About TB Alliance

Putting science to work for better, faster TB cures
Fighting pandemics

**COVID-19** pandemic caused by virus

- Caused by SARS-CoV-2, a type of coronavirus
- Primarily affects the respiratory system but other organs as well
- An airborne disease
- More than 5 million people dead from COVID-19
  (likely significant underestimation)

**Tuberculosis**

- Caused by bacteria *Mycobacteria tuberculosis*
- Affect mainly the respiratory system but other organs as well
- An airborne disease responsible for more than 1.5 million deaths in 2020
- Has been with humanity for millennia
TB is a Pandemic

TB is one of the LEADING infectious disease killers 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 every year.

Leading killer of people with HIV/AIDS.
Drug-resistance is on the rise with about half a million cases annually.
Evolution of New TB Therapies

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:
- 1998: Rifapentine (P)

2000s:
- 2005: Bedaquiline (BDQ)
- 2012: Delamanid (DLM)

2010s:
- 2019: Pretomanid (Pa)
  - 6-month, all-oral therapy for highly resistant TB

2020s:
- 2020: 2PHZM/2PHM
  - 4 months of therapy
The Cape Town Declaration was issued to accelerate the development of new drugs to shorten the treatment of TB and to facilitate its control in the poorest countries.

Signatories included the Rockefeller Foundation, US NIH, Bill and Melinda Gates Foundation, the Welcome Trust, Doctors Without Borders, among others.

This provided a road map for Global Alliance for TB Drug Development (TB Alliance).

We are a Product Development Partnership (PDP) and rely heavily on the collaborations with academic laboratories and the pharmaceutical industry to maximize the speed and the efficiency of drug discovery and development.

We cover the entire drug development process including 1) target selection, 2) screening, 3) hit-to-lead, 4) lead optimization, 5) preclinical development, 6) Phase I studies, 7) Phase II studies, 8) Phase III studies, 9) registration, and 10) commercialization.

TB Alliance has approximately 60 employees and based in New York City, USA and Pretoria, South Africa.
Story of Pretomanid (Pa-824)

- The original compound was licensed from Pathogenesis (Chiron)
- New chemotype and new mechanism of action
- Potent *in vitro* and *in vivo* activity
- Drug combinations studies at Johns Hopkins University (JHU) showed promising synergistic activity in animal models especially in combination with bedaquiline and linezolid – i.e. the “BPaL regimen”

![Chemical structures of Pretomanid, Bedaquiline, and Linezolid.]
Nix-TB Phase 3 Clinical Trial

Patients with XDR-TB or who have failed or are intolerant to MDR-TB Treatment

Followed throughout 30 months

**Extensively Drug-Resistant***

<table>
<thead>
<tr>
<th>Pretomanid 200 mg qd</th>
<th>6-9 MONTHS OF TREATMENT***</th>
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<tbody>
<tr>
<td>Bedaquiline 200 mg tiw after 2 week load</td>
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<tr>
<td>Linezolid 1200 mg qd**</td>
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</tbody>
</table>

Evaluated 6 months after end of treatment

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

*Using definition of XDR-TB prior to 2020
**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
Nix-TB Results

New England Journal of Medicine, March 2020

PARTICIPANT STATS

109 participants with confirmed TB

71 with XDR TB*
65%

38 with MDR TB**
34%

THE RESULTS

Favourable outcomes

with XDR TB
89%
79-95 (95% CI)

with MDR TB
92%
79-98 (95% CI)

90% of all participants had favourable outcomes

95% CI (83-95)

Bacteriological and Clinical Resolution
6 months after end of therapy

*Using definition of XDR-TB prior to 2020
**Treatment-intolerant or non-responsive MDR-TB
The BPaL regimen (bedaquiline + pretomanid + linezolid) received U.S. approval for people with XDR-TB or treatment-intolerant/non-responsive MDR-TB

- Pretomanid was approved under the LPAD* pathway for the treatment of XDR-TB or treatment-intolerant/non-responsive MDR-TB in August 2019
- The three-drug, all-oral, six-month regimen was studied in the Nix-TB clinical trial
- Nix-TB data have demonstrated a successful outcome in 90 percent of patients after six months of treatment with BPaL and six months of post-treatment follow-up
- This high efficacy was sustained through two-year follow-up after end of treatment

Please see Full Prescribing Information at: tballiance.org/pretomanid

* Limited Population Pathway for Antibacterial and Antifungal Drugs

About Pretomanid (Pa-824)

Pretomanid is only the third new anti-TB drug approved for use by U.S. FDA in more than 40 years, and the first non-conditional approval

- Pretomanid is the first anti-TB drug to be developed and registered by a not-for-profit organization
- It is a new chemical entity and a member of a class of compounds known as nitroimidazooxazines
  - Novel compounds are important in pursuing new TB treatments because resistance to many drugs and drug classes currently used to treat TB is relatively widespread

For more on pretomanid’s unique mechanism of action, visit: [tballiance.org/pretomanid](http://tballiance.org/pretomanid)

*as of Aug 2021*
The Future of TB Treatment

Novel drug combinations enable shorter, simpler and more effective treatment
The future, however, is not here yet and we need as many drug hits/leads as possible, not only in quantity because of their attrition rates but also in quality (mechanism and target) for fighting drug resistance and for shortening treatment duration.
Possible Game Changers in Identifying Hits/Leads

Going from empirical approaches to more target-based approaches

1. CRISPR-interference technology to identify vulnerable genes in Mtb -> J M Rock and D Schappinger, Cell, 2021, 184, 4579-4592
4. Mtb: Bacterial fitness within the host macrophage, D. G. Russell, Microbiol Spectr 2019, 7(2)
5. Efficient Measurement of Drug Interactions with DiaMOND, B. B. Aldridge, Methods Mol Biol 2021, 2314, 703-713
6. Computational approaches to drug-combination therapies, R. Savic, Eur Respir J., 2021, 57, 2001756
• GHIT Fund enables Japanese academic and industrial researchers (or any international researchers accessing targets or compounds originating from Japan) to contribute to global health

• TB Alliance has collaborated with GHIT Fund since its inception. It has enabled us to establish connections with Japanese pharmaceutical companies and research organizations

• We have been able to screen unique collections of compounds and to learn diverse approaches toward drug development

• The Japanese organizations we have collaborated under the GHIT sponsorship include: Astellas Pharma, Chugai Pharmaceutical, Daiichi Sankyo, Daiichi Sankyo RD Novare, Fujifilm Pharmaceuticals, HyphaGenesis, Japan Anti-Tuberculosis Association (JATA), Mitsubishi Tanabe Pharma, OP Bio Factory, Shionogi Inc, Sumitomo Dainippon Pharma, and Takeda Pharmaceutical Co.

• Ongoing projects in the Hit-to-Lead Stage with Astellas Pharma, Chugai Pharmaceutical, Daiichi Sankyo RD Novare, and Takeda Pharmaceutical Co.
TB Alliance and GHIT Fund

There are several stages we can apply for funding, 1) target research, 2) screening, 3) hit-to-lead, and 4) product development platforms

- Bacterial physiology, genetics → Novel targets for drug discovery
- Screening methodology, unique collection of compounds → Screening
- Repurposing existing compounds → Screening
- Host-directed therapy potential → Novel targets
- AI-Based approaches to drug discovery → Various stages

For the criteria of hits and leads, see

Natural product chemistry is an area of special interest

Japan has a rich history of natural product development in the areas of antibiotics, anti-cancer agents, and anti-parasitic agents, for example:

- Kanamycin, Amikacin-aminoglycosides used against TB, H. Umezawa (Institute of Microbial Chemistry), H. Kawaguchi (Bristol-Banyu),
- Avermectin, S. Omura (Kitasato University)
- Mitomycins, H. Hata (Kitasato Institute)

Our co-presenters, Dr. Isshin Tanaka of Daiichi Sankyo RD Novare and Professor Scott Franzblau of University of Illinois at Chicago both have significant experience and interest in this area

Dr. Tanaka is Scientist at Daiichi Sankyo RD Novare and we have collaborated in the area of fermentation natural products since 2014. This has been a very productive area

Professor Franzblau is Director of Institute for Tuberculosis Research at University of Illinois at Chicago and has been involved in most of the GHIT-funded TB projects since 2013
TB Alliance Donors

Australian Aid
Bill & Melinda Gates Foundation
Cystic Fibrosis Foundation
EDCTP
Federal Ministry of Education and Research

GHIT Fund
India Health Fund
IMI
Innovative Medicines Initiative
Irish Aid
Government of Ireland
Rialtas na hÉireann
KOICA
Korea International Cooperation Agency

Ministry of Foreign Affairs of the Netherlands
NIAID
The Rockefeller Foundation
UKaid
from the British people
Unitaid
Innovation in Global Health
USAID
from the American people
Thank you!
Back-up slides
# 2021 Global New TB Drug Pipeline

<table>
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<tr>
<th>Discovery</th>
<th>Preclinical Development</th>
<th>GMP / GLP Tox.</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Regulatory Market Approvals</th>
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<tr>
<td><strong>Lead Optimization</strong></td>
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<tr>
<td>PanD inhibitors</td>
<td>JSF-3285*</td>
<td>FNDR-20081*</td>
<td>BVL-GSK098*</td>
<td>Delpazolid</td>
<td>Pretomanid* / Moxifloxacin / Bedaquiline* / PZA (4-month regimen)</td>
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<td>Indazole sulfonamides</td>
<td>MPL-446, 447*</td>
<td>TB-47*</td>
<td>GSK-286*</td>
<td>Sutezolid</td>
<td>Bedaquiline*</td>
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<td>Diarylthiazoles</td>
<td>CPZEN-45*</td>
<td>GSK-839*</td>
<td>TBAJ-587</td>
<td>BTZ-043*</td>
<td>Delamanid*</td>
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<tr>
<td>DprE1 inhibitors</td>
<td>NTB-3119*</td>
<td>OTB-658</td>
<td>TBAJ-876</td>
<td>TBA-7371*</td>
<td>Pretomanid*</td>
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<tr>
<td>Direct InhA Inhibitors</td>
<td>TZY-5-84</td>
<td>Sanfetrinem</td>
<td>TBI-223</td>
<td>OPC-167832*</td>
<td>Truncate TB (2-month regimens)</td>
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<tr>
<td>Mtb energy metabolism</td>
<td>MBX-4888A (1810)*</td>
<td>FNDR-10045*</td>
<td>Macozinone* (PBTZ-169)</td>
<td>GSK-656* (070)</td>
<td>Rifapentine / Moxifloxacin / INH/PZA (4-month regimen)</td>
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<tr>
<td>Macrolides</td>
<td>FNDR-20364*</td>
<td>Pyrifazimine (TBI-166)</td>
<td>SQ-109*</td>
<td>Telacebec*</td>
<td>Underline = updates since March 2021</td>
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<td>Mycobacterial Gyrase Inhibitors</td>
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<td>SPR720*</td>
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<td>Arylsulfonamides</td>
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<td>Macozinone*</td>
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<td>Inhibitors of MmpL3, Translocase-1, Ctp, PKS13, F-ATP synthase</td>
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<td>Oxazolidinones</td>
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*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

1 New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline/clinical](http://www.newtbdrugs.org/pipeline/clinical)

Ongoing projects without a lead compound series identified: [http://www.newtbdrugs.org/pipeline/discovery](http://www.newtbdrugs.org/pipeline/discovery)
Recent Discovery Progress at TB Alliance

Advancing the pipeline

- **TBI-223**: SAD study completed
  - MAD study began in January 2021
  - 3-month and 6-month animal GLP studies confirmed the lack of bone marrow toxicity
- **TBAJ-876**: Completed IND enabling studies
  - Began Phase 1 trials in 2020
- **TBAJ-587**: Advanced in partnership with Innovative Medicines Initiative (IMI)
  - Began clinical-stage testing in 2020
  - 3-month safety studies completed; revealed no new findings to the 4-week study
- **MmpL3**: Selected 2 preclinical leads
  - MPL-446 initiated safety studies
  - MPL-447 endorsed into IMI portfolio; safety studies began Q1 2021
- **GHIT-sponsored collaborations with Astellas, Chugai, Daiichi Sankyo RD Novare, and Takeda**