Critical Path to TB Drug Regimens
Role in Facilitating TB Drug Development

Debra Hanna, Executive Director, Critical Path to TB Drug Regimens
19 July 2017
TB DRUG REGIMEN DEVELOPMENT NEEDS

Novel regimen development requires emphasis on combination study approaches

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
CPTR’S MISSION AND FOCUS

• Mission: The Critical Path to TB Drug Regimens (CPTR) is a cross-sector initiative that aims to speed the development of safer and shorter duration anti-tuberculosis (TB) drugs. Focus on:
  – drug development tools and methodologies to support go/no-go decisions during each stage of research and development
  – curation of supportive data through establishment of collaboration network to support new methods and tool validation (and ensure public access wherever possible)
  – developing pathways for new TB treatment regimens that include drugs that are not yet individually approved
  – providing regulatory excellence in the development, validation, and advancement of these drug development tools and methodologies

• CPTR Partners and Members: Consortium of 8 pharma / 18 diagnostic companies, 26 academic institutions, 20 NGOs, and 5 governmental bodies.
PUBLIC PRIVATE PARTNERSHIP MODEL

- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for pre-competitive sharing of data/expertise
  - The best science
  - The broadest experience
  - Active consensus building
  - Shared risk and costs
- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Pursue official regulatory recognition through “qualification” of Novel Methodologies and Drug Development Tools

*Multiple companies within each sector*
Start at the end approach: Up-front conversations around the context of use (COU) since the COU drives the level of evidence needed
SHARED LEARNING CAN SHORTEN THE TIMELINE

- Data Standardization and Sharing
- Biomarker Development and Qualification
- Clinical Outcome Assessment Measures
- Modeling and Simulation Tools

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

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

**Rapid DST Consortium**
- Rapid DST Assay Developers
- Clinicians
- Researchers

**Supportive Evidence Base**
- CDISC Data Standard Integration

**TB Data Share Platform**
- TB Clinical Trial Data
- WHO/C-Path Partnership Phase 3 Studies
- Pre-Clinical Research Data
- Whole Genome Sequence, Phenotypic, Patient Outcome Data
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
EVIDENCE BASED EVALUATION OF HOLLOW FIBER SYSTEM MODEL FOR TB
• HFS-TB qualified for use in drug development programs as additional and complementary tool
• HFS-TB can be used in regulatory submissions, esp. for informed design and interpretation of clinical studies
• HFS-TB is recommended to be useful as follows:
  ✓ To provide preliminary proof of concept for developing a specific drug or combination to treat TB
  ✓ To select the pharmacodynamic target (e.g. $T_{\text{MIC}}$, AUC/MIC)
  ✓ To provide data to support PK/PD analyses leading to initial dose selection for non-clinical and clinical studies
  ✓ To assist in confirming dose regimens for later clinical trials taking into account human PK data and exposure-response relationships
Appropriate Dose Selection in Mice

Combination Efficacy (Mouse Acute Model)

Combination Efficacy (Mouse Relapse Model)

PK/Chemical Interaction

Confirmation of Efficacy

Secondary Species Infection Model

Combination Safety (if needed)

MOUSE MODEL OF STERILIZING ACTIVITY

Single Drug PK in Mouse

Bactericidal Activity: Initial Screening

Sterilizing Activity: Duration of Therapy

15 mice held for 3 months after treatment completion to determine the proportion with microbiological evidence of relapse

Day -14

Day 0

M2

M3

M4

M5

Clinical Studies
EVIDENCE-BASED EVALUATION OF STERILIZING MOUSE MODEL

General Aim:
Quantify the predictive accuracy of mouse TB efficacy models to estimate the treatment-shortening potential of a test regimen, by evaluating differences in the treatment duration necessary to prevent relapse compared to control (standard TB regimen).

Intended Application:
The data from experiments in mice infected with *M. tuberculosis*, using relapse as the main endpoint will be used to:

- Calculate treatment effect sizes, to then rank-order regimens
- Estimate clinical treatment duration
High unmet need for real-time assessment of efficacy in TB drug development trials

- Field requires a tool that:
  - Assesses Early Bactericidal Activity (EBA) and Sputum Culture Conversion (SCC), endpoints recommended by FDA and EMA, in real-time, allowing for quick decision making
  - Reduces cost associated with delayed results in development of drugs for TB, a therapeutic area with limited treatment options and few commercial incentives
  - Can be easily utilized in any laboratories that are suitable for clinical trials
  - Is not affected by contamination or drug carry-over effect

- EBA and SCC are useful but challenging to conduct
  - Time delays and labor intensive
  - Issues with contamination and drug carry over effects
THE OPPORTUNITY: LAM AS A REAL-TIME EVALUATION OF TREATMENT RESPONSE

• LAM: Lipoarabinomannan; a major cell wall component

• A new immunoassay was developed (LAM-ELISA) that measures sputum LAM
  – Specific for LAM from MTB and a few slow growing mycobacterium strains
  – No cross-reactivity with oral bacteria
  – Strong correlation between sputum LAM and cfu counts/TTD

• Not affected by contamination or drug carry-over

• LAM-ELISA: 20 min LAM extraction; 5 hours ELISA

• Quicker tests being developed (results in <1 hour)
LAM BIOMARKER EFFORT

• An expert team convened to assess lipoarabinomannan (LAM) as a pharmacodynamic biomarker for quantitative measurement of bacterial load in sputum.

• This is one of the first pharmacodynamic biomarkers C-Path has advanced to a proposed Context of Use discussion with FDA.

• A Letter of Intent was submitted to FDA on June 9, 2017 to pursue regulatory qualification.
Use Statement

• LAM is a pharmacodynamic biomarker for quantitative measurement of bacterial load in sputum. A decrease of LAM in sputum likely reflects the reduction of bacterial load in the lung.

• This pharmacodynamic biomarker should be considered with other microbiological measurements, such as culture, as a real-time evaluation of treatment response in clinical trials of patients with pulmonary tuberculosis and positive smears and cultures, such as:
  – 14-day early bactericidal activity (EBA) trials,
  – Clinical trials of pulmonary tuberculosis up to 56 days, or
  – Clinical trials to provide evidence for early decision making in adaptive trial designs.
The Envisioned Impact: Potentially Shortens Development Time by 2-3 Years

**Traditional**

<table>
<thead>
<tr>
<th>Regimen 1</th>
<th>EBA</th>
<th>Regimen 2</th>
<th>12-18 months for regulatory approvals in many TB endemic countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen 2</td>
<td></td>
<td>Regimen 2</td>
<td></td>
</tr>
<tr>
<td>Regimen 3</td>
<td></td>
<td>Regimen 3</td>
<td></td>
</tr>
<tr>
<td>Regimen 4</td>
<td></td>
<td>Regimen 5</td>
<td></td>
</tr>
<tr>
<td>Regimen 5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12-18 months

**With qualified biomarker**

<table>
<thead>
<tr>
<th>EBA/Phase 2/Phase 3 (1 protocol; seamless enrollment)</th>
</tr>
</thead>
</table>

**Phase 2**

<table>
<thead>
<tr>
<th>Phase 2 (2-mo SCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen 2</td>
</tr>
<tr>
<td>Regimen 3</td>
</tr>
<tr>
<td>Regimen 5</td>
</tr>
</tbody>
</table>

12-18 months for regulatory approvals in many TB endemic countries

**Phase 3**

<table>
<thead>
<tr>
<th>Pivotal endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen 3</td>
</tr>
</tbody>
</table>

36-48 months

**Total**

| 7-10 years |

Regimen 1 -> STOP
Regimen 2 -> STOP
Regimen 3 -> STOP
Regimen 4 -> STOP
Regimen 5 -> STOP

Evaluate for pivotal endpoint 5-7 years

Real-time test for biomarker (stop for lack of efficacy)
CPTR INITIATIVE MEMBERS AND PARTNERS

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

**Industry members**
- AstraZeneca
- Pfizer
- Sanofi
- Celgene
- Cepheid
- Portola
- Vertex
- Becton Dickinson
- Qiagen
- Janssen
- Epistem
- Alere
- TIB MOLBIOL
- Thermo Fisher Scientific
- Tibotec
- GSK
- GlaxoSmithKline
- Biomerieux
- Otsuka
- Abbott

**Nonprofit research members**
- TB Alliance
- Bill & Melinda Gates Foundation
- EDCTP
- TAG
- PATH
- REAGAN-UDALL Foundation
- 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 Diego
- 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
Thank you