant TB

Expensive
Drug-resistant TB medication can cost more than $10,000 per treatment

Inadequate
Can lead to resistance; can be incompatible with some HIV treatments; unacceptably high failure rate for DR-TB

Patient with drug-resistant TB in the Philippines
As an NIH-assigned Center of Excellence, we are a nonprofit R&D organization that has:

- Developed a **new treatment** for highly drug-resistant TB
- Launched **improved treatments** for children with TB
- **Transformed** how TB treatments are developed
- **Revived** the pipeline for new TB drugs
- **Mobilized** a global network of partners

**AAA Mandate**: Ensuring TB Alliance products are accessible to every person who needs them
Achieving maximum impact will require:

• A sustainable pipeline of novel drugs to form the basis for universal regimens effective in all people with active TB

• An ultra-short and effective therapy for latent infection

• All TB treatments appropriately formulated for children

Our Vision: Better TB Medicines for All

Discover, develop and deliver better and faster TB regimens

Simple
All-oral, highly effective regimens

Short
Two to four months of treatment

Accessible
Adopted, available and affordable to people with TB

Millions of lives saved
Fight the TB epidemic and accelerate eradication
Challenges of Treating Drug-Resistant TB

If treatment isn’t strictly adhered to, it can lead to drug resistance.

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>About 500,000 new cases of DR-TB each year</td>
<td></td>
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<tr>
<td>More than 50% of DR-TB cases are caused by direct transmission</td>
<td></td>
</tr>
<tr>
<td>Only 43% historical XDR-TB treatment success rate</td>
<td>DR-TB treatment typically takes 9 months to 2 years or longer</td>
</tr>
<tr>
<td>It can take 14,000+ pills to cure a single case of DR-TB</td>
<td>Estimated 75M people will die from DR-TB by 2050 without new cures</td>
</tr>
<tr>
<td>Estimated 1 in 3 deaths from antimicrobial resistance are due to DR-TB</td>
<td>Estimated $16.7 T financial toll of DR-TB by 2050 without new cures</td>
</tr>
</tbody>
</table>
**Benefits of New Regimens**

Potential positive impacts of new treatments are wide-reaching and multi-faceted

<table>
<thead>
<tr>
<th>Lower cost</th>
<th>More lives saved</th>
<th>Better outcomes</th>
<th>Reduced health system burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fewer side effects</td>
<td>More patient satisfaction</td>
<td>Simple supply management</td>
<td>Reduced transmission</td>
</tr>
</tbody>
</table>

Novel regimens can simplify TB treatment, facilitate its scale-up and reduce its burden on health systems.
Evolution of New TB Therapies

- **1943**: Streptomycin (S)
- **1948**: p-aminosalicylic acid (PAS)
- **1952**: Isoniazid (H)
- **1954**: Pyrazinamide (Z)
- **1955**: Cycloserine (Cs)
- **1957**: Kanamycin (Z)
- **1960**: Ethionamide (ETO)
- **1961**: Ethambutol (E)
- **1963**: Capreomycin (Cm) & Rifampicin (R)

**1940s**: First randomized trial: S Monotherapy
Led to S resistance

**1950s**: 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 months, oral therapy

**1990s**: Rifapentine (P)

**2000s**: BPaL
6-month, all: oral therapy for highly resistant TB

**2010s**: Delamanid (DLM)

**2019**: Pretomanid (Pa)

**2012**: Bedaquiline (BDQ)

**2020s**: 2PHZM/2PHM
4 months of therapy
### TB Drug Development Pipeline

**As of March 2021**

<table>
<thead>
<tr>
<th>Lead Identification</th>
<th>Lead Optimization</th>
<th>Preclinical Development</th>
<th>Phase 1</th>
<th>Phase 2A/2B</th>
<th>Phase 3</th>
<th>Marketed Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clp Lead ID Programs</td>
<td>Anti-TB Natural Products</td>
<td>Preclinical TB Regimen Development JHU</td>
<td>TBAJ-876 / Diarylquinoline</td>
<td>Sutezolid / Oxazolidinone Gates MRI</td>
<td>NixTB Bedaquiline / Pretomanid / Linezolid (BPaL) Mylan</td>
<td></td>
</tr>
<tr>
<td>Harvard University</td>
<td>Evotec</td>
<td></td>
<td>TBAJ-587 / Diarylquinoline ERA4TB</td>
<td>TBA-7371 / DprE1 Inhibitor FNDR Gates MRI</td>
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<tr>
<td>UIC</td>
<td>ClpC1</td>
<td>TBI-223 / Oxazolidinone IMM</td>
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<tr>
<td>CETR</td>
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<tr>
<td>GHT HIT ID Programs</td>
<td>InhA Inhibitors</td>
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<td>Daiichi Sankyo RD Novare</td>
<td>GHDDI</td>
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<tr>
<td>GHT Hit-to-Lead Programs</td>
<td>Intracellular Active Series</td>
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<tr>
<td>Astellas</td>
<td>GSK</td>
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<td>Chugai</td>
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<td>KasA</td>
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<td>Takeda</td>
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<td>Malate Synthetase Inhibitors</td>
<td>Mnpl3 Inhibitors</td>
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<td>Texas A&amp;M</td>
<td>AbbVie</td>
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<tr>
<td>Pantothenamide</td>
<td>ERA4TB</td>
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<td>Triclo</td>
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<td>WCM</td>
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<td>PknB</td>
<td>U01/Schrödinger</td>
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<td>RNA Polymerase Inhibitors</td>
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<td>CETR</td>
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<tr>
<td>Whole Cell Hit-to-Lead Program</td>
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<tr>
<td>GSK</td>
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### TB Alliance Portfolio Partners

- AbbVie
- Astellas
- Bill & Melinda Gates Medical Research Institute (Gates MRI)
- Center for Excellence in Translational Research (CETR)
- Chugai
- Daiichi Sankyo RD Novare ERA4TB Consortium
- Erasmus University Rotterdam Evotec
- Foundation for Neglected Disease Research (FNDR)
- GiaoSmithKline (GSK)
- Global Health Drug Discovery Institute (GHDDI)
- Harvard University
- Hongqi Pharmaceutical Institute of Materia Medica (IMM)
- IMPAACT
- International Tuberculosis Research Center (ITRC)
- Johns Hopkins University (JHU)
- KNCV Tuberculosisfonds
- Macleods Pharmaceuticals
- Medical Research Council (MRC) at UCL
- Medecins Sans Frontieres (MSF)
- Mylan
- US National Institutes of Health (NIH)
- PanACEA
- Radboud University Nijmegen
- Schrödinger
- Stellenbosch University
- Takeda Pharmaceuticals
- TB Drug Accelerator (TDA)
- Texas A&M University
- TroplQ
- University College London (UCL)
- University of Auckland, New Zealand
- University of Illinois at Chicago (UIC)
- Weil Cornell Medical (WCM)
- Yonsei University
- Zelixion

### Optimized Pediatric Formulations

- Ethambutol Macleods
- Isoniazid Macleods
- Pyrazinamide Macleods
- Rifampicin/Isoniazid Macleods
- Rifampicin/Isoniazid/Pyrazinamide Macleods

### Pediatric Formulation Development

- Pretomanid Mylan

### Pretomanid for use in BPaL

- Mylan
- Macleods
- Hongqi
- KNCV
- ITRC

*Phase 3 clinical trials are added to the pipeline after enrollment of the first patient and are removed after completion of the Clinical Study Report. This document is updated on a quarterly basis.*
Shorter, Simpler Treatment for Highly Drug-Resistant Forms of TB

One day of typical BPaL regimen
6 months / <750 pills

One day of typical XDR-TB treatment
18+ months / 14,000+ pills

Please see Full Prescribing Information at: www.accessdata.fda.gov
Nix-TB Results

*Treatment intolerant or non-responsive MDR-TB
Methods

Phase 3 Trial in XDR-TB

- Primary and secondary endpoint = bacteriologic or clinical failure or relapse at 6- and 24-months post-treatment respectively
- Success of trial - lower bound of 95% CI > 50% favorable rate
- Peripheral neuropathy associated with linezolid was assessed serially with standard symptoms rated from none (0) to worst (10) using the Brief Peripheral Neuropathy Symptom questionnaire (BPNS)
- Explore the fate of those participants with no neuropathy symptoms at baseline who completed treatment i.e.
  - Maximum score post baseline
  - Score at end of the study (24 months)

<table>
<thead>
<tr>
<th>Extensively Drug-Resistant</th>
<th>Treatment-Intolerant or Non-Responsive Multidrug-Resistant TB Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretomanid 200 mg qd</td>
<td>Followed throughout 30 months</td>
</tr>
<tr>
<td>Bedaquiline 200 mg tiw after 2 week load</td>
<td></td>
</tr>
<tr>
<td>Linezolid 1200 mg qd*</td>
<td>6-9 months of treatment</td>
</tr>
</tbody>
</table>

Sites
- Sizwe Hospital, Johannesburg, South Africa
- Brooklyn Chest Hospital, Cape Town, South Africa
- King Dinuzulu Hospital, Durban, South Africa

*Amended from 600 mg bid strategy
**If sputum culture is positive at 4 months, patients received an additional 3 months of treatment
Primary endpoint is measured at six months of post-treatment follow up
Results - Efficacy

- 109 participants (65% XDR-TB, 35% MDR-TB; 51% HIV+) were enrolled and comprised the ITT* population (MITT* population = 107)

- All surviving participants, except 1 withdrawal, completed the full course of therapy

- At the primary endpoint six months after treatment, as previously reported, there were 98 with favorable outcomes (90% ITT, 92% mITT)

- After the primary endpoint one participant relapsed 15 months after treatment and one was lost to follow up

- Favorable outcomes 24 months post completion of treatment were sustained (88% ITT, 91% mITT) independent of sex or HIV status.

* ITT – Intention to treat, mITT – modified intention to treat
Kaplan Meier curve of time (days) to 1\textsuperscript{st} Linezolid dose interruption and/or reduction due to Peripheral Neuropathy (Safety Analysis Population)
# Peripheral Neuropathy Score (Pain, aching, burning in feet or legs)

## Linezolid (LZD)

<table>
<thead>
<tr>
<th></th>
<th>600mg BD (n = 44)</th>
<th>1200mg QD (n = 65)</th>
<th>Total (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants who completed treatment</td>
<td>40</td>
<td>63</td>
<td>103</td>
</tr>
<tr>
<td>Participants received full uninterrupted 26 weeks of LZD at any dose</td>
<td>10</td>
<td>27</td>
<td>37</td>
</tr>
<tr>
<td>Participants received full uninterrupted 26 weeks of LZD at 1200mg daily</td>
<td>4</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>LZD duration in treatment completers</td>
<td></td>
<td></td>
<td>23,3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Max. After Baseline</th>
<th>Month 24 After End-of-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None: 84</td>
<td>Always None: 27</td>
<td>None: 27</td>
</tr>
<tr>
<td></td>
<td>(Mild/Mod: 15)</td>
<td>Max. Mild/Mod: 34</td>
<td>Mild/Mod: 29</td>
</tr>
<tr>
<td></td>
<td>(Severe: 1)</td>
<td>Max. Severe: 23</td>
<td>Severe: 13</td>
</tr>
</tbody>
</table>

- None: 84
- Always None: 27
- Max. Mild/Mod: 34
- Max. Severe: 23

0 = None
1-7 = Minimal/moderate
8-10 = Severe
Conclusion

• Results of this simplified, shortened all oral regimen for highly drug resistant TB show sustained high efficacy through 2-year follow-up from end of treatment

• Peripheral neuropathy from linezolid was common, but manageable, and symptoms improved over 24 months of follow-up

• Can we manage the peripheral neuropathy through an optimal dosing and scheduling of linezolid?
Scheme for Murine Relapse Experiments to Evaluate New Regimens

(15) mice held for (3) months without treatment and then sacrificed to determine permanent cure without relapse
The duration of Linezolid (L) treatment does not affect the Sterilizing Activity on Background of Bedaquiline Plus Pretomanid (BPa) in BALB/c Mice

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Proportion relapsing after treatment for:</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2RHZ/RH</td>
<td></td>
<td></td>
<td>8/14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(57%)</td>
</tr>
<tr>
<td>BPa</td>
<td></td>
<td></td>
<td>3/14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(21%)</td>
</tr>
<tr>
<td>3BPaL</td>
<td></td>
<td>6/15</td>
<td>0/15*†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(40%)</td>
<td>(0%)</td>
</tr>
<tr>
<td>2BPaL/1BPa</td>
<td></td>
<td></td>
<td>0/15*†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0%)</td>
</tr>
<tr>
<td>1BPaL/2BPa</td>
<td></td>
<td>9/15</td>
<td>0/15*†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(60%)</td>
<td>(0%)</td>
</tr>
</tbody>
</table>

*p = 0.11 vs. BPa; †p≤ 0.001 vs. RHZ
ZeNix: Linezolid Optimization Trial

Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB treatment

- Extensively Drug-Resistant
- Pre-Extensively Drug-Resistant
- Treatment-Intolerant or Non-responsive
- Multidrug-Resistant TB Participants

**Extensively Drug-Resistant, Pre-Extensively Drug-Resistant**

随机化

- B-Pa-L
  - L=1200 mg/d x 6 mos
  - 6 MONTHS OF TREATMENT*
  - 18 MONTHS OF FOLLOW-UP

- B-Pa-L
  - L=1200 mg/d x 2 mos
  - 6 MONTHS OF TREATMENT*
  - 18 MONTHS OF FOLLOW-UP

- B-Pa-L
  - L=600 mg/d x 6 mos
  - 6 MONTHS OF TREATMENT*
  - 18 MONTHS OF FOLLOW-UP

- B-Pa-L
  - L=600 mg/d x 2 mos
  - 6 MONTHS OF TREATMENT*
  - 18 MONTHS OF FOLLOW-UP

*Additional 3 months if sputum culture positive between week 16 and week 26 treatment visits

Pa pretomanid dose = 200 mg daily
Bedaquiline dose = 200 mg x 8 weeks, then 100 mg x 18 weeks

Enrollment completed Dec 2019. 181 patients enrolled from Georgia, South Africa, Russia and Moldova
Strategic Overview

A new standard of TB drug development

• Nix-TB has provided proof of principle that the most resistant forms of TB can be treated in the same timeframe and with as few drugs as is used for drug-sensitive TB - and with comparable results

• Next challenge is one regimen for all patients with active TB (Universal Regimen)

• Initial goal is to shorten timeframe of treatment to 2-3 months

• Long term objective is a universal regimen that cures in days to weeks

• Needs of the market dictate our R&D agenda – requires a constant feedback loop
Early-Stage Research: Filling the Pipeline

A three-pronged approach

TB Alliance leverages industry and other partners to support the continued growth of the global TB drug pipeline.

- **Optimize known compound classes**
  - Fully capitalize on the success of compounds already in development or approved

- **Develop novel classes based on known targets**
  - Leverage validated drug targets, discover novel classes to address resistance

- **Develop novel classes based on novel targets**
  - Discover new drug classes with novel modes of action
What’s Next: Finding the Next Regimen

Substituting linezolid with a safer oxazolidinone

<table>
<thead>
<tr>
<th>Regimen</th>
<th>D-15</th>
<th>D0</th>
<th>M1</th>
<th>M1.5 (+3)</th>
<th>M2 (+3)</th>
<th>M3 (+3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>4.7</td>
<td>8.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;25&lt;/sub&gt;Pa&lt;sub&gt;100&lt;/sub&gt;</td>
<td></td>
<td>5.9</td>
<td></td>
<td></td>
<td>14/15</td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;25&lt;/sub&gt;Pa&lt;sub&gt;100&lt;/sub&gt;L&lt;sub&gt;100&lt;/sub&gt;</td>
<td>4.5</td>
<td></td>
<td>14/15</td>
<td>7/15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;25&lt;/sub&gt;Pa&lt;sub&gt;100&lt;/sub&gt;O&lt;sub&gt;100&lt;/sub&gt;</td>
<td>4.9</td>
<td></td>
<td>15/15</td>
<td>2/15</td>
<td></td>
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</tr>
</tbody>
</table>

B, Bedaquiline; Pa, Pretomanid; L, Linezolid, O, TBI-223. Subscripted figures are daily doses of drugs in mg/kg

- TBI-223 is a novel oxazolidinone with efficacy similar to linezolid and significantly reduced inhibition of mammalian protein synthesis
- No bone marrow toxicity observed in preclinical safety studies up to 3 months
- Single ascending dose (SAD) in healthy human volunteers completed up to 3000 mg dose
- Well tolerated

*O = TBI-223
A more potent diarylquinoline and a safer oxazolidinone is significantly more effective than the Nix regimen

Substituting bedaquiline with a more potent and safer diarylquinoline

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Lung CFUs</th>
<th>Proportion of Mice Relapsing After:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>W-2</td>
</tr>
<tr>
<td>Untreated</td>
<td>4.0</td>
<td>D0</td>
</tr>
<tr>
<td>B25 PaO</td>
<td></td>
<td>W4 (+12)</td>
</tr>
<tr>
<td>587_{25}PaO</td>
<td>7/13</td>
<td>W6 (+12)</td>
</tr>
<tr>
<td>587_{50}PaO</td>
<td>2/15</td>
<td>W8 (+12)</td>
</tr>
<tr>
<td>876_{6.25}PaO</td>
<td>2/15</td>
<td></td>
</tr>
<tr>
<td>876_{12.5}PaO</td>
<td>3/15</td>
<td></td>
</tr>
</tbody>
</table>

BPaL typically cures all mice in 3-4 months, and would perform similarly to BPaO here

- TBAJ-587 and TBAJ-786 are significantly more potent than bedaquiline in vitro (MIC90 = 0.003 ug/mL) and in vivo with a better safety profile
- TBAJ-876 completed SAD studies and was well tolerated up to 400 mg
- TBAJ-587 initiated Phase 1 SAD studies

*O = TBI-223
Emerging evidence of BDQ resistance in BDQ-treated and BDQ-naïve TB patients is a concern.

BDQ resistance in *Mtb* isolates is rarely due to mutations in its target, *atpE*, but rather in *Rv0678*, a regulator of the MmpL5/MmpS5 efflux transporter.

**Further advantage of the novel diarylquinolines**

<table>
<thead>
<tr>
<th>MICs against <em>H37Rv</em> and a panel of <em>Rv0678</em> (165 aa) mutants</th>
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<tbody>
<tr>
<td><strong>Compound</strong></td>
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<tr>
<td>BDQ</td>
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<tr>
<td>BDQ-M2</td>
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<tr>
<td>TBAJ-587</td>
</tr>
</tbody>
</table>

- *Rv0678*: provided by Stewart Cole, EPFL, Switzerland (Hartkoorn et al, AAC, 2014)
- ITM 1-7 provided by Leen Rigouts, ITM, Belgium

A. Upton et al, ASM Microbe, 2017
S. Franzblau et al, ASM Microbe, 2017
Efficacy of B- and S-containing regimens against wild-type *M. tuberculosis* H37Rv

One month of treatment

- **TBAJ-587**, is more active than B, BDQ, as monotherapy, and in combination with either PaL

Two months of treatment

- **TBAJ-587**, is more active than B, BDQ, as monotherapy, and in combination with either PaL
Efficacy of B- and S-containing regimens against *M. tuberculosis* with *Rv0678* mutation

One month of treatment

- Against the *Rv0678* mutant (IS6110 insertion, aa116/nt349): S, TBAJ-587, is more active than B, BDQ, as monotherapy, and in combination with PaL.
Mid term: Targeting Pathways to find alternative short regimens

Five Ways to Target TB

**PROVEN PATHWAY**
Electron Transport Chain
Stop the generation of cell energy so TB bacteria can’t grow

**PROVEN PATHWAY**
Cell Wall Disruption
Weaken cell walls and in the process, destroy TB bacteria

**NEW PATHWAY**
Central Carbon Metabolism
Starve TB bacteria so it can’t grow

**NEW PATHWAY**
Protein Synthesis
Block TB’s ability to make protein necessary for its survival

**NEW PATHWAY**
Protein Degradation
Poison the cell by inhibiting the ability to eliminate waste
Modulation of Protein Synthesis and Protein Degradation

Integrated targeting of proteostasis

- **Protein Synthesis**
  - Clinically well validated
  - Inhibition of ribosome
    - Oxazolidinones
  - Inhibition of RNA polymerase
    - Rifamycins

- **Protein Degradation**
  - Demonstrated essentiality of ClpC1 and ClpP1P2 complexes
  - Genetic validation
  - Natural product modulators
    - Rufomycin, Ecumicin, Cyclomarin
  - Peptidic inhibitors
CETR (Center of Excellence in Translational Research)

National Institute of Allergy and Infectious Diseases (NIAID)
Setting a New Course for TB Drug Development

Exploring Immunotherapy and Leveraging Artificial Intelligence

2000s
Establishing the PDP* Paradigm for TB Drugs

2010s
Proving the Theory of Regimen Development and Advancing New Drugs

2020s
What comes next?

* PDP – Product development partnership
The Next Innovations in TB Treatments: Artificial Intelligence

New Partnerships to Identify the Components of Tomorrow’s TB Regimens

**AI to Support Immunotherapy**

- AI driven analysis of immunomodulatory pathways and targets with greatest impact on bacterial clearance (InveniAI)
- Targets and pathways have either clinical or research compounds available
- With Advisory group select top candidates to evaluate in a relapse mouse model on top of a novel regimen and standard of care (SOC)

**AI-Assisted Screening Process**

- Combine large scale screening approach such (DNA encoded Library) and AI to select advanced drug like lead (ZebiAI)
- Could significantly reduce the time and cost to discover novel leads against traditional targets as well as potential immunotherapy targets of value
The Next Innovations in TB Treatments: Immunotherapy

Harnessing the Immune System to Shorten Treatment Duration

Available TB Therapies
- 1st line regimen (HRZE)
- BPaL

Universal Regimen
- All-novel regimen

The Next Paradigm
- All-novel regimen
  + Immunotherapy

6+ months to cure
<3 months to cure
7-10 days to cure
What Could the Patient Experience Look Like in the Future?

- **Available Therapies**: 6+ Months
- **Universal Regimen**: ≤3 Months
- **Universal Regimen + Immunotherapy**: 7-10 Days
MOBILIZING

a global network of partners
How to submit your questions

The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.
Today’s speakers

Discovering and developing new treatments for tuberculosis

**Nader Fotouhi**
*Chief Scientific Officer*
TB Alliance (US)

**Moderator:**
*Lydia Nakiyingi,*
*Infectious diseases physician, research scientist and senior lecturer*
Makerere University College of Health Sciences, Kampala (Uganda)
Join us for our next webinar

29 April 2021, 17:00-18:30 CEST

AMR R&D efforts in the CMC and formulation arena: Do it right the first time!

Speaker:
• Aleksandar Danilovski, Xellia Pharmaceuticals

Registration link and more information available on: revive.gardp.org/webinars
Thank you for joining us

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