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

Christopher B. Cooper, Ph.D.
Senior Director, Chemistry
Global Alliance for TB Drug Development (TB Alliance)
40 Wall Street, 24th Floor
New York, NY 10005
USA
Christopher.cooper@tballiance.org

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Streamlining Drug Discovery and Development Symposium
14 April 2016
South San Francisco, CA

TB Pandemic

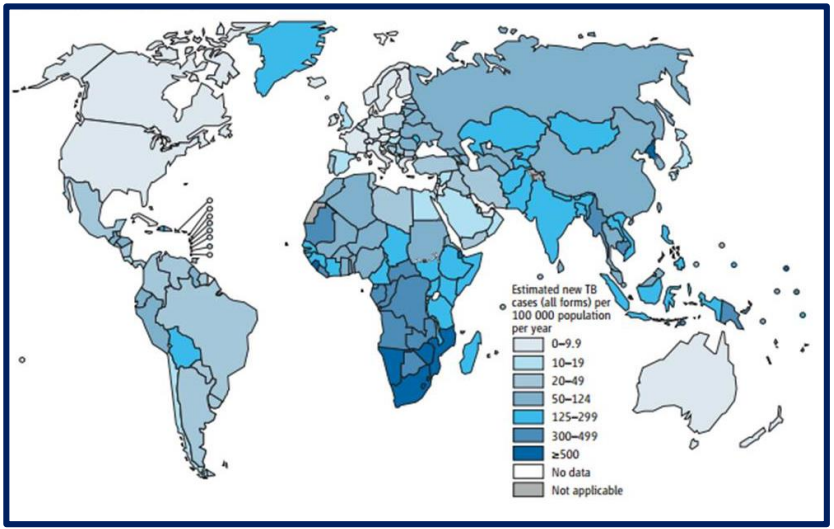
Tuberculosis is one of the leading global killers

- 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

Global incidence rate 2012 (WHO)



TB Anywhere is TB Everywhere

Bugs do not respect borders

- 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

Indian Woman With Tuberculosis Sets Off Scare In 3 US States

Race is on to track hundreds of people exposed to woman with 'extreme' TB who traveled across three states while contagious

PHARMA & HEALTHCARE 5/01/2015 @ 7:00AM | 3,147 views

The World Is Not Prepared For Terrifying Superbugs

+ Comment Now + Follow Comments

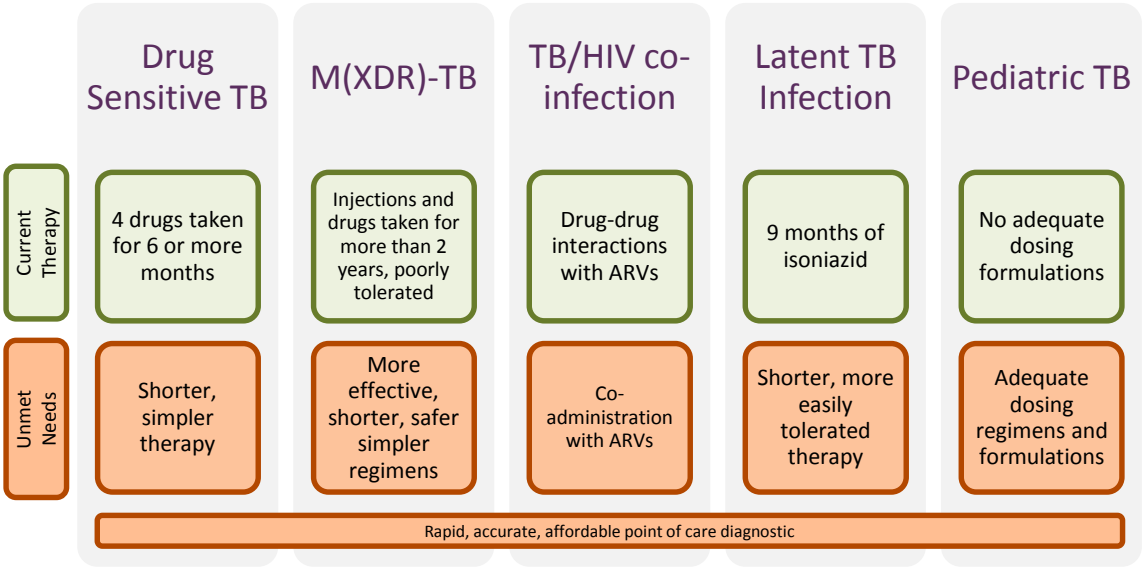
Exclusive: Patient With Extreme Form of TB Sent to NIH

News Alerts > Medscape Medical News

Patient With XDR TB Sets Off Contacts Hunt

Robert Lowes

Current TB Therapy and Unmet Needs



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

About TB Alliance

TB ALLIANCE
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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

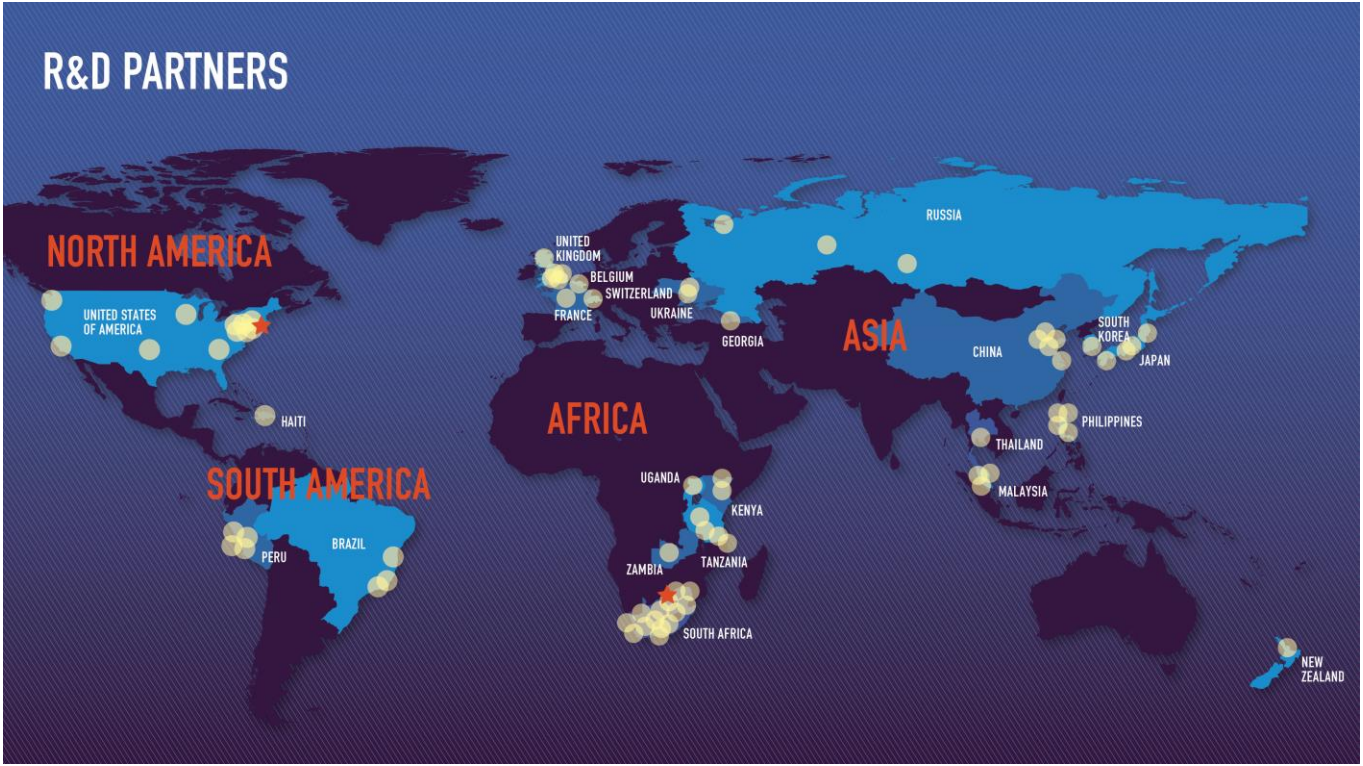
- Offices in New York, USA; Pretoria, South Africa; Brussels, Belgium (total staff: 48)

- 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

Current Treatment

6-30
Months

New Treatments in Development

2-4
Months

Aspirational Goal

7-10
Days

- Shorter, simpler regimens
- No pre-existing drug resistance (“universal”)
- Success requires novel drug combinations

TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

2016 Q2

Discovery

Early Development

Late Development

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- Preclinical TB Regimen Development *JHU*

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- TBA-354
- Pharmacokinetics of first-line drugs in children < 5kg *Stellenbosch University*

PHASE 2A

- Linezolid Dose-Ranging Study

PHASE 2B

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  - Ethambutol/ Rifampicin/ Pyrazinamide for children > 5kg
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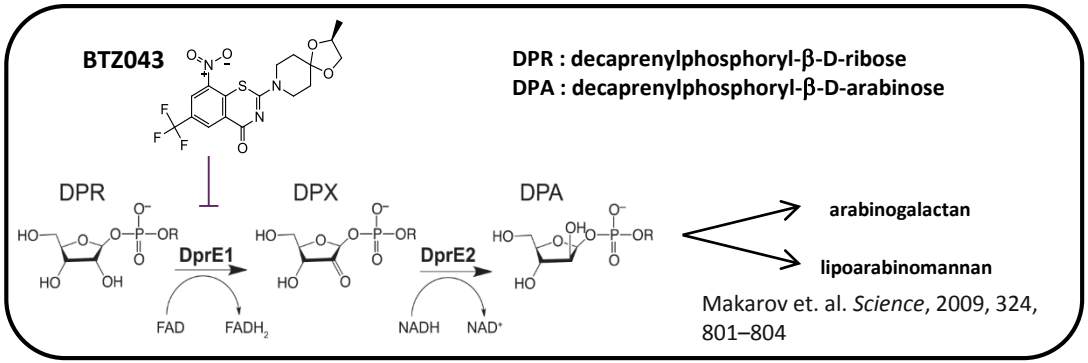
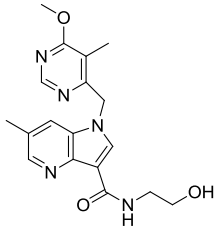
1,4-azaindoles: novel, non-covalent inhibitors of DprE1

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



Makarov et. al. *Science*, 2009, 324, 801–804



Compound **1** (**TBA-7371**)

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

Chatterji, et. al. *Antimicrob Agents Chemother*., 2014, 58, 5325-5331.

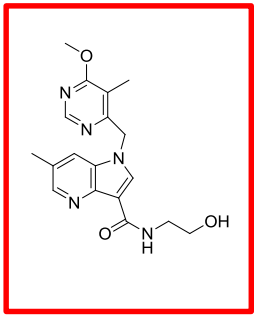
Kolly et. al., *Mol Microbiology*, 2014, 92, 194-211

AstraZeneca

1,4-azaindole: Potential Drug Candidate for Treatment of Tuberculosis

Chatterji M, Shandil R, Manjunatha MR, Solapure S, Ramachandran V, Kumar N, Saralaya R, Panduga V, Reddy J, K R P, Sharma S, Sadler C, Cooper CB, Mdluli K, Iyer PS, Narayanan S, Shirude PS.

Antimicrob Agents Chemother, **2014**, 58, pp. 5325-31.



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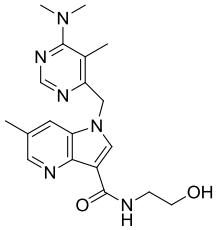
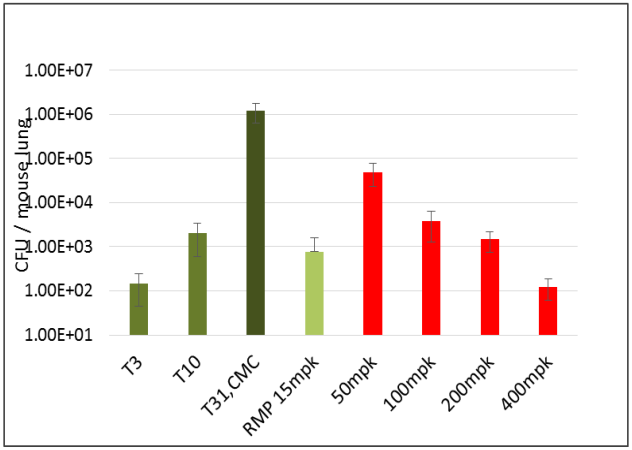


Compound **2**
TBA-8140

Mtb DprE1 IC_{50} (nM)	**10.2**
Mtb MIC (µM)	0.78-3.12
Mtb MBC (µM)	1.56
Mtb LORA (uM)	≥32
Drug sensitive clinical isolates MIC (µM)	0.4-6.25
INH^R, RIF^R clinical isolates (µM)	0.78-3.12
Mtb DprE1 over-expression strain MIC (µM)	50-200
Mtb DprE1 C387S/G ($BTZ043^R$) MIC (µM)	0.78-1.56
Intracellular THP1 (log_{10}CFU reduction)	~1.5
Cytotoxicity (µM) THP-1	>100
Ames	Negative
hERG IC_{50} (µM)	>33
PDE6 IC_{50} (µM)	4 (only sec. pharm. hit)

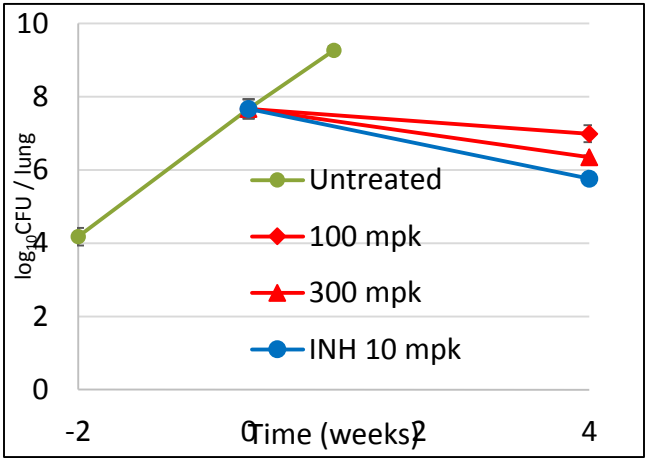
AstraZeneca

TBA-7371 demonstrates dose-responsive bactericidal efficacy in mice



UIC UNIVERSITY OF ILLINOIS AT CHICAGO

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



JOHNS HOPKINS MEDICINE

High dose aerosol model of acute infection
H37Rv, BALB/c mice, 4 wks Rx

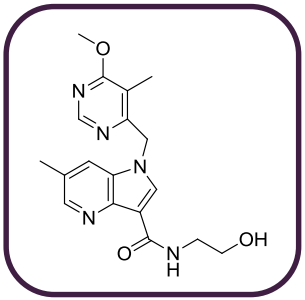
- Estimated MED: 100 mg/kg with $AUC_{0\text{-}24h}$ in mice = ~30 h*ug/mL (25-40 h*ug/mL)

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): >=1000 mg/kg; $AUC_{0\text{-}24h}$ = 643/1163 hr*ug/mL (M/F)
- MED in Mice: 100 mg/kg; $AUC_{0\text{-}24h}$ = ~30 h*ug/mL
- **Safety margin: ~21/39X (M/F)**

Projected preliminary efficacious human dose: ~ 500 mg QD



TBA-7371

Initiated 14 day dog non-GLP safety study

- Data expected mid-May, 2016

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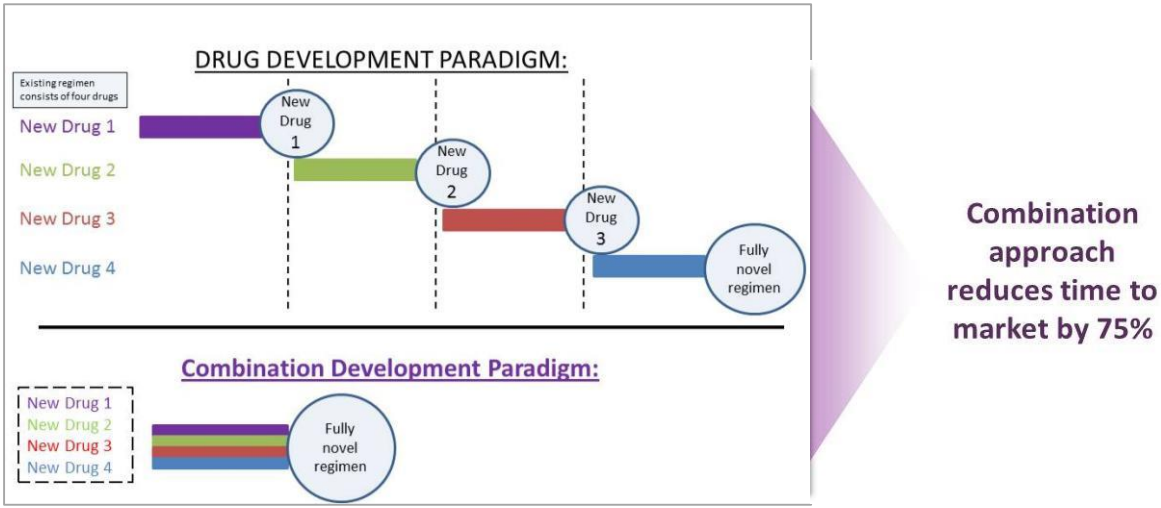
Accelerating Progress: From Drugs to Regimens

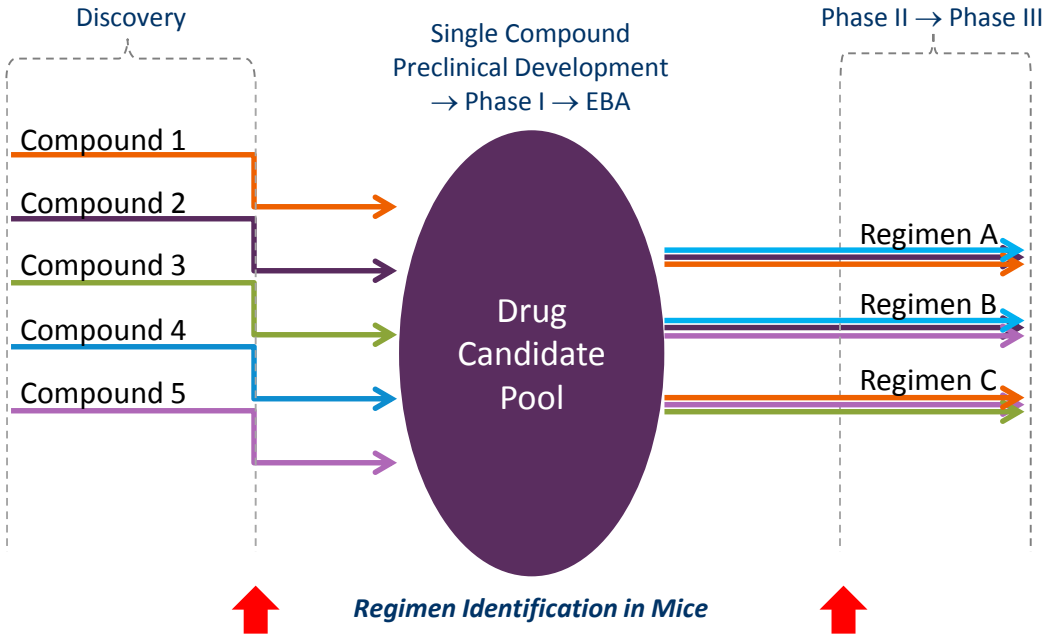
TB Alliance is searching for the best combinations of novel drugs

- 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

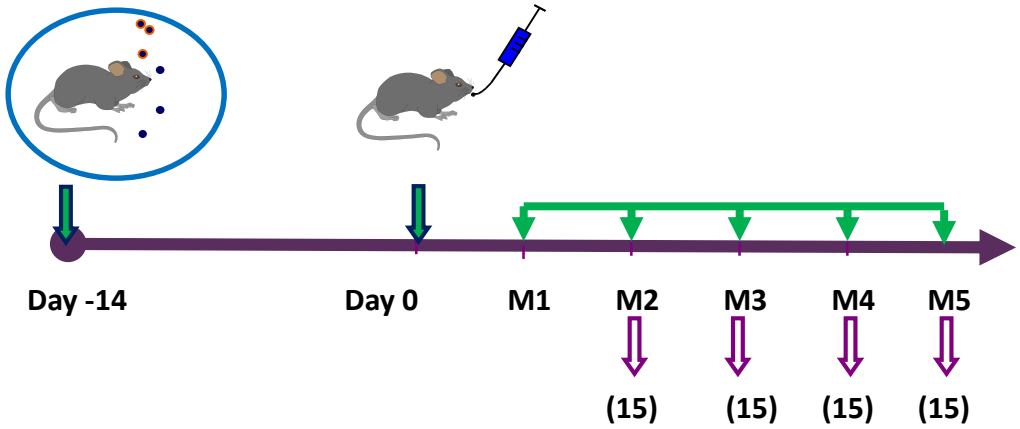


TB Drug/Regimen

Discovery and Development Process



Scheme for Relapse Experiments



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

Multiple Drug Combinations of J, Pa, L, U, Z and M

	Mean lung CFU count (proportion of mice relapsing)							
	D-17	D0	M1	M1.5 (+3)	M2 (+3)	M3 (+3)	M4 (+3)	M5 (+3)
RHZ			4.16±0.24		2.47±0.26		(10/15)	(2/15)
PaMZ			3.50±0.06		1.39±0.54	(10/14)	(3/15)	
JPaM			3.61±0.15		2.33±0.18	(2/15)	(0/14)	
JPaZ			1.71±0.11	(13/14)	(0/15)	(0/15)		
JPaZM			1.74±0.03	(3/15)	(0/15)	(0/15)		
JPaZ			**2.89± 0.35**	(9/15)	(1/15)			
1JPaZL$_{100}$/1JPaZ			**0.07***	(0/15)	(0/15)			
2JPaZL$_{100}$				(0/15)	(1/15)			
JPa			4.48±0.20		2.34±0.34	(3/14)		
JPaU			1.88±0.22		(1/14)	(0/14)		
3JPaL$_{100}$						(0/15)		
2JPaL$_{100}$/1JPaL$_{50}$						(1/12)		
2JPaL$_{100}$/1JPa					(6/15)	(0/15)		
1JPaL$_{100}$/2JPa			2.45±0.16		(9/15)	(0/15)		

- 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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OP-BIO
Roche Pharmaceuticals
Rutgers University
Sanofi
Schrödinger
Shionogi
Stellenbosch University
Takeda Pharmaceuticals
TB Drug Accelerator (TBDA)
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

TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

2016 Q2

Discovery

LEAD IDENTIFICATION

- ATP Synthesis Inhibitors *Calibr*
- Whole-Cell Hit-to-Lead Program *Sanofi*
- Whole-Cell Hit-to-Lead Program *GSK*
- RNA Polymerase Inhibitors *Rutgers University*
- Energy Metabolism Inhibitors Univ. Auckland
- POA Prodrugs *Yonsei*
- Clp-C/PIP2 *Schrödinger*
- PEPCK *Roche/TAMU*
- Hit ID Programs
  - *Daiichi Sankyo*
  - *OP-BIO*
  - *Takeda*
  - *Shionogi*

LEAD OPTIMIZATION

- Macrolides *Sanofi*
- Ureas *Sanofi*
- Diarylquinolines *Janssen/University of Auckland/UIC*
- DprE1 Inhibitors
- MmpL3 Inhibitors
- InhA Inhibitors
- Cyclopeptides *Sanofi*
- Oxazolidinones *IMM*
- Squaramides
- *Pyrimidines GSK*
- PKS-13 *Dundee/TAMU*
- Indazoles *GSK*

PRECLINICAL DEVELOPMENT

- Preclinical TB Regimen Development *JHU*

Early Development

PHASE 1

- TBA-354
- Pharmacokinetics of first-line drugs in children < 5kg *Stellenbosch University*

PHASE 2A

- Linezolid Dose-Ranging Study

Late Development

PHASE 2B

- NC-005: Pretomanid/ Bedaquiline/ Pyrazinamide (BPaZ)
- Nix-TB: Pretomanid/ Bedaquiline/ Linezolid

PHASE 3

- STAND: Pretomanid/ Moxifloxacin/ Pyrazinamide (PaMZ)

PHASE 4

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

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)
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Nix-TB: Accelerating solutions for XDR-TB

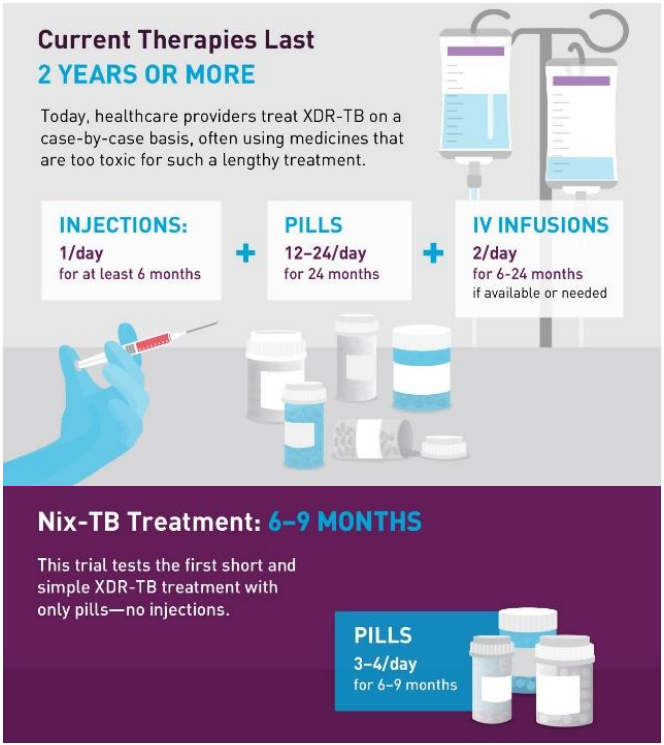
New Investigational Drugs for XDR-TB

- 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.

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AIDS Clinical Trial Group

European Commission

United States Food and Drug Administration

Global Health Innovative Technology Fund

Australian AID

Irish Aid

Thank you!

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