Academia (Consortia) Perspective
Topic I: Selection of Agents, Doses and Regimens for Clinical Study

Debra Hanna, Executive Director, Critical Path to TB Drug Regimens

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Critical Path to TB Drug Regimens

CRITICAL PATH INSTITUTE

Outline

Critical Path to TB Drug Regimens

Consortium Driven Methods Perspective

- Integrate Academic / Industry / Regulatory Perspective on Methods
- Required for Evidence-based approach

Current Methodologies Landscape: TB Drug Development Pathway

- Academic approach to method development ***versus***
- Methodologies designed as drug development tools
- Evidenced-based methodology evaluation

In vitro HFS-TB Model

- Evidence-based approach
- EMA qualification for use

In vivo Methods focus on Sterilizing Mouse Model

- Next models for evaluation

CPTR Initiative
Members and Partners

Critical Path to TB Drug Regimens

Government/Regulatory participants

- CDC
- FDA
- European Medicines Agency
- World Health Organization
- IMI Innovative Medicines Initiative
- National Institutes of Health
- National Institute of Allergy and Infectious Diseases
- DAIDS RSC Regulatory Support Center

Industry members

- AstraZeneca
- Pfizer
- Sanofi
- Celgene Global Health
- Vertex The Science of Possibility
- Cepheid A better way.
- epistem
- GlaxoSmithKline
- bioMérieux
- Alere
- Qiagen
- Otsuka
- Janssen Pharmaceutical Companies of Johnson & Johnson
- tibotec
- Abbott Molecular
- Sequella Incorporated
- ThermoFisher Scientific
- BD

Nonprofit research members

- TB Alliance Global Alliance for TB Drug Development
- Bill & Melinda Gates foundation
- EDCTP
- TAG Treatment Action Group
- Reagan-Udall Foundation for the Food and Drug Administration
- PATH A catalyst for global health
- FIND foundation for innovative new diagnostics
- Stop TB Partnership

CPTR Academic Partners

Critical Path to TB Drug Regimens

- Baylor Institute for Immunology Research
- Case Western Reserve University TB Research Unit
- ***Colorado State University***
- Duke University
- Forschungszentrum Borstel
- Harvard
- ***Johns Hopkins University***
- London School of Hygiene and Tropical Medicine
- Munich University
- NYU
- O'Neill Institute at Georgetown Law Center
- Partners In Health [Harvard University]
- 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 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

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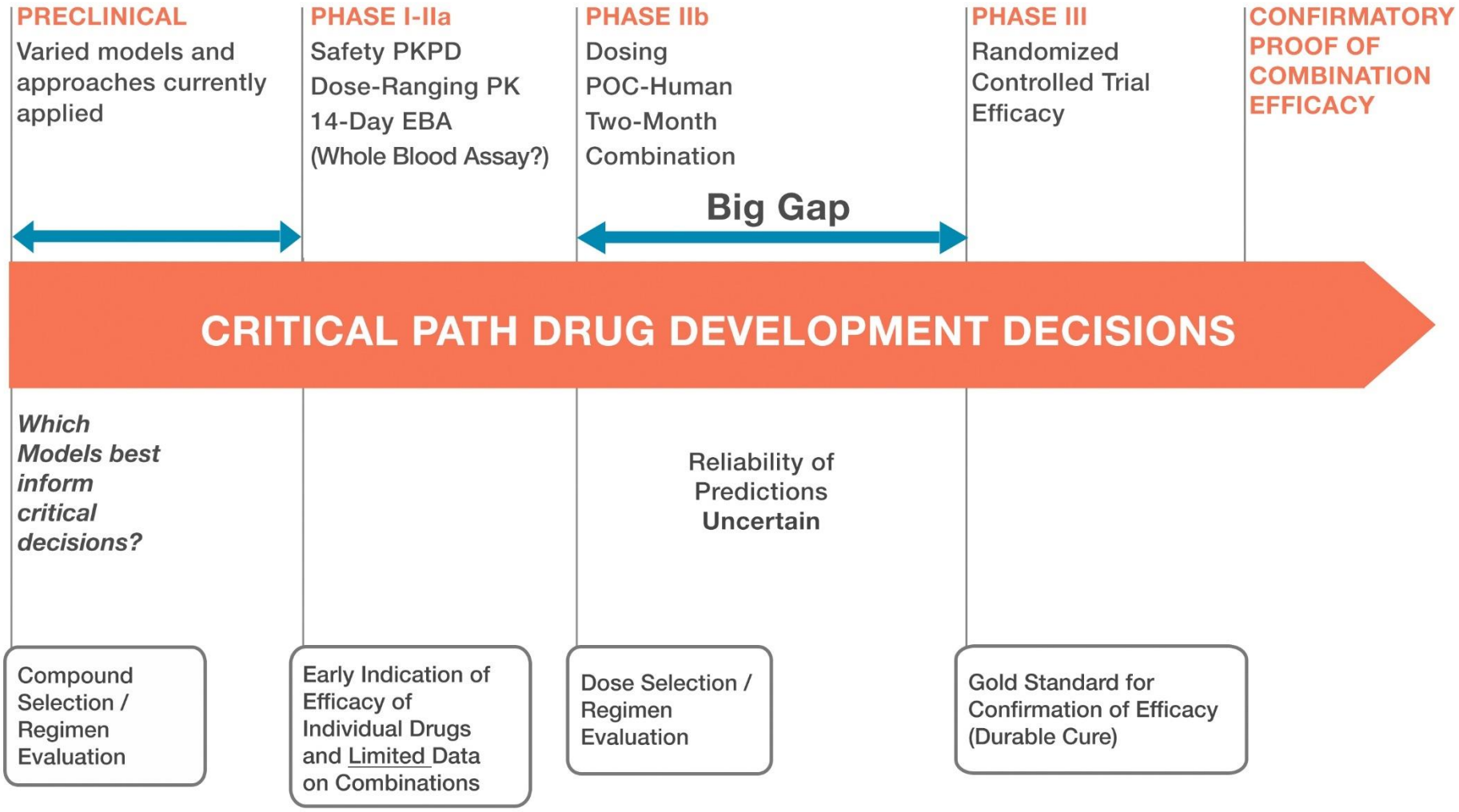
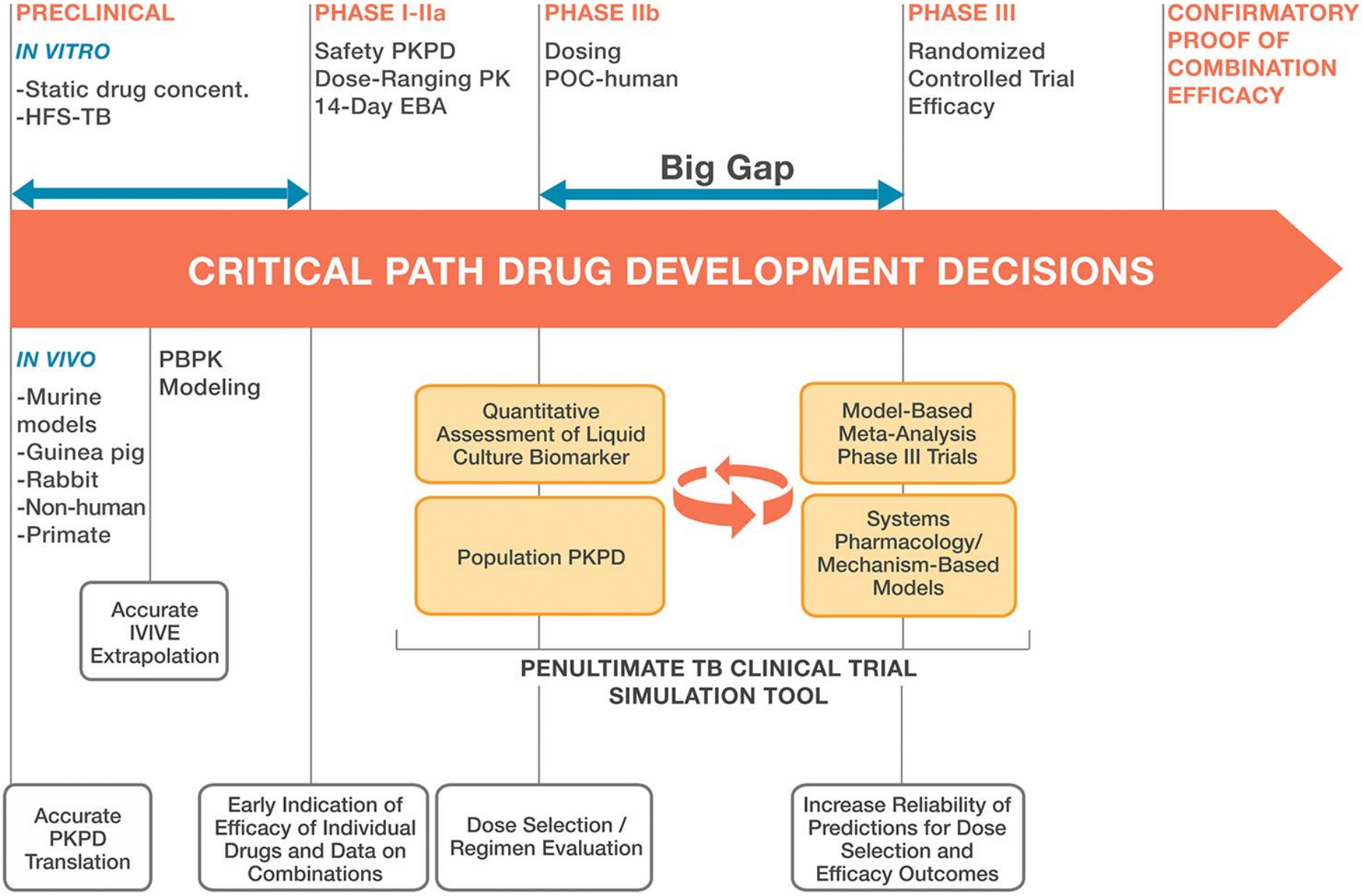
Current TB Regimen Development
Risk of Late-Stage Attrition

Critical Path to TB Drug Regimens




PRECLINICAL
IN VITRO
-Static drug concent.
-HFS-TB
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
CRITICAL PATH DRUG DEVELOPMENT DECISIONS
IN VIVO
-Murine
models
-Guinea pig
-Rabbit
-Non-human
-Primate
PBPK
Modeling
Accurate
IVIVE
Extrapolation
Quantitative
Assessment of Liquid
Culture Biomarker
Population PKPD
Model-Based
Meta-Analysis
Phase III Trials
Systems
Pharmacology/
Mechanism-Based
Models
PENULTIMATE TB CLINICAL TRIAL
SIMULATION TOOL
Accurate
PKPD
Translation
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

CPTR Evidence-Based Roadmap

Critical Path to TB Drug Regimens

Degree of Evidence Required

Pre-CPTR Stage

1. DDT Identification

- Identify candidate *in vivo* models as possible DDT
- Determine data needs

2. Exploration

- Proof of concept
- Find best candidate and assay
- Determine data needs

3. Demonstration

- Probable or emerging model/DDT
- Scientifically validated
- Define model performance, sensitivity and reproducibility; predictivity

CPTR

4. Characterization

- Type of DDT
- DDT CoU
- Qualification Strategy

Drug Development Pipeline

Target Validation → Lead Optimization → Translational Medicine → Phase I & II → Phase III → Commercial

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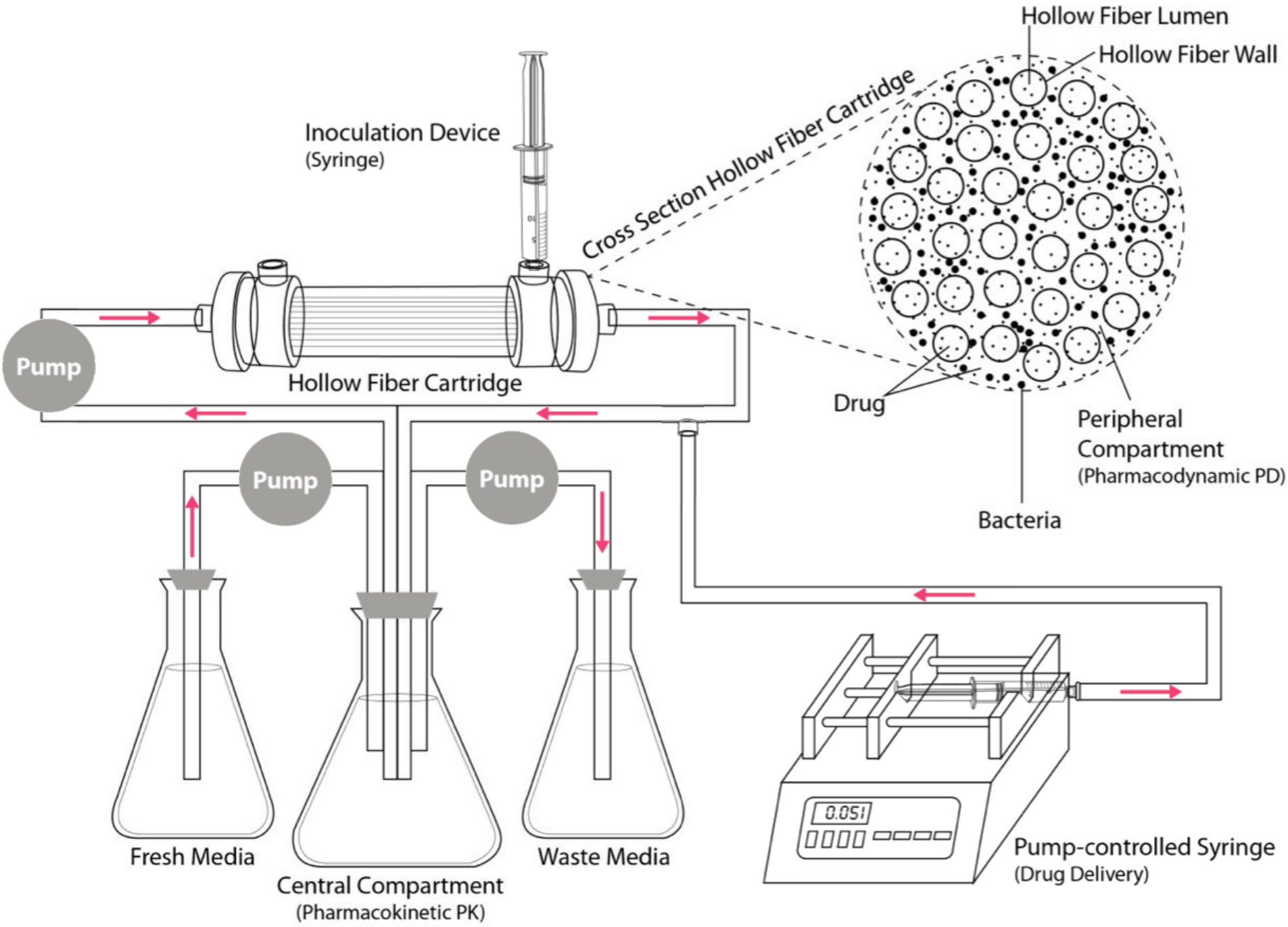

Hollow Fiber Lumen
Hollow Fiber Wall
Inoculation Device
(Syringe)
Cross Section Hollow Fiber Cartridge
Pump
Hollow Fiber Cartridge
Drug
Peripheral
Compartment
(Pharmacodynamic PD)
Bacteria
Pump
Pump
Fresh Media
Central Compartment
(Pharmacokinetic PK)
Waste Media
0.051
Pump-controlled Syringe
(Drug Delivery)

Mission

- Evidence-based evaluation of innovative drug development tools to address preclinical to clinical translation
- Focus on *in vitro* methodologies supporting efficacy and safety toxicology assessment
- Submission for regulatory endorsement

Goal

- Follow EMA and FDA Guidance on novel methodology and DDT qualification
- Gather all relevant published and unpublished data sources or aggregation
- Assess clinical translation of innovative preclinical novel methodologies/DDTs to test new TB drug candidates and regimens

HFS-TB Evidence

- Significantly more quantitative HFS-TB PKPD data available than for any *in vivo* methodology for TB
- Supported thorough assessment of predictive accuracy for clinical outcomes

Quantitative Outputs of HFS-TB

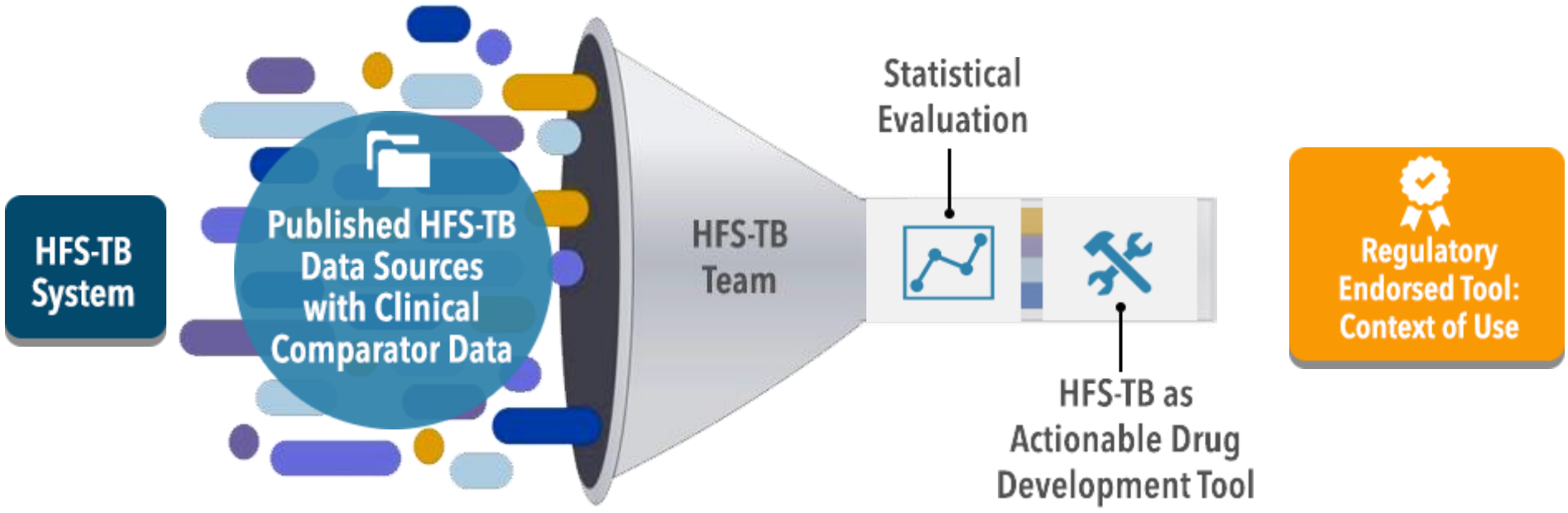
Critical Path to TB Drug Regimens

Outputs from HFS-TB experiments

- Drug concentration
- Total and drug-resistant *Mtb* CFU counts
- RNA expression
- Whole genome sequencing of sampled material
- Macrophage count and no. bacteria/macrophage

Quantitative analysis and simulation yields

- Quantitative PK/PD relationships useful for target selection
- Prediction of dose-response curves and target attainment expected in patients useful for optimal dose selection
- Expected rates of clinical response and resistance emergence


HFS-TB System
Published HFS-TB Data Sources with Clinical Comparator Data
HFS-TB Team
Statistical Evaluation
HFS-TB as Actionable Drug Development Tool
Regulatory Endorsed Tool: Context of Use

Use best dose first time

Optimize doses of drugs in regimens to reduce the need for dose response clinical study

Identify best combinations

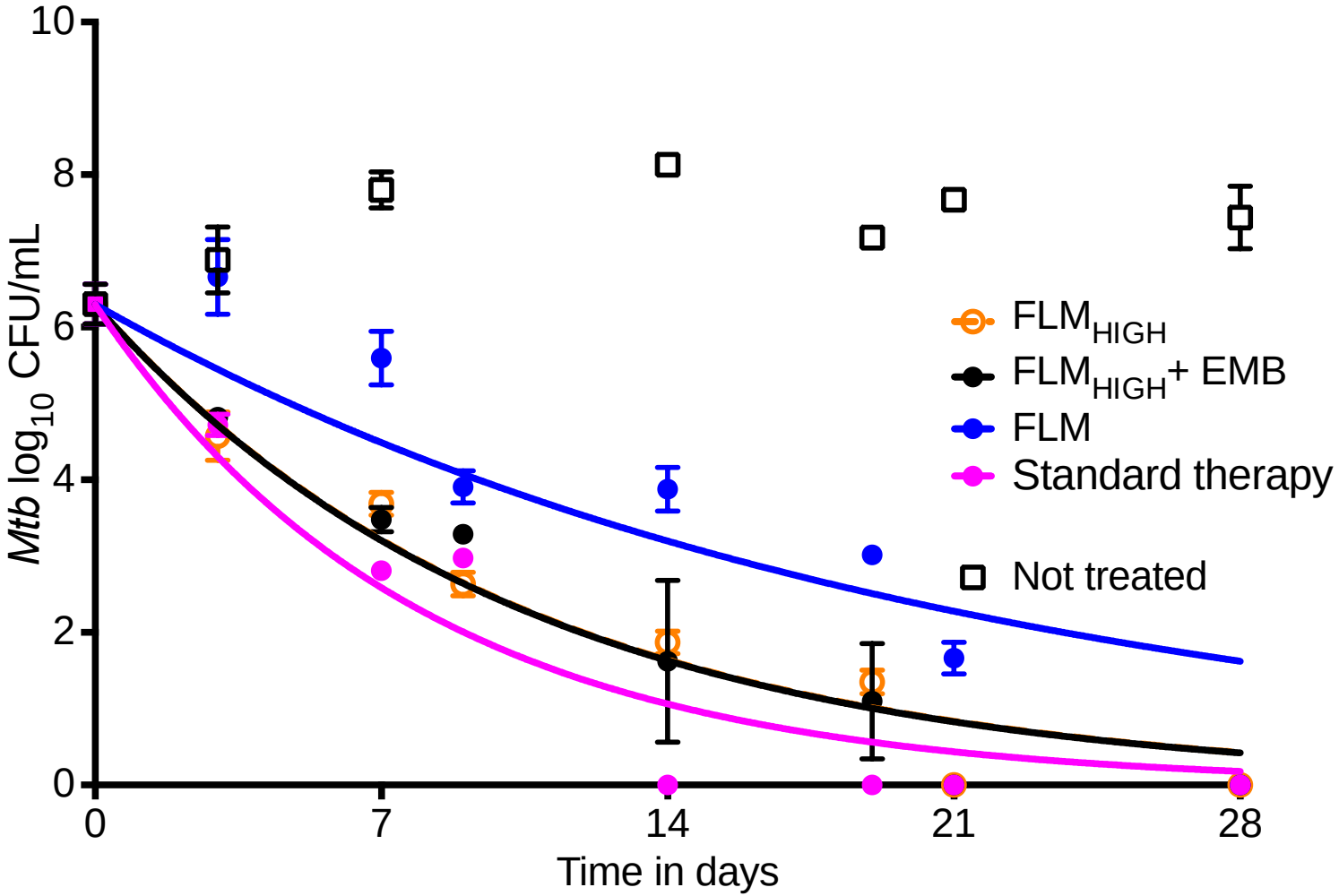
Optimize selection of drugs for regimen design by evaluating synergy and antagonism

Rank regimens by speed of sterilizing effect

- **Analysis Objective** to determine predictive accuracy of HFS-TB outputs for clinical trial results
- **Literature Search** to identify relevant HFS-TB and clinical data from published literature
- **Systematic Review** to summarize HFS-TB-generated hypotheses and outcomes of clinical trials
- **Quality of Evidence Scoring** to provide basis for weighting in the predictive accuracy analysis
- **Statistical Analysis** comparing HFS-TB predictions with clinical findings to examine:
  - descriptive correlations where HFS-TB studies post-dated clinical studies
  - predictive accuracy where HFS-TB studies pre-dated clinical studies

- *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 tuberculosis
  - ✓ To select the pharmacodynamic target (e.g. $T_{>MIC}$, 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

New Regimen Design: "FLAME"



Deshpande et al. A faropenem, linezolid, and moxifloxacin regimen for both drug susceptible and multidrug-resistant tuberculosis in children. Clin Infect Dis. 2016;63:S95

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Evaluation of *In Vivo* Models

Critical Path to TB Drug Regimens

*Correlations between drug concentration and pathogen survival that are based on in vitro models cannot be expected to reiterate **all** aspects of in vivo antimycobacterial treatment*.

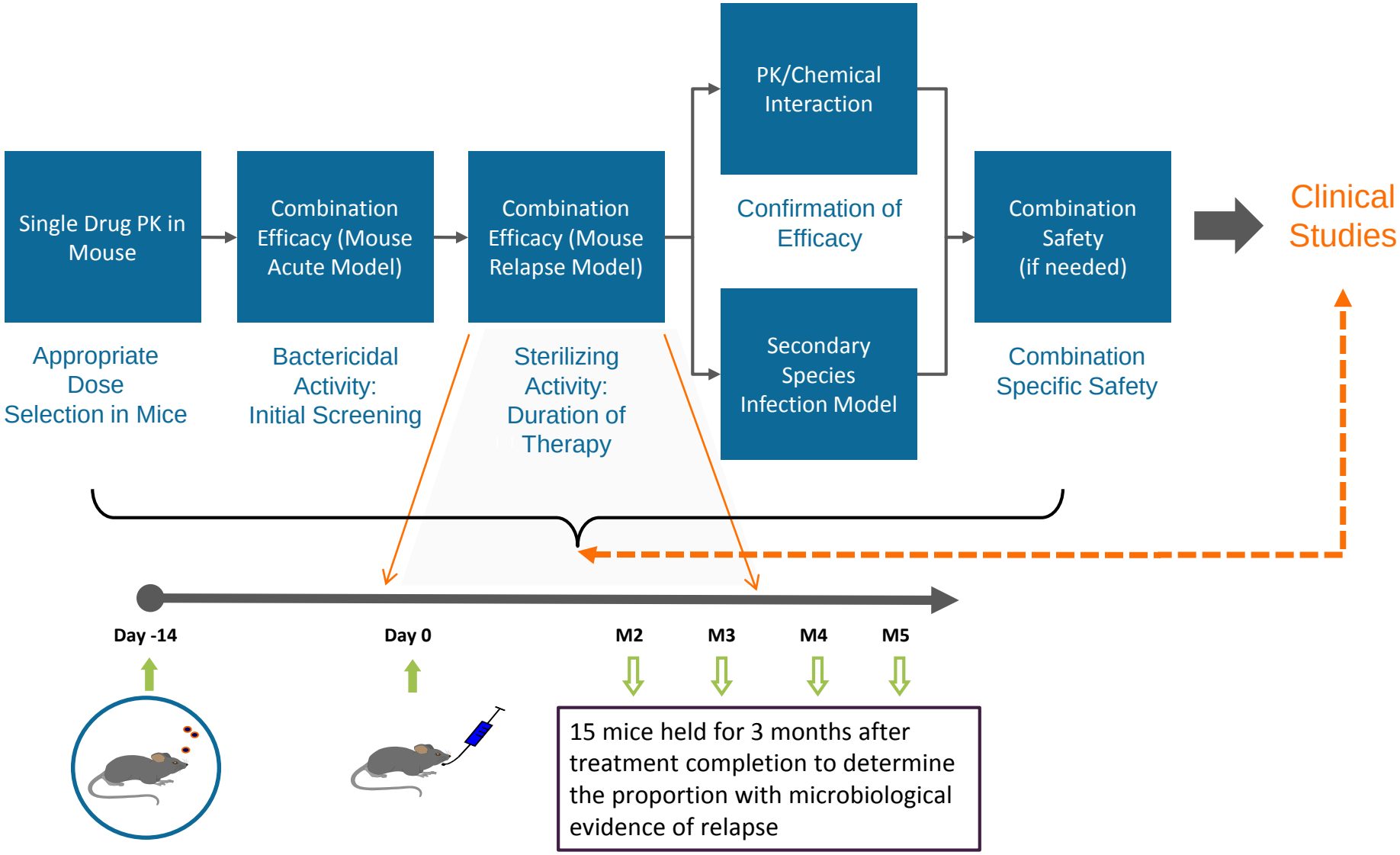
Chilukuri et al, CID 2015; 61(S1):S32

HFS-TB qualified for use in drug development programs ***as additional and complementary tool*** – EMA Qualification Decision

Advantages of *in vivo* models

- Better reflect the phenotypic heterogeneity in bacterial populations as determined by host-pathogen interactions, including tissue pathology
- Present complexities of drug distribution to, and action within, various sites of infection

Mouse Model of Sterilizing Activity



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).

Rationale

- Past and present role in TB regimen development
  - Relapse endpoint considered closest correlate of current phase 3 endpoint
  - Track record in forecasting treatment-shortening potential of RIF, PZA
- Amount of available data on regimens evaluated in clinical trials

Intended Application

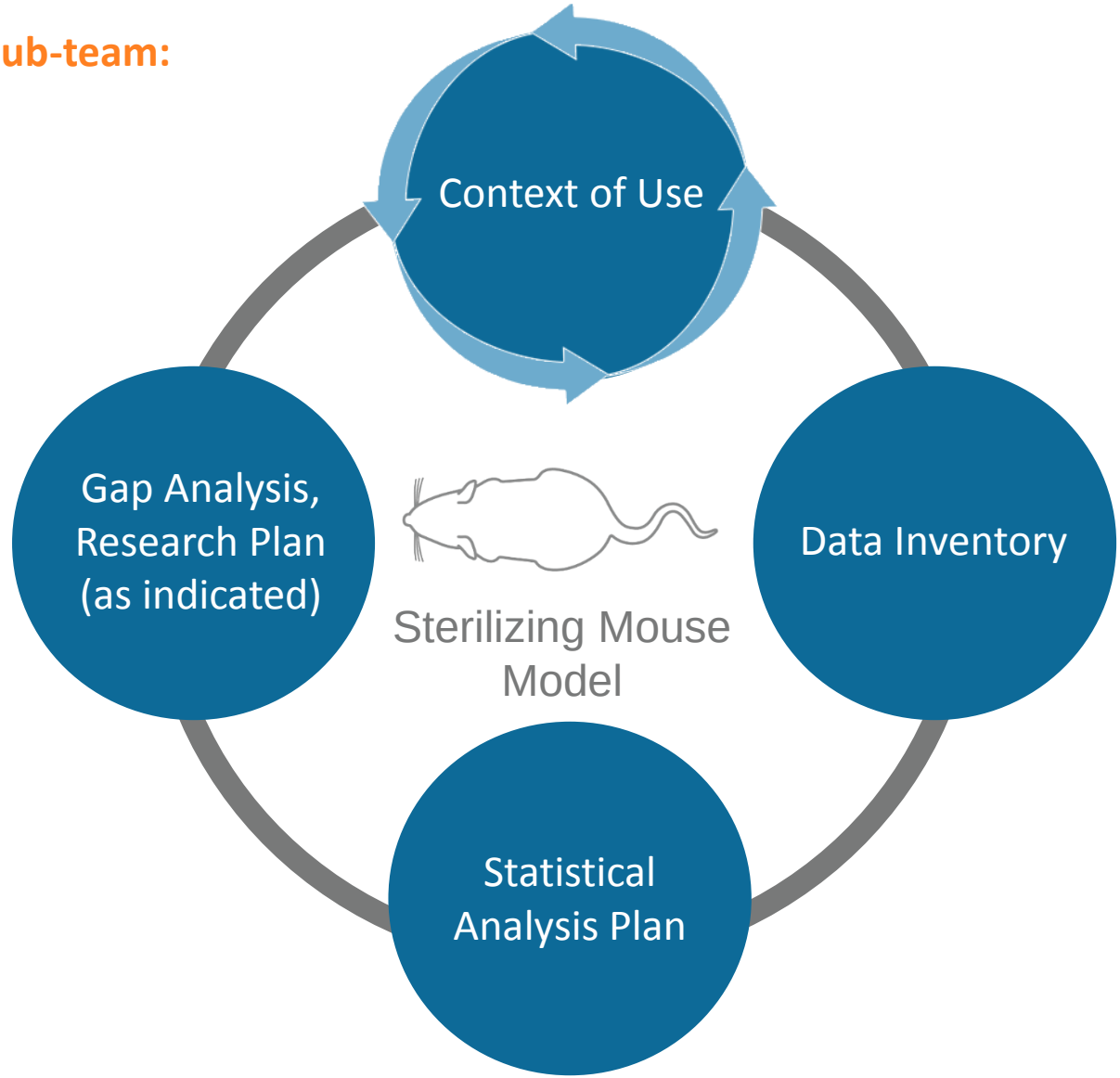
- The data from experiments in mice infected with *M. tuberculosis*, using relapse as the main endpoint
  - Will be used to calculate treatment effect sizes, to then rank-order regimens, and
  - Estimate clinical treatment duration

Evidence-Based Evaluation of Sterilizing Mouse Model

Critical Path to TB Drug Regimens

CPTR PCS-WG Mouse Model Sub-team:

- Dr. Dakshina Chilukuri
- Dr. Geraint Davies
- Dr. Geo Derimanov
- Dr. Nader Fotouhi
- Dr. Tawanda Gumbo
- Dr. Debra Hanna
- Dr. Barbara Laughon
- Lindsay Lehmann
- Dr. Anne Lenaerts
- Dr. Owen McMaster
- Dr. Khis Mdluli
- Dr. Eric Nuermberger
- Dr. Klaus Romero
- Dr. Rada Savic
- Dr. Christine Sizemore
- Dr. Peter Warner



Data Inventory

Critical Path to TB Drug Regimens

- Focus first on mouse strains other than C3HeB/FeJ ("Kramnik")
- Inventory identified a variety of relapse-based preclinical studies with corresponding clinical trial outcomes data

Test regimen intervention	Regimen comparison	# of expts
Combining INH+STR	HS vs. H or S monotherapy	1
Shortening duration of INH+STR	6HS vs. 18HS	1
Adding RIF to INH+STR or INH+EMB+PZA	HR (or HRS or HREZ) vs. HS (or HEZ)	4
Adding STR to INH+RIF	HRS vs. HR	1
Adding PZA to INH+RIF (±STR/EMB)	HRZ (or HRSZ or HREZ) vs. HR (or HRS or HRE)	4
Shortening duration of PZA	2HREZ/4RH vs. 6HREZ	1
Increasing dose of RIF	High-dose R plus HEZ vs. HREZ	2
Extending dosing interval of 1st-line Rx	HREZ (2/7) vs. HREZ (daily)	1
Replacing EMB with MXF	HRMZ vs. HRZ(E)	3
Replacing INH with MXF	MRZ(E) vs. HRZ(E)	10
Replacing RIF with RPT	HPZ(E) vs. HRZ(E)	7
Replacing RIF+EMB with RPT+MXF	HPMZ vs. HRZ	3
Replacing RIF with RPT and extending dosing interval (in continuation phase)	HP(1/7) cont phase vs. HR(2/7)	2
Replacing INH+RIF+EMB with PMD+MXF	PaMZ vs. HRZ(E)	8

Summary Points

Critical Path to TB Drug Regimens

- Initial step to address the “translational gap” is to learn what data from what models analyzed in what way informs key trial design decisions
- Evidence-based validation of preclinical models is important:
  - To confidently place preclinical models on the critical development path
  - To increase the efficiency of regulatory interactions
  - To set a precedent for objective, data-driven process to apply to other models and tools (e.g., C3HeB/FeJ mouse, marmoset)
  - To identify/clarify knowledge and tool gaps to drive future research
- The successful HFS-TB qualification process has accomplished each of these goals
- Evaluation of sterilizing mouse model is the appropriate next step, with other models to follow

New Tools and Approaches

Critical Path to TB Drug Regimens

	Novel Assays	Goal
In Vitro Activity	Multiple media	Mimic lesion environment
	Non-replicating	Mimic bacterial phenotypes
	Deletion mutant or down regulator of promiscuous targets	Avoid promiscuous targets
	Cell lysis	Identify rapid killing drugs
	Macrophage assay coupled with confocal microscopy	Exploit direct antibacterial and host-directed efficacy at once
PK/PD	Caseum binding assay	Studying *ex vivo* binding
	Caseum MBC assay	Mimic lesion environment
	Lesion PK studies (MALDI, laser capture microdissection)	Identify drugs that can partition in various lesions
	Artificial granuloma	Same
Modeling	Integrate efficacy with PK/PD	Identify PD drivers
Animal Models	C3HeB/FeJ mice, rabbit, marmoset	Models with lesion heterogeneity and diverse bacterial phenotypes present in TB patients

Acknowledgements

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Dr. Tawanda Gumbo (Baylor University)

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Dr. Nandini Konar (Critical Path Institute)

Lindsay Lehmann (Critical Path Institute)

Dr. Eric Nuermberger (Johns Hopkins University)

Dr. Jotam Pasipanodya (Baylor University)

Dr. Klaus Romero (Critical Path Institute)

Dr. Christine Sizemore (National Institutes of Health)

Dr. Omar Vandal (Bill & Melinda Gates Foundation)

Dr. Tian Yang (Global Alliance for TB Drug Development)

CPTR Health Authorities Submission Team:

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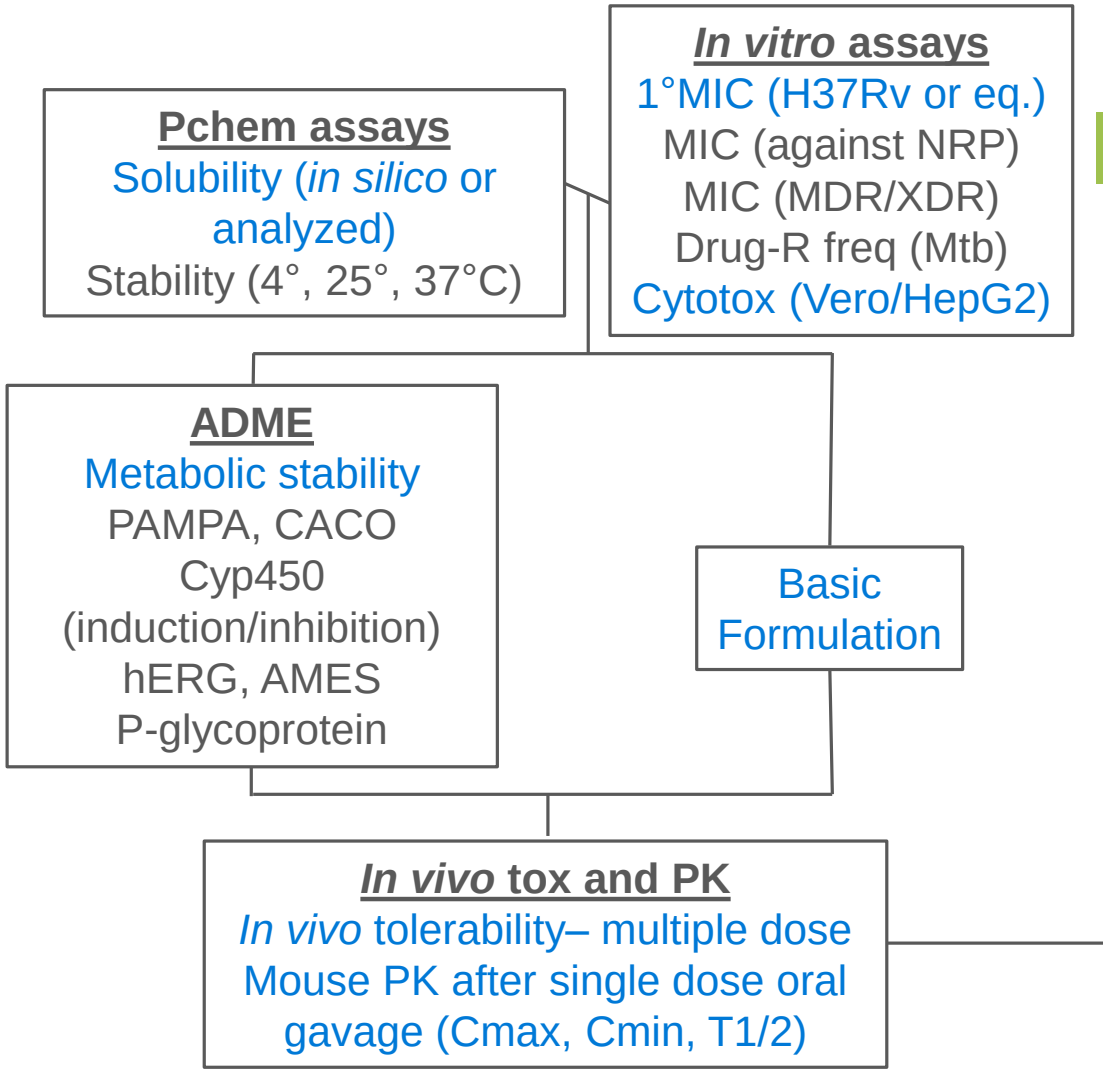
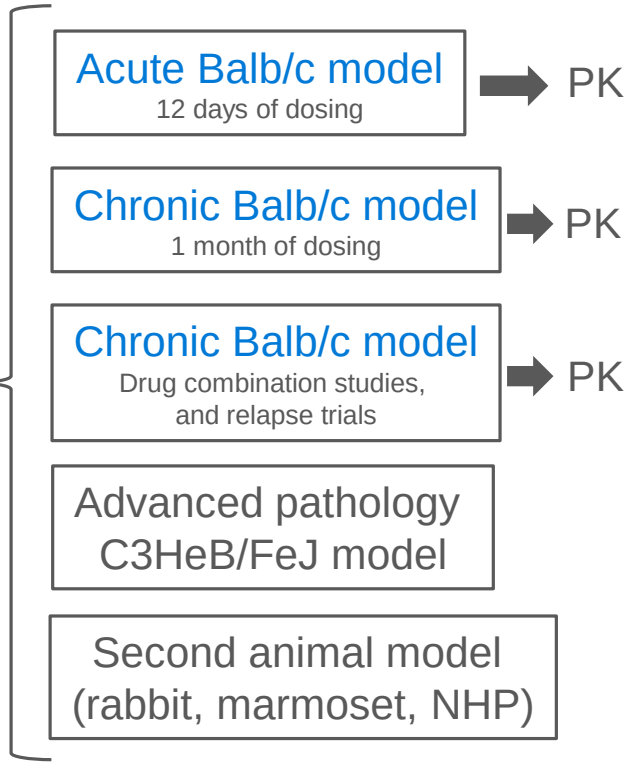
Current Paradigm Early Compounds

Critical Path to TB Drug Regimens

In Vitro Evaluation of Early Compounds



In Vivo Efficacy Testing of Compounds



In Blue: on Critical Path

Implementation of Animal Efficacy Models for TB

Critical Path to TB Drug Regimens

Drug Discovery (H2L)

Single agent testing:

Efficacy at highest safe dose

Efficacy against active replicating and non-act replicating bacteria:

- **Acute Balb/c mouse model**
- **Chronic Balb/c mouse model**

[Choice of model can change depending on target/Mode of Action, or PK characteristics]

Efficacy versus drug exposure relationship (PK/PD) – initial understanding of dose response

Lead Optimization (LO)

Single agent testing:

Efficacy versus drug exposure relationship (PK/PD):

- Dose ranging studies (MED, Emax)
- Drug fractionation studies
- *In vivo* killing kinetics over time, etc.

Efficacy against heterogeneity of lesion types:

- correlating efficacy with pathology
- Lesion/caseum PK, MALDI

using C3HeB/FeJ, marmoset model

Additional assays

Regimen Development

Combination testing:

- What combinations to test?
- What combinations are more effective than others?
- What doses and schedules are to be used for every drug?
- What duration of treatment is required?

Studying sterilizing activity/Rx shortening in long-term efficacy studies:

- Bactericidal activity during treatment
- **Relapse studies in Balb/c mice**
- **Confirm relapse results in CH3HeB/FeJ (or marmoset model)?**

Pyrazinamide (PZA) Example

Critical Path to TB Drug Regimens

Two clinical studies that examined effect of PZA exposure in combination on microbial effect

Study 1

142 patients in Western Cape of South Africa

Prospective cohort with measurement of drug concentrations

Quality of study score=2

Published 2013

Study 2

58 patients in Western Cape of South Africa

Part of a randomized controlled trial

Drug concentrations and MICs measured

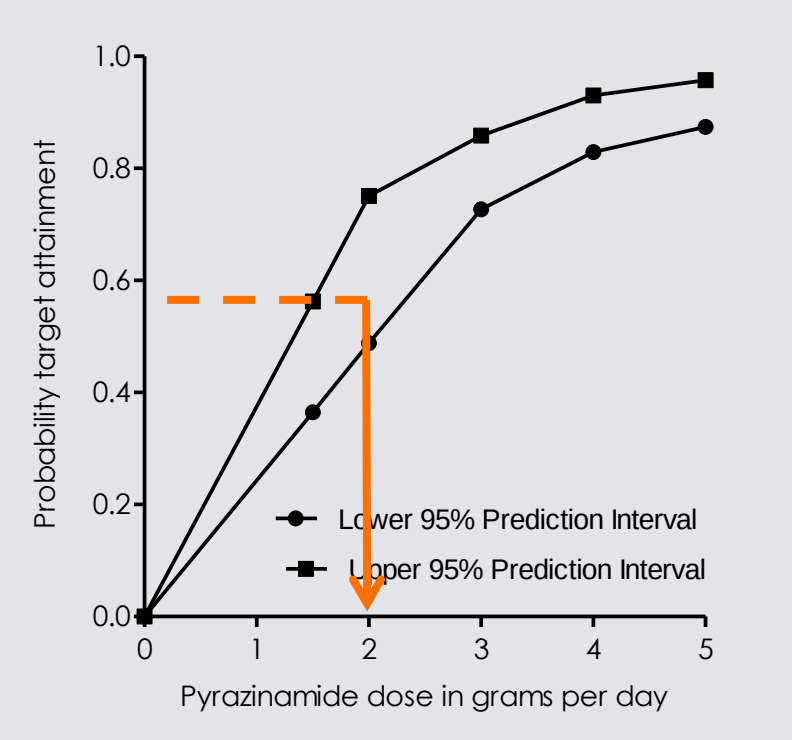
Quality of study score=1

Oral Presentation at TB pharmacology meeting 2013

HFS-TB Forecasting PZA

Critical Path to TB Drug Regimens

- HFS-TB PK/PD: Optimal effect AUC/MIC=209 (11.7)
- Monte Carlo Simulation of HFS-TB findings for dose finding prediction



58% target attainment with 2G in 10,000 simulated subjects

Result: higher doses of up to 4 grams needed in the clinic, as predicted by HFS-TB and MCS

Gumbo et al. Antimicrob. Agents Chemother. 2009:53;3197-3204

PZA Clinical Findings (Analysis 2C)

Critical Path to TB Drug Regimens

Study	HFS-TB Prediction (2009)	Guinea Pigs/Mice (2011)	Clinical Study #1 (2013)
PK/PD driver selected	AUC/MIC	AUC/MIC	AUC/MIC
Optimal $AUC_{0\text{-}24}$ /MIC	Lung: 209 Serum: 11.7	-	Serum: 11.3
Pts with optimal exposure at 2G	58%	-	57%
Optimal dose (G)	4	4	
Breakpoint MIC (mg/L)	50	-	50

FE= (T-P)*100/T

FE=(|11.3-11.7|)*100/11.3

FE=3.54%

Accuracy =100-FE=96.46% for optimal AUC/MIC