Critical Path to TB Drug Regimens

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The Challenge - New Regimens Needed

- Emphasis on combination study approaches rather than development of single agents needed
- Increasingly “fragile” TB drug development pipeline with the continued divestment of companies in the Anti-infective space
- Develop and validate models and methods that can accelerate the drug development process, de-risk programs and decrease risk of failure
Accelerate the development of new, safe, and highly effective regimens for TB by enabling early testing of drug combinations.
Accelerate the development of a regulatory approvable in vitro diagnostic assay for rapid drug susceptibility testing of TB to facilitate drug development and rational use of new drug regimens.

**AND**

Develop a suite of modeling and simulation tools to de-risk & accelerate TB drug and drug regimen development. Additionally, continue to build the evidence base to evaluate predictivity of HFS-TB for clinical outcomes.
Current TB Regimen Development
Risk of Late Stage Attrition

**PRECLINICAL**
- Varied models approached currently applied

**PHASE I-IIa**
- Safety PKPD
- Dose-Ranging PK
- 14-Day EBA (Whole Blood Assay?)

**PHASE IIb**
- Dosing
- POC-human
- Two-Month Combination

**PHASE III**
- Randomized Controlled Trial Efficacy

**CONFIRMATORY**
**PROOF OF COMBINATION EFFICACY**

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**Which models best inform critical decisions?**

- Compound Selection / Regimen Evaluation
- Early Indication of Efficacy of Individual Drugs and Limited Data on Combinations
- Dose Selection / Regimen Evaluation
- Gold Standard for Confirmation of Efficacy (Durable Cure)

**BIG GAP**
- Reliability of Predictions Uncertain

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Critical Path Drug Development Decisions
Role in Enabling & Accelerating the Drug Development Process:

- Identify tools/methods that can bring the most value
- Reach scientific consensus by sharing expertise, information, data
- Collaborate with regulators on DDT development & use
- Proceed with regulatory qualification when appropriate
Regulatory Path: Novel Drug Development Tools

- Potential Drug Development Tool or Biomarker
- Actionable Drug Development Tool
- Supporting Data & Evidence Scattered Across Multiple sources
- Integrated Database: TB Data Standard
- Regulatory-endorsed Tool or BM: Context of Use, Supporting Evidence, Available Data Sources

C-Path/CPTR Regulatory Teams
Six projects covering a spectrum of drug-development stages:

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<th>Project Area</th>
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<td>Systems Pharmacology Modeling</td>
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<td>Hollow-Fiber System platform for <em>Mtb</em></td>
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<td>Physiologically-Based Pharmacokinetic Modeling</td>
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<td>Liquid Culture Empirical Modeling</td>
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<td>Risk Stratification Modeling for drug-induced cardiac arrhythmias</td>
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Future State TB Regimen Development

Increase Confidence & Decrease Risk

Critical Path Drug Development Decisions

**PRECLINICAL**
- HFS-TB: biologic rationale/strain/dose response/compound selection
- PBPK Modeling
- Murine models/Balbc. CoU-Evidence base
- Lesion-based
- Kramnick CoU-generate data

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

**PHASE IIb**
- Dosing
- POC-human

**PHASE III**
- Randomized Controlled Trial Efficacy

**CONFIRMATORY PROOF OF COMBINATION EFFICACY**

**BIG GAP**

- Quantitative Assessment of Liquid Culture Biomarker
- PopPKPD Modeling
- Population PKPD

**Penultimate Clinical Trial Simulation Tool**

- Drug-Disease-Trial Model
- Systems Pharmacology/Mechanism Based Models

**HPF-TB:** biologic rationale/strain/dose response/compound PBPK

- Accurate PKPD Translation
- Accurate IVIVE Extrapolation
- Early Indication of Efficacy of Individual Drugs and Data on Combinations
- Dose Selection / Regimen Evaluation

**Increase Reliability of Predictions for Dose Selection and Efficacy Outcomes**

**TPP:** 3mo Regimen

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Integrated HFS-TB Model Components

Inoculation Device (Syringe)

Hollow Fiber Cartridge

Pump

Fresh Media

Central Compartment (Pharmacokinetic PK)

Waste Media

Cross Section Hollow Fiber Cartridge

Drug

Peripheral Compartment (Pharmacodynamic PD)

Hollow Fiber Lumen

Hollow Fiber Wall

Bacteria

Pump-controlled Syringe (Drug Delivery)
HFS-TB Predicted vs. Clinic Observed Outcomes

Positive Qualification Opinion issued by EMA!!!!
PBPK: Model structure

Right lung:
- Low lobe
- Middle lobe
- Top lobe

Left lung:
- Low lobe
- Top lobe

Lower airway

Upper airway

Alveoli

Mass

Blood

Pulmonary Blood Reservoir

Venous Blood

Arterial Blood
Model Implemented on SIMCYP Platform

Plasma

Adipose

Brain

Bone

Gut

Heart

Kidney

Liver

Muscle

Pancreas

Port Vein

Skin

Spleen

Artery

Lung
**GOAL:** Develop population PK-PD (POPPK-PD) model for TB. Explore PK-PD data where therapeutic drug monitoring was practiced in clinical setting.

- Develop a POPPK understanding for 1st line drugs in patients with active disease
- Develop a POPPK understanding for 2nd line drugs in patients with active disease
- Develop a comprehensive POPPK-PD model for relevant endpoints for efficacy and safety
GOAL 1
Develop a quantitative model of TTP trajectory (EBA and Phase II studies)

GOAL 2
Develop a quantitative model linking TTP trajectory (Goal 1) to long term relapse with REMox

GOAL 3
Develop a model to derive TTP data from CFU data (“TTP/CFU” model). Link grouped trajectories of TTP incorporating treatment duration will be constructed (“TTP-duration” model)
TTP model (Goal 1)

Clinically-relevant Outcome (Goal 2)

GOAL: To develop an integrated model to simulate new and improved drug therapy alternatives for pulmonary TB infection

- New drugs and drug combinations
- Different dose, schedule, and duration
- Population-specific therapies
- Insights to adherence and bacterial resistance
- Impact due to granuloma dynamics
- Framework for accelerated hypothesis development and concept exploration
- Complement and enhance other TB models, e.g., animal models, population epidemiology
- Focus clinical trials likely to yield best results
Host-Mtb-Drug System
GOAL: Develop quantitative clinical trial simulation tools to identify risk predictors for TdP in “real world” patients.

Risk Stratification Modeling

Drug-Induced Cardiac Arrhythmias

- CYP variants
- IKr+IKs effects
- Impaired repolarization reserve
- Electrolyte effects
- Genetic susceptibility
Further Integration
Towards a Clinical Trial Simulation Tool

Critical Path to
TB Drug Regimens
Integration of Efforts #2 (towards a CTS):
Bridging the Gap in the Prediction of Clinical Outcomes

Current status

- Initial infection
- Drug treatment

Bacterial proliferation

Physiological Response ?

Clinical outcome

CFU, TTP

Diagnosis, time, disease status
Useful biomarkers play a useful role:

*Is pathogen load enough?*

Currently only 1 common clinical biomarker *(CFU sputum count)* can be related to a model variable *(bacterial load)*

CFU data alone appear not informative enough to characterize all clinically relevant disease trajectories for CTS

Accuracy and precision of model parameter values not clear No sensitivity analysis or parameter correlation available.

Are there any additional clinical biomarker*(s)* to guide model selection & development process ?
Addition of Appropriate Marker Describing Important Parts of the Disease Process

**Future prospects**

- **Initial infection**
- **Drug treatment**
  - Immune status & response
  - Granulomas & lesions
  - Additional biomarker

**Clinical outcome**

**Diagnosis, time, disease status**

- CFU, TTP
- Bacterial proliferation
- Additional biomarker

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*Note: The image contains a flowchart illustrating the disease process with various stages and markers. The chart includes elements such as bacterial proliferation, initial infection, drug treatment, immune status, granulomas, lesions, and clinical outcomes, with specific markers like CFU, TTP, and additional biomarkers.*
Currently available systems biology models have no clinical connection. **To arrive at clinically relevant PK-PD models for TB:**

- **Consider appropriate parts of the system biology models and simplifying them by 'lumping' states**
- **Consider options for remapping and rescaling of ‘General infectious proliferation model’ to Mtb**
  - Including influence of pop. PK-PD variability on outcome
- **Connect to multiple clinical biomarkers, responding on various time scales to inform model**
  - Review databases for available clinical trial data
  - Optimize designs of upcoming trials
  - Model-based quantitative validation of clinical biomarkers
  - Predictive simulation of different disease trajectories (‘bifurcation’)
  - Use clinical results to determine population distribution of parameters
Thank you!