Critical Path to TB Drug Regimens
Global Collaboration for Accelerating Novel TB Regimen Development

Debra Hanna, Executive Director, Critical Path to TB Drug Regimens
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### Global New TB Drug Pipeline

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclinical Development</th>
<th>Clinical Development</th>
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<tbody>
<tr>
<td><strong>Lead Optimization</strong></td>
<td><strong>Early Stage Development</strong></td>
<td><strong>GLP Tox.</strong></td>
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<tr>
<td>Diarylquinolines</td>
<td>CPZEN-45*</td>
<td>BTZ-043*</td>
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<tr>
<td>Diarylthiazoles</td>
<td>SATB082*</td>
<td>GSK-070*</td>
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<tr>
<td>DprE Inhibitors</td>
<td>Spectinamide - 1810*</td>
<td>TBA-7371*</td>
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<tr>
<td>InhA Inhibitor</td>
<td>SPR-720 (pVXc-486)*</td>
<td>TBAJ-587</td>
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<tr>
<td>Macrolides, Azaindoles</td>
<td>TBI-166*</td>
<td><strong>OPC-167832</strong>*</td>
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<tr>
<td>Mycobacterial Gyrase Inhibitors</td>
<td><strong>PBTZ169</strong>*</td>
<td>SQ-109*</td>
</tr>
<tr>
<td>Ruthenium(II)Complexes</td>
<td><strong>Q203</strong>*</td>
<td><strong>Sutezolid (PNU-100480)</strong></td>
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<tr>
<td>Arylsulfonamides</td>
<td>TBI-223</td>
<td>Pretomanid (PA-824)</td>
</tr>
<tr>
<td>Translocase-1 Inhibitors, Clp, MmpL3 Oxazolidinones, Pyrimidines DprE1,PKS13 Squaramides</td>
<td>TB-47*</td>
<td></td>
</tr>
</tbody>
</table>

*New chemical class. Known chemical classes are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

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 can be viewed at [http://www.newtbdrugs.org/pipeline/discovery](http://www.newtbdrugs.org/pipeline/discovery)
Advance TB drug pipeline emphasizing combination study approaches informed by *translational science*. Define, based on evidence, best drug development tools to de-risk compounds and improve understanding of efficacy.

Define, based on evidence, novel biomarkers to inform improved trial design and adaptivity.
The Critical Path to TB Drug Regimens (CPTR) is a global, cross-sector initiative that aims to speed the development of a safer and shorter duration TB drug regimen.

Four Critical Areas of Focus:

- Advance drug development tools and methodologies to support go/no-go decisions during each stage of research and development.
- Acquire and curate supportive data through establishment of collaboration network to support new methods and tool validation.
- Develop pathways for new TB treatment regimens that include drugs that are not yet individually approved.
- Provide regulatory excellence in the development, validation, and advancement of these drug development tools and methodologies.
**CPTR INITIATIVE MEMBERS AND PARTNERS**

### Government/Regulatory participants
- CDC
- FDA
- European Medicines Agency
- World Health Organization
- National Institute of Health
- National Institute of Allergy and Infectious Diseases
- DAIDS/RSC

### Industry members
- AstraZeneca
- Pfizer
- SANOFI
- Celgene
- Cepheid
- VERTEX
- epistem
- GlaxoSmithKline
- Qiagen
- Janssen
- tibotec
- Thermo Fisher
- BD

### Nonprofit research members
- TB ALLIANCE
- Bill & Melinda Gates Foundation
- REAGAN-UDALL Foundation for the Food and Drug Administration
- EDCTP
- TAG
- PATH
- FIND
- Stop TB Partnership

### Academic Partners
- Baylor Institute for Immunology Research
- Case Western Reserve University TB Research Unit
- Colorado State University
- Duke University
- Forschungszentrum Borstel
- Harvard University
- Johns Hopkins University
- London School of Hygiene and Tropical Medicine
- Munich University
- NYU
- O’Neill Institute at Georgetown Law Center
- Radboud University
- RESIST-TB [Boston University]
- Rutgers [University Of Medicine & Dentistry]
- St. George’s, University of London
- Stanford University
- Stellenbosch University
- University of Florida
- University of California, San Francisco
- University College of London
- University of Arkansas for Medical Sciences
- University of Cape Town
- University of Liverpool
- University of St. Andrews
- University of Virginia
- University of Texas Health Science Center at San Antonio
- University of Toronto
- Uppsala University, Dept. of Pharmaceutical Biosciences
- Vanderbilt University School of Medicine
GLOBAL, CROSS-SECTOR PARTNERSHIP

**Eight** Pharmaceutical Partners
Non-Profit Product Development Partners

**Eighteen** Diagnostic Companies

**Twenty-six** Academic Institutions

**Twenty** Non-Governmental Agencies

**Five** Governmental Agencies
Shared learning can shorten the timeline

- Data Sharing and Data Standardization
- Biomarker Development and Qualification
- Drug Development Tool Advancement and Qualification
- Development and Implementation of Modeling and Simulation Tools

Adapted from “A virtual space odyssey”, Cath O'Driscoll (2004)
http://www.nature.com/horizon/chemicalspace/background/odyssey.html
CDISC TB 2.0 THERAPEUTIC AREA USER GUIDE
DATA COLLABORATION IS CRITICAL

- **Validated Drug Development Tools**
- **Validated Biomarkers**
- **TB Clinical Trial Modeling and Simulation Tools**

**Regulatory Science Consortium**

**Rapid DST Consortium**

**Supportive Evidence Base**

**CDISC Data Standard Integration**

**TB DATA SHARING PLATFORM**

- **CPTTR TB Clinical Trial Data**
- **TB-PACTS WHO C-Path**
- **Pre-Clinical Research Data**
- **Whole Genome Sequence, Phenotypic, Patient Outcome Data**

**Rapid DST Assay Developers**

**Clinicians**

**Researchers**
GAPS IN THE TB DRUG DEVELOPMENT PROCESS

PRECLINICAL
In Vitro HFS-TB

PHASE I-IIa
Safety PKPD
Dose-Ranging PK
14-Day EBA

PHASE IIb
Dosing
POC-human

PHASE III
Randomized
Controlled Trial
Efficacy

CONFRMATORATORY
PROOF OF
COMBINATION
EFFICACY

Varied Models

Big Gap

CRITICAL PATH DRUG DEVELOPMENT DECISIONS

PBPK Modeling

Evidence based evaluation of in vivo PKPD models by PCS-WG

Quantitative Assessment of Liquid Culture Biomarker

PopPKPD Modeling
Population PKPD

Drug-Disease-Trial Model

Systems Pharmacology/
Mechanism Based Models

PENULTIMATE TB CLINICAL TRIAL SIMULATION TOOL
CPTR MODELING AND SIMULATION PROGRAMS

REGULATORY SCIENCE CONSORTIUM

RAW DATA
- Clinical Trials Data
- Registry Data
- Observational Study Data
- Non-Clinical Data

MODELING AND SIMULATION WORKING GROUP
- Meta-Analysis Phase III Trials
- Population PKPD
- HFS-TB
- PBPK
- Mechanistic Modeling
- QTc
- Liquid Culture

USER COMMUNITY
- Clinical Trialists
- Regulators
- Researchers

Right Target
Right Drug(s)
Right Dose(s)
Right Patients
REGULATORY & POLICY SUCCESSES

Hollow Fiber System Model
- Qualified as a translational drug development tool
- Submitted Letter of Intent and Briefing book for Scientific Advice Qualification
- Pursue Innovation Task Force Meeting 1Q2018

Physiologically Based Pharmacokinetic Model

LAM Biomarker

TB-ReFLECT

TB-PACTS

ReSeqTB

- Inserted into Draft Guidance on Drug Development for Pulmonary TB
- Pursue Critical Path Innovation Meeting 1Q2018
- Letter of Intent accepted into the biomarker qualification program

- Inform programmatic decisions based on meta-analysis of Phase III clinical trials
- Sponsored C-Path to aggregate and share TB clinical data
- Implement as the global srv. platform for TB resistance
HOW WE WORK TOGETHER

Bill & Melinda Gates Foundation
TB Team
Diagnostics
Integrated Development

Food and Drug Administration
and
European Medicines Agency

World Health Organization
Tuberculosis
Tropical Diseases
National Laboratory teams

Industry Leads R&D
TB Alliance and Foundation for Innovation Diagnostics
Product Development Partners
FOCUS AREAS

- Drug Development Tools & Methodologies to Support Go/No-Go Decisions During Each Stage of R&D
- Curation of Supportive Data Through Establishment a Collaborative Network to Support New Methods and Tool Validation
- Develop Pathways for New TB Regimens That Are Not Yet Individually Approved
- Provide Regulatory Excellence in the Development, Validation, and Advancement of New Drug Development Tools and Methodologies

WORKING GROUPS

- Data Standards and Integration
- Biomarkers and Clinical Endpoints
- Modeling and Simulation
- Pre-clinical and Clinical Sciences
- Health Authorities Submission

REGULATORY SCIENCE

SUPPORTIVE EVIDENCE BASE

CDISC DATA STANDARD INTEGRATION

TB DATA SHARING PLATFORM

TB Clinical Trial Data

WHO/C-Path Partnership Phase 3 Studies

Pre-Clinical Research Data

Whole Genome Sequence, Phenotypic, Patient Outcome Data