TB Alliance

About TB Alliance

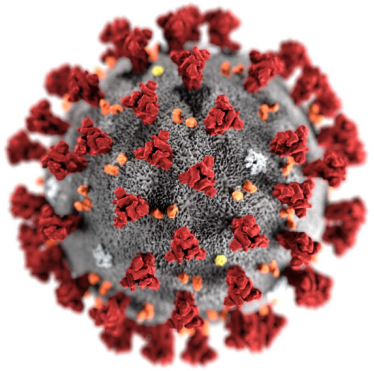
Putting science to work for better, faster TB cures

Fighting pandemics

COVID-19 pandemic caused by virus

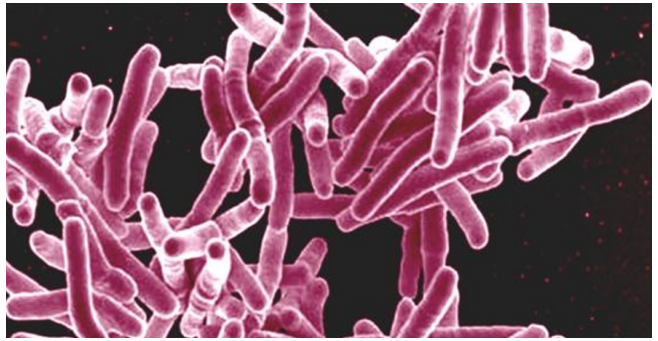
- Caused by SARS-CoV-2, a type of coronavirus
- Primarily affects the respiratory system but other organs as well
- An airborne disease
- More than 5 million people dead from COVID-19

  (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



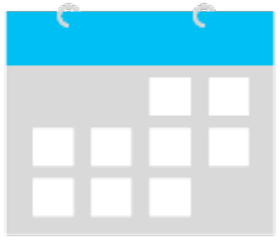
TB is a Pandemic

TB is one of the **LEADING** infectious disease killers

and a **TOP 10** killer worldwide

killing one person every **22 SECONDS**

every year

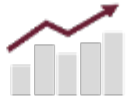


1 MILLION children become ill with TB

1.4 MILLION people die from TB

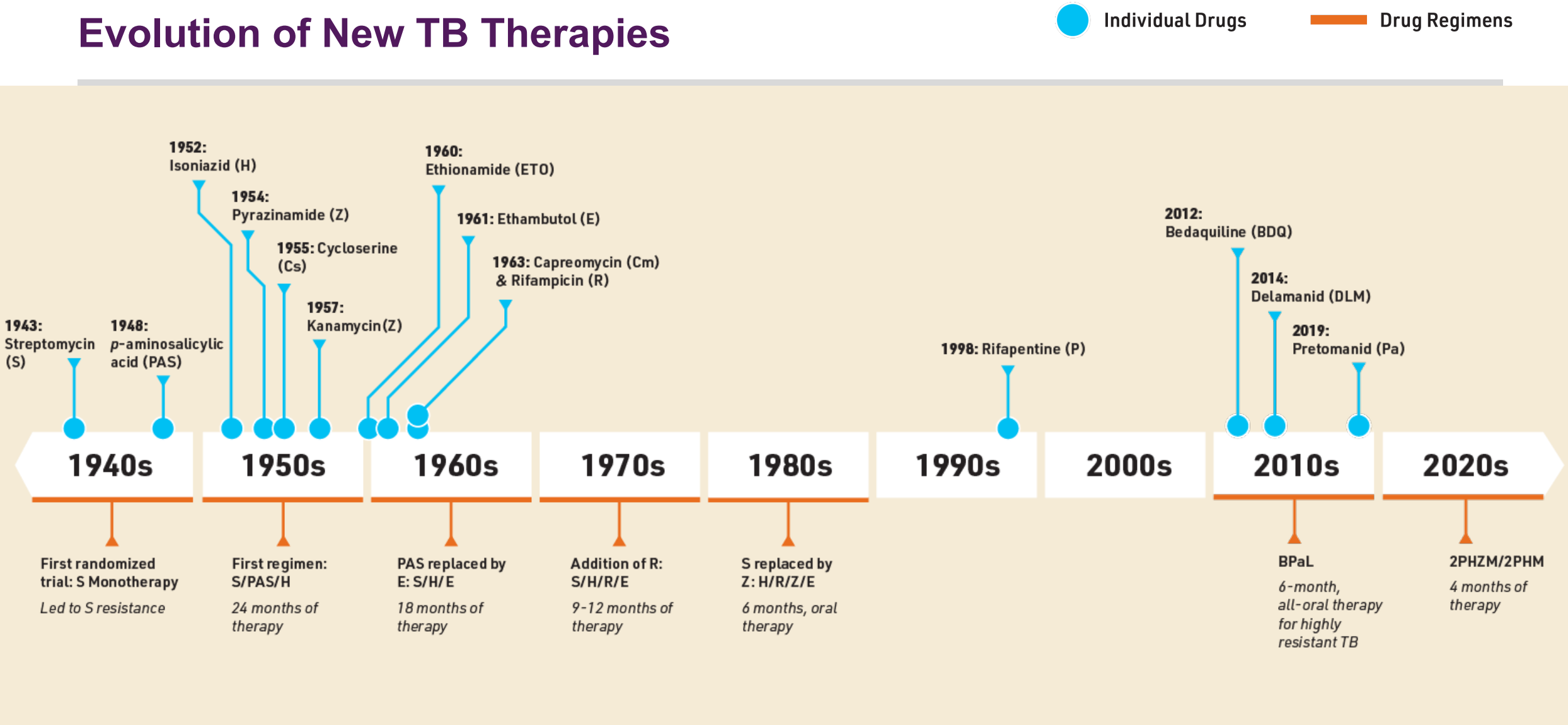
10 MILLION new TB cases develop

Leading killer of people with HIV/AIDS



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

Evolution of New TB Therapies



Cape Town Declaration (Feb 2000)

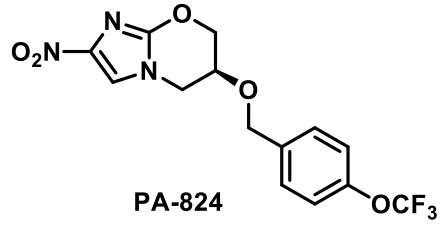
- The Cape Town Declaration was issued to accelerate the development of new drugs to shorten the treatment of TB and to facilitate its control in the poorest countries
- Signatories included the Rockefeller Foundation, US NIH, Bill and Melinda Gates Foundation, the Welcome Trust, Doctors Without Borders, 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)

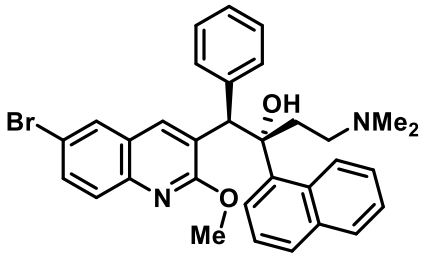
- The original compound was licensed from Pathogenesis (Chiron)
- New chemotype and new mechanism of action
- Potent *in vitro* and *in vivo* activity
- Drug combinations studies at Johns Hopkins University(JHU)

  showed promising synergistic activity in animal models

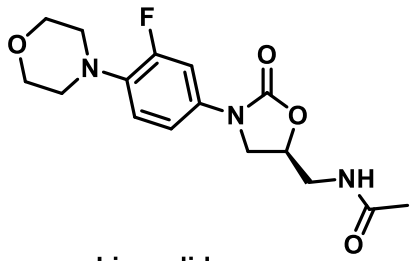
  especially in combination with bedaquiline and linezolid – i.e. the “BPaL regimen”



PA-824



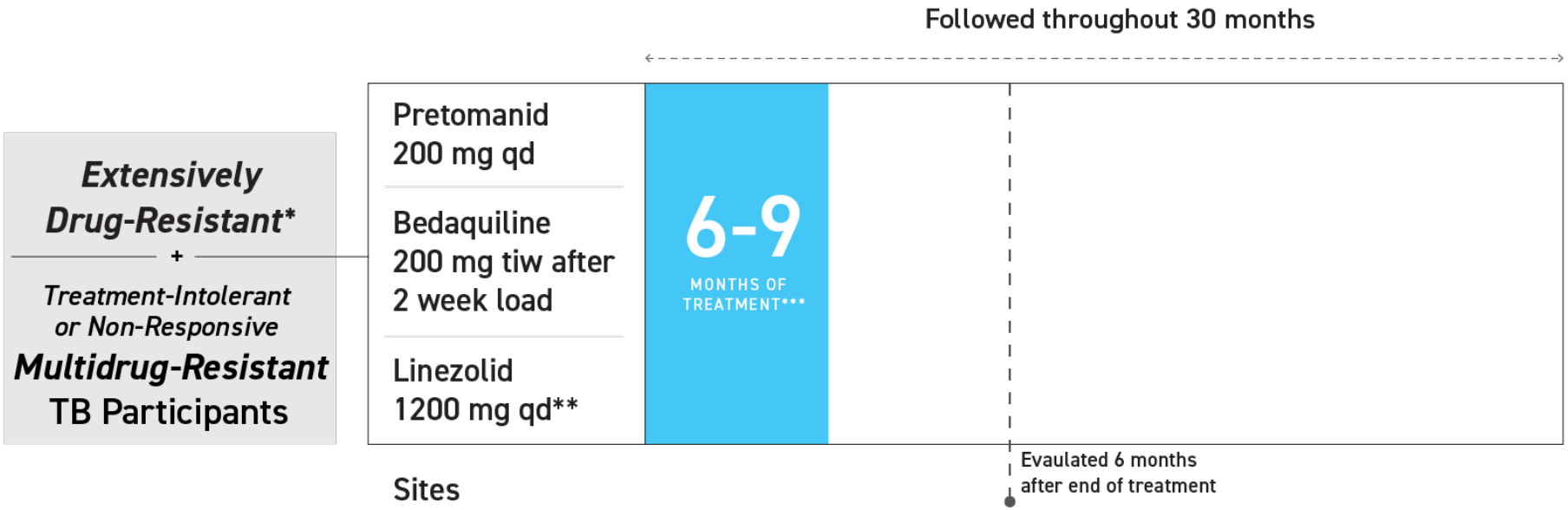
Bedaquiline



Linezolid

Nix-TB Phase 3 Clinical Trial

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



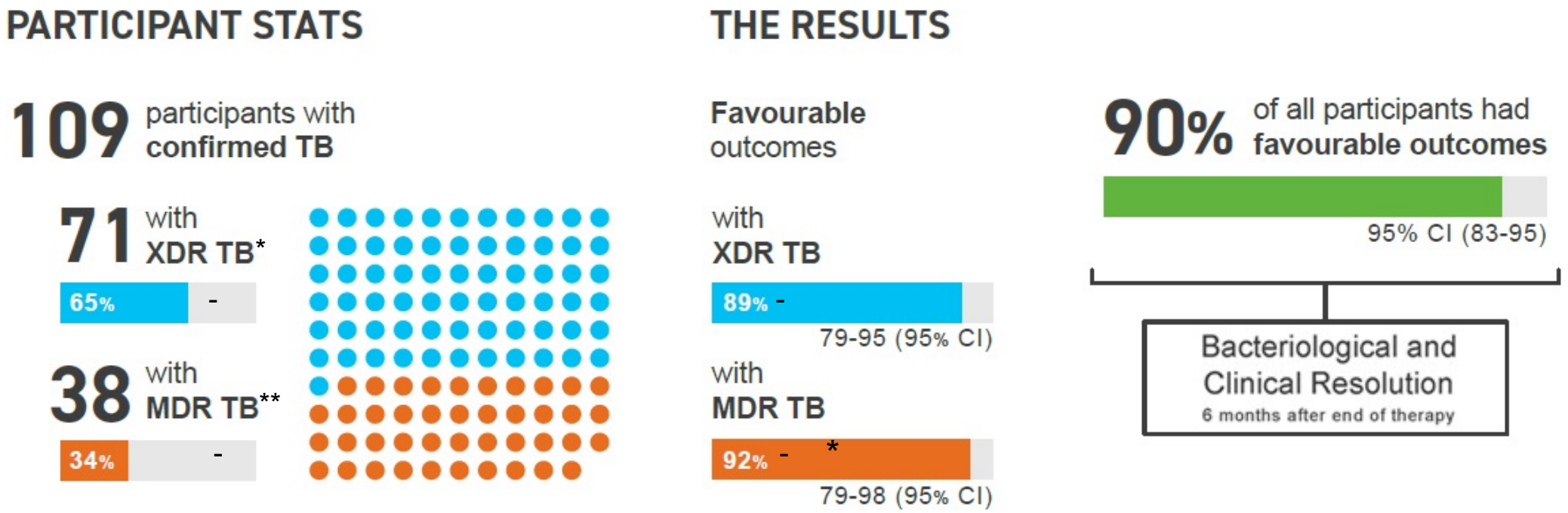
Sites

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



*Using definition of XDR-TB prior to 2020
**Treatment-intolerant or non-responsive MDR-TB

U.S. FDA Approves New Treatment for Highly Drug-Resistant Forms of 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

Source: Conradie et al. Bedaquiline, pretomanid and linezolid for treatment of extensively drug resistant, intolerant or non-responsive multidrug resistant pulmonary tuberculosis. *N Eng J Med* 2020;382:893-902.

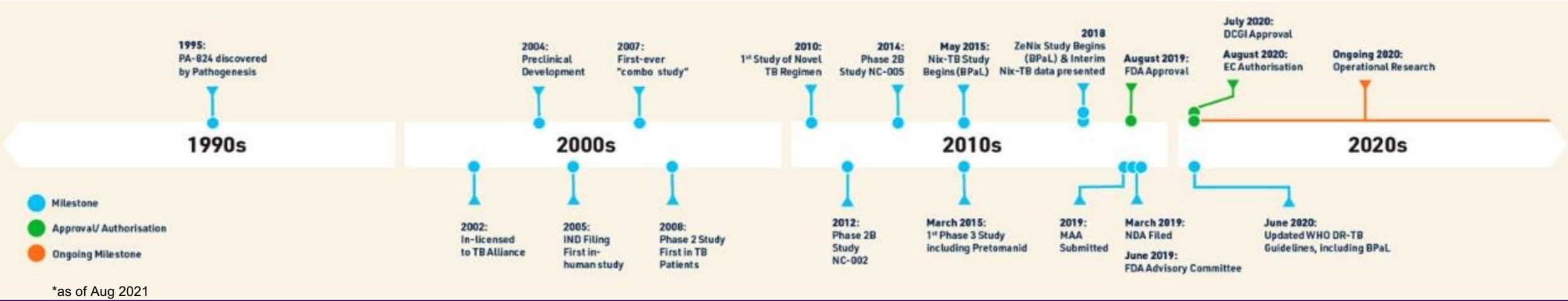
* Limited Population Pathway for Antibacterial and Antifungal Drugs

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

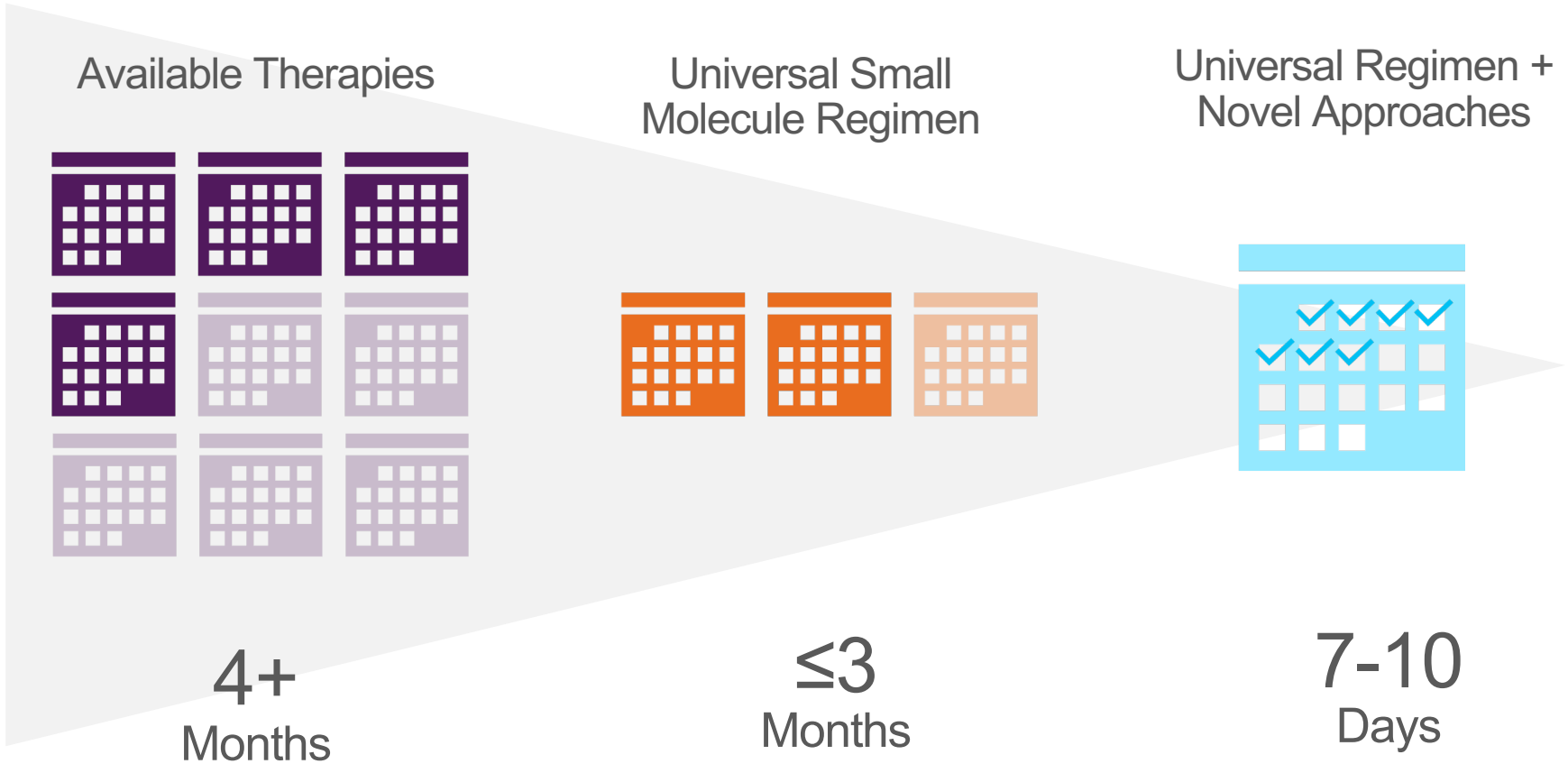
For more on pretomanid's unique mechanism of action, visit: tballiance.org/pretomanid



*as of Aug 2021

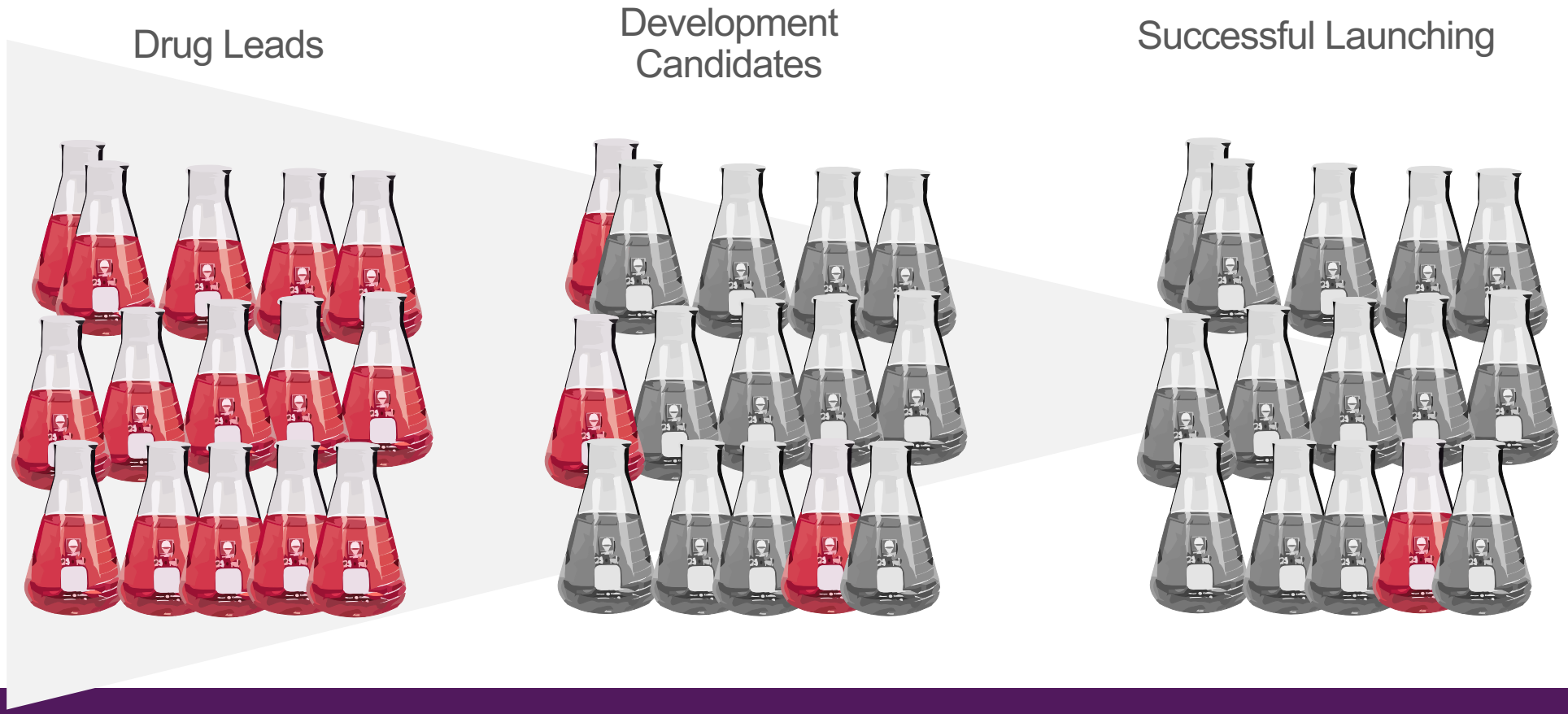
The Future of TB Treatment

Novel drug combinations enable shorter, simpler and more effective treatment



The Future of TB 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
2. Metabolomics of Mtb -> K. Planck and K. Rhee, Methods Mol Biol, 2021, 2314, 579-593
3. Caseum: a Niche for Mtb Drug-Tolerant Persisters, J. J. Sarathy and V. Dartois, Clinical Microbiol Rev. 2020, 33 (3) e00159-19
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
7. Artificial Intelligence, Machine Learning, and Deep Learning in Real-Life Drug Design Cases, C. Mueller, et al., Artificial Intelligence in Drug Design, 2022, 2390, 383-407
8. Host-directed Therapeutic Strategies for TB, A. Kolloli and S. Subbian, Front. Medicine, 2017, 4: 171

TB Alliance and GHIT Fund

GHIT Fund
Global Health Innovative Technology Fund

- 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.

astellas
CHUGAI
Daiichi-Sankyo
Takeda
UIC

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

Hit and lead criteria in drug discovery for **infectious diseases** of the developing world. Katsuno K, Burrows JN, Duncan K, Hooft van Huijsduijnen R, Kaneko T, Kita K, Mowbray CE, Schmatz D, Warner P, Slingsby BT. Nat Rev Drug Discov. 2015, 14(11):751-8.

TB Alliance and GHIT Fund

- 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

20 YEARS OF IMPACT

Australian Aid

BILL & MELINDA GATES foundation

CYSTIC FIBROSIS FOUNDATION

EDCTP

Federal Ministry of Education and Research

국제질병퇴치기금
Global Disease Eradication Fund | KOREA

GHIT Fund
Global Health Innovative Technology Fund

Indonesia 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

Ministry of Foreign Affairs
Republic of Korea

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 [1]

Discovery | Preclinical Development | Clinical Development

Lead Optimization

PanD inhibitors

Indazole sulfonamides

Diarylthiazoles

DprE1 Inhibitors

Direct InhA Inhibitors

Mtb energy metabolism

Macrolides

Mycobacterial Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase

Oxazolidinones

Early Stage Development

JSF-3285*

MPL-446, 447*

CPZEN-45*

NTB-3119*

TZY-5-84

MBX-4888A (1810)*

FNDR-10045*

FNDR-20364*

GMP / GLP Tox.

FNDR-20081*

TB-47*

GSK-839*

OTB-658

Sanfetrinem

Phase 1

BVL-GSK098*

GSK-286*

TBAJ-587

TBAJ-876

TBI-223

Macozinone* (PBTZ-169)

Pyrifazimine (TBI-166)

Phase 2

Delpazolid

Sutezolid

BTZ-043*

TBA-7371*

OPC-167832*

GSK-656* (070)

SQ-109*

Telacebec*

SPR720*

Macozinone*

Phase 3

Pretomanid* / Moxifloxacin / Bedaquiline*/ PZA (4-month regimen)

Truncate TB (2-month regimens)

Rifapentine / Moxifloxacin / INH/PZA (4-month regimen)

Regulatory Market Approvals

Bedaquiline*

Delamanid*

Pretomanid*

Underline = updates since March 2021

*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

Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: October 2021

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