CPTR-NIAID 2017 Workshop

TB Drug Discovery and Development: Challenges and Goals
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TARGET PRODUCT PROFILE

TARGET indication
3 or 4 drug regimen Indicated as First Line treatment of active pulmonary TB infection, regardless of rifampin resistance – Universal or Pan TB Regimen

SIMPLER
• No Drug Sensitivity Testing to establish Treatment
• All Oral (no injectables), Fixed Dose Combination
• No DDIs (particularly with ARVs), no dose modification of ARVs or TB drugs

SAFER
• No Routine Safety Lab or ECG Monitoring

SHORTER
• < 4 months

AFFORDABLE
TARGET DURATION

- Standard DS TB regimen duration stands at 6 months
- WHO Universal Regimen TPP
  - Minimum 6 months
  - Optimum ≤ 4 months
- BMGF Drug Initiative
  - Aspirational Target 1-2mos
  - Current Clinical Trials
    - Evaluating 4 months in DS
    - Contingency, 6 months in DS
    - MDR 6 months
TARGET POPULATION – PAN TB
ACCELERATE DECLINE IN EPIDEMIC – TARGET DS TB TO IMPACT EPIDEMIC,
IMPACT BUDGETARY BURDEN – TARGET MDR

2015 TB burden (million cases/yr)

Note: 11 countries include India, China, Indonesia, Nigeria, Pakistan, S Africa, Bangladesh, Myanmar, DRC, Mozambique, and Ethiopia.

Source: Global Tuberculosis Report 2016; WHO (2015); End TB Strategy (2016)
Global TB Drug Pipeline

Discovery

Preclinical Development

Clinical Development

Lead Optimization

Early Stage Development

GLP Tox.

Phase 1

Phase 2

Phase 3

Diarylquinolines

CPZEN-45*

BTZ-043*

Q203*

Sutezolid (PNU-100480)

Bedaquiline

Rifapentine - Moxifloxacin for Drug Sensitive TB

DprE Inhibitors

PBTZ169*

PBTZ169*

Linezolid EBA

High Dose Rifampicin for DS-TB

InhA Inhibitor

TBA-7371*

TBI-166

SQ-109*

Bedaquiline (TMC207)-

Bedaquiline-Pretomanid-

Pretomanid (PA-824) -

Pretomanid-Moxifloxacin-

Pyrazinamide Regimen

Pyrazinamide Regimen

Pyrazinamide Regimen

Pyrazinamide Regimen

Ruthenium(II)Complexes

GSK-070*

OPC-167832

High Dose Rifampicin for DS-TB

Translocase-1 Inhibitors,

Lee 1810*

Levofoxacin with OBR for MDR-TB

Cip, MmpL3,

Oxazolidinones,

Pyrimidines DprE1, Aryl

Sulfonamides, PKS13,

Squaramides

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline,
benzothiazinone, Imidazopyridine amide. New chemical class*

1 Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing

projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

2 OBR = Optimized Background Regimen

www.newtbdrugs.org

Updated: April 2017

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How we currently develop TB drugs / Regimens

**Pre-clinical**
- BALB/c mice 4wk & 8w, mono and combos evaluated empirically, best regimen(s) graduate
- Mouse relapse model to explore regimen duration and best candidate(s) for shortening graduate

**Ph I / IIa**
- SAD / MAD HVTs
  - No ex vivo PK/PD
- 14-Day EBA Mono
- 14-Day EBA Combo, best regimens graduate to SSCC

**Late Phase Development**
- Phase IIB 2-month SSCC, regimen(s) with culture conversion result “better” than HRZE graduate to Phase III. How much “better” to support 2, 3, or 4mos regimen in Phase III?
- Phase III regimen shortening, Non-Inferiority, n=300/arm, ~$75M USD
  - DS2 HRZE (6m)
  - DS Test Regimen (6m)
  - DS Test Regimen (4m)
  - MDR Test Regimen (6m)

Hi uncertainty and risk carried into Ph III
EMERGING CHALLENGES IN TB

• How do we find the best compound within a class, across organizations?

• How do we systematically and efficiently find the optimal drug/exposure combination from a large pool of possibilities?

• How do we improve translation from Ph 2 to Ph 3 for regimen shortening and De-Risk late stage development? Take attrition early.

• How do we efficiently evaluate new combinations in late stage development?