Evidence-based predictive accuracy evaluation of the sterilizing mouse model

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Current TB regimen development

Risk of late-stage attrition

**PRECLINICAL**
Varied models and approaches currently applied

**PHASE I-IIla**
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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**CRITICAL PATH DRUG DEVELOPMENT DECISIONS**

*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
CPTR Pre-Clinical and Clinical Sciences Workgroup
Mission & Goals

Mission

Develop and/or validate tools and innovative approaches to address pre-clinical issues including *in vitro* and *in vivo* efficacy, PKPD analyses using appropriate biomarkers, drug safety, metabolism, DDI, etc. These tools may be submitted to regulatory authorities for regulatory review and/or qualification as appropriate.

**Early goal related to pre-clinical *in vitro and in vivo* models**

Evaluate the evidence base and develop criteria for evaluating the utility of various preclinical models to inform and test new drug regimens.

**Early Evidence**

Landscape analysis* identified HFS-TB as having an appropriate data inventory to assess predictive accuracy of a preclinical model for clinical outcomes.

*Gumbo et al, JID 2015; 211(S3):S83*
Early success

EMA qualification opinion on the HFS-TB

June 26, 2014

• 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
Evaluation of in vivo models

“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

Advantages of in vivo models

• Better reflect the phenotypic heterogeneity in bacterial populations as determined by host-pathogen interactions, including development of tissue pathology

• Present complexities of drug distribution to, and action at, various sites of infection
Improving TB regimen development
Decreasing risk of attrition

CRITICAL PATH DRUG DEVELOPMENT DECISIONS

PRECLINICAL

IN VITRO
- Static drug concen.
- 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

IN VIVO

PBPK Modeling

- Murine models
- Guinea pig
- Rabbit
- Non-human
- Primate

Quantitative Assessment of Liquid Culture Biomarker

Model-Based Meta-Analysis Phase III Trials

Population PKPD

Systems Pharmacology/
Mechanism-Based Models

PENULTIMATE TB CLINICAL TRIAL SIMULATION TOOL

Accurate IVIVE Extrapolation

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
Mouse model of sterilizing activity

- Single Drug PK in Mouse
- Combination Efficacy (Mouse Acute Model)
- Combination Efficacy (Mouse Relapse Model)
- PK/Chemical Interaction
- Confirmation of Efficacy
- Secondary Species Infection Model
- Combination Safety (if needed)

- Appropriate Dose Selection in Mice
- Bactericidal Activity: Initial Screening
- Sterilizing Activity: Duration of Therapy

15-20 mice held for 3-6 months after treatment completion to determine the proportion with microbiological evidence of relapse.
Evaluating the sterilizing mouse model

Rationale

• Past and present role in TB regimen development
  – track record in forecasting treatment-shortening potential of RIF, PZA
  – relapse endpoint considered closest correlate of current phase 3 endpoint

• Amount of available data on regimens evaluated in clinical trials

• Does not preclude evaluation of other models
  – eg, C3HeB/FeJ mouse, marmoset
Evaluating the sterilizing mouse model

**General Aim**

- Quantify the predictive accuracy of mouse models using relapse as an endpoint for the purpose of rank ordering regimens and estimating the effective treatment duration
Workplan for evidence-based evaluation of sterilizing mouse model

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Dr. Christine Sizemore
Dr. Peter Warner
Lindsay Lehmann
Experiments testing drug combinations in mice provide an additional and complementary tool to existing methodology to inform regimen selection, to maximize sterilizing effects. Data produced will support submissions to regulatory agencies throughout the drug development process, to optimize design of clinical trials.

Non-clinical PK/PD testing

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.
Data inventory

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

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Proposed statistical analysis plan

An initial analysis approach using logistic regression based on relapse data is proposed. The following metrics will be obtained from the proposed analyses:

- Covariate-adjusted probability of relapse for each regimen and duration
  - Can be used for rank order comparison
  - Absolute proportions can be compared across regimens and evaluated for correlations with human data when treated for the same duration

- Covariate-adjusted treatment duration required to achieve a specified relapse-free proportion (50% or 90%)
  - Can be used to rank order regimens on treatment shortening potential
  - Absolute differences between regimens can be compared to obtain the magnitude of treatment shortening relative to a control arm

Subsequent analyses may examine bactericidal activity (CFU vs. time) and exposure-response
Lessons learned

• Overall, the amount of relevant preclinical and clinical data available are limited
  – few regimens are confirmed clinically to have different efficacious treatment durations
  – mouse expts not designed for precise delineation of treatment-shortening effects
  – little dose-ranging mouse data or human exposure-response analysis to examine the impact of variability in human PK, Mtb MIC
  – limited ability to explore potentially important covariates (eg, Mtb strain, route of infection, infectious dose, incubation period)

• As a categorical variable assessed monthly in individual mice, relapse is not as amenable to quantitative analysis as CFU cts

• Adopting a common data management system and/or common data elements could make such analyses simpler, more robust
Summary points

• An initial step to address the “translational gap” is to learn what data from what models analyzed in what way best inform key trial design decisions.

• Evidence-based validation of pre-clinical 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 processes to apply to other models (e.g., C3HeB/FeJ mouse, marmoset), and
  – to identify gaps in knowledge & in existing tools to drive future research.

• Evaluation of sterilizing mouse models is the appropriate first step for in vivo models, with other models to follow
Acknowledgements

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