Evidence-based predictive accuracy evaluation of the sterilizing mouse model

Eric Nuermberger, MD
Center for TB Research, Johns Hopkins University

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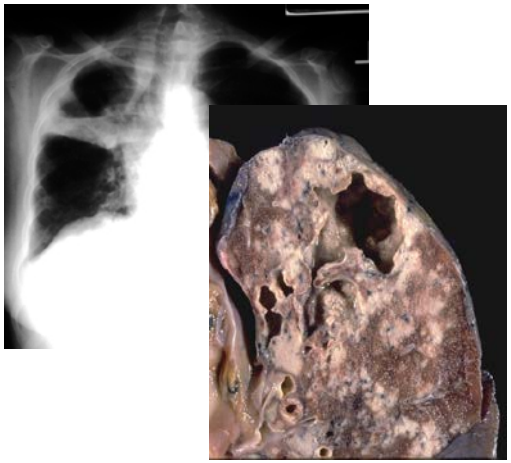
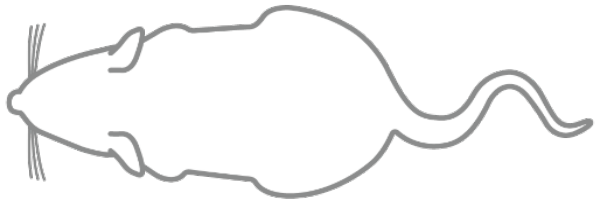
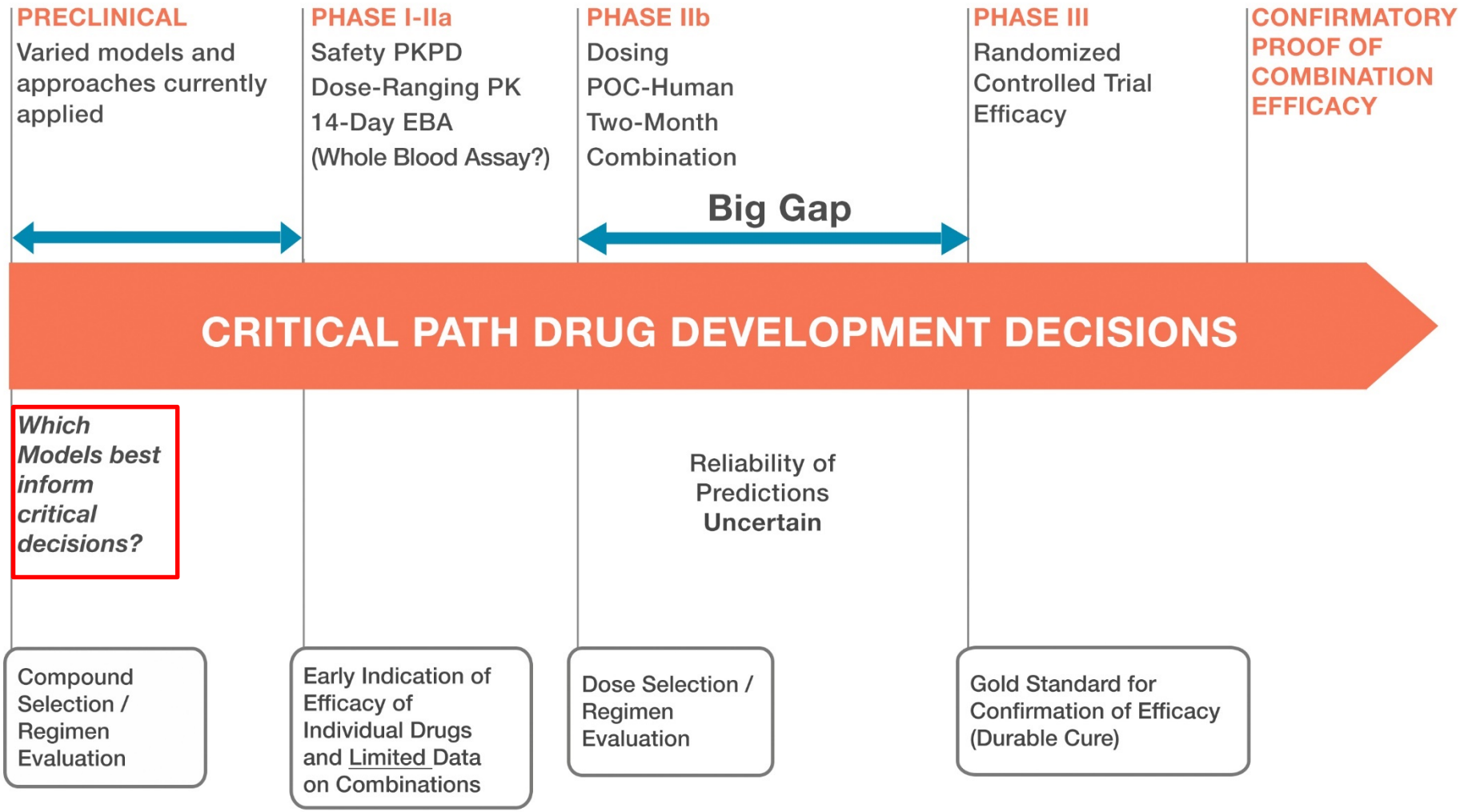




Current TB regimen development

Risk of late-stage attrition



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."

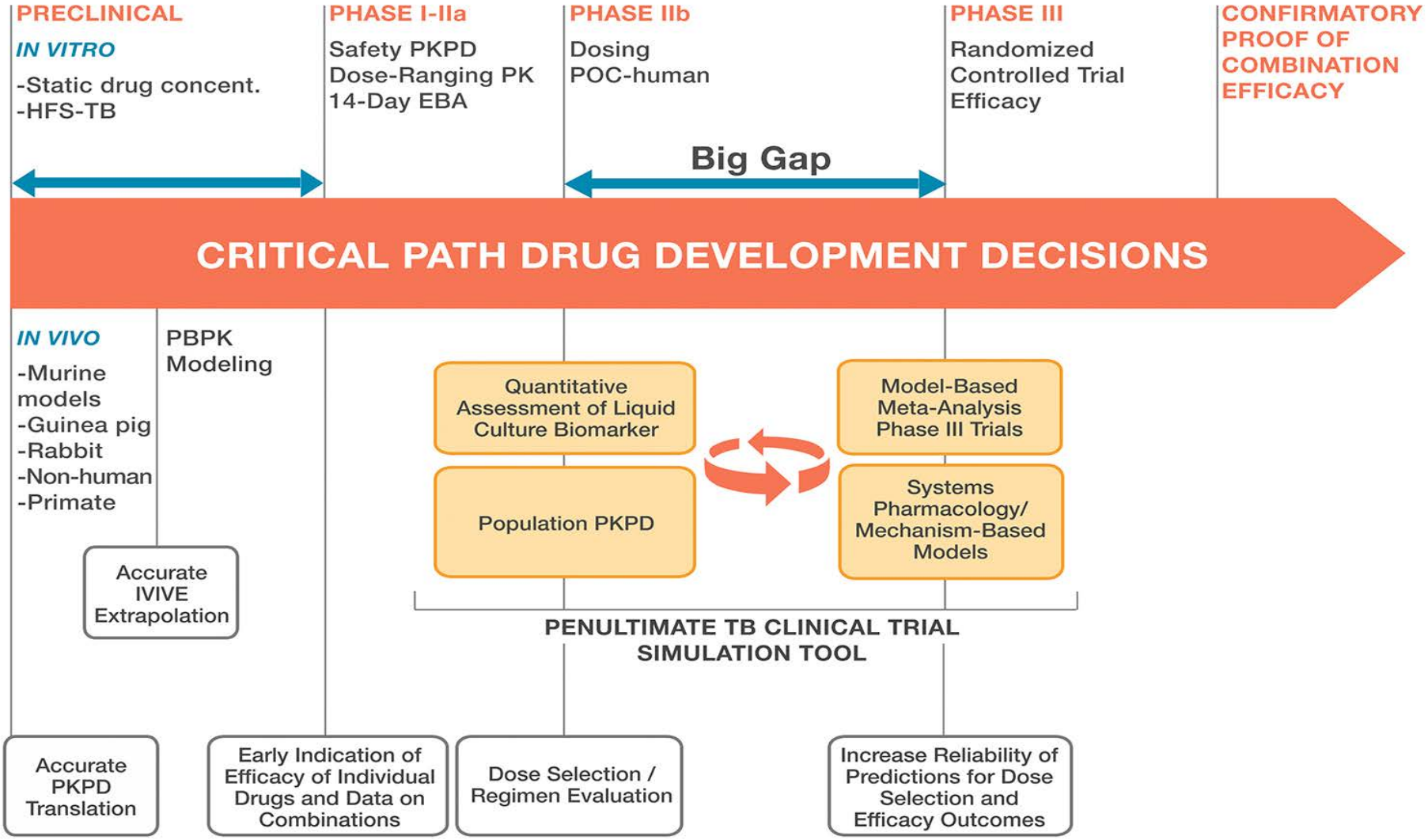
Chilukuri et al, CID 2015; 61(S1):S32

Advantages of *in vivo* models

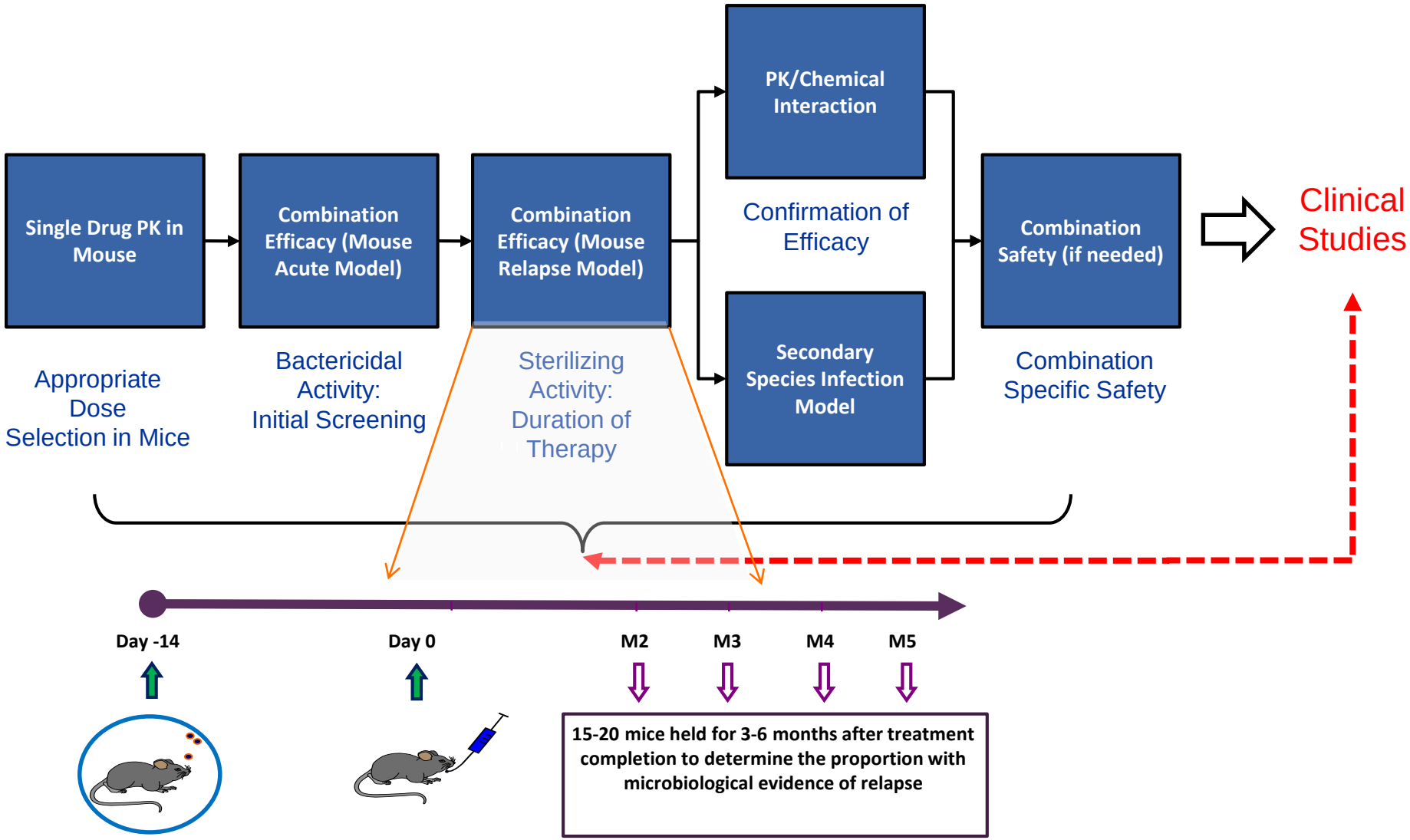
- Better reflect the phenotypic heterogeneity in bacterial populations as determined by host-pathogen interactions, including development of tissue pathology
- Present complexities of drug distribution to, and action at, various sites of infection

Improving TB regimen development

Decreasing risk of attrition



Mouse model of sterilizing activity



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

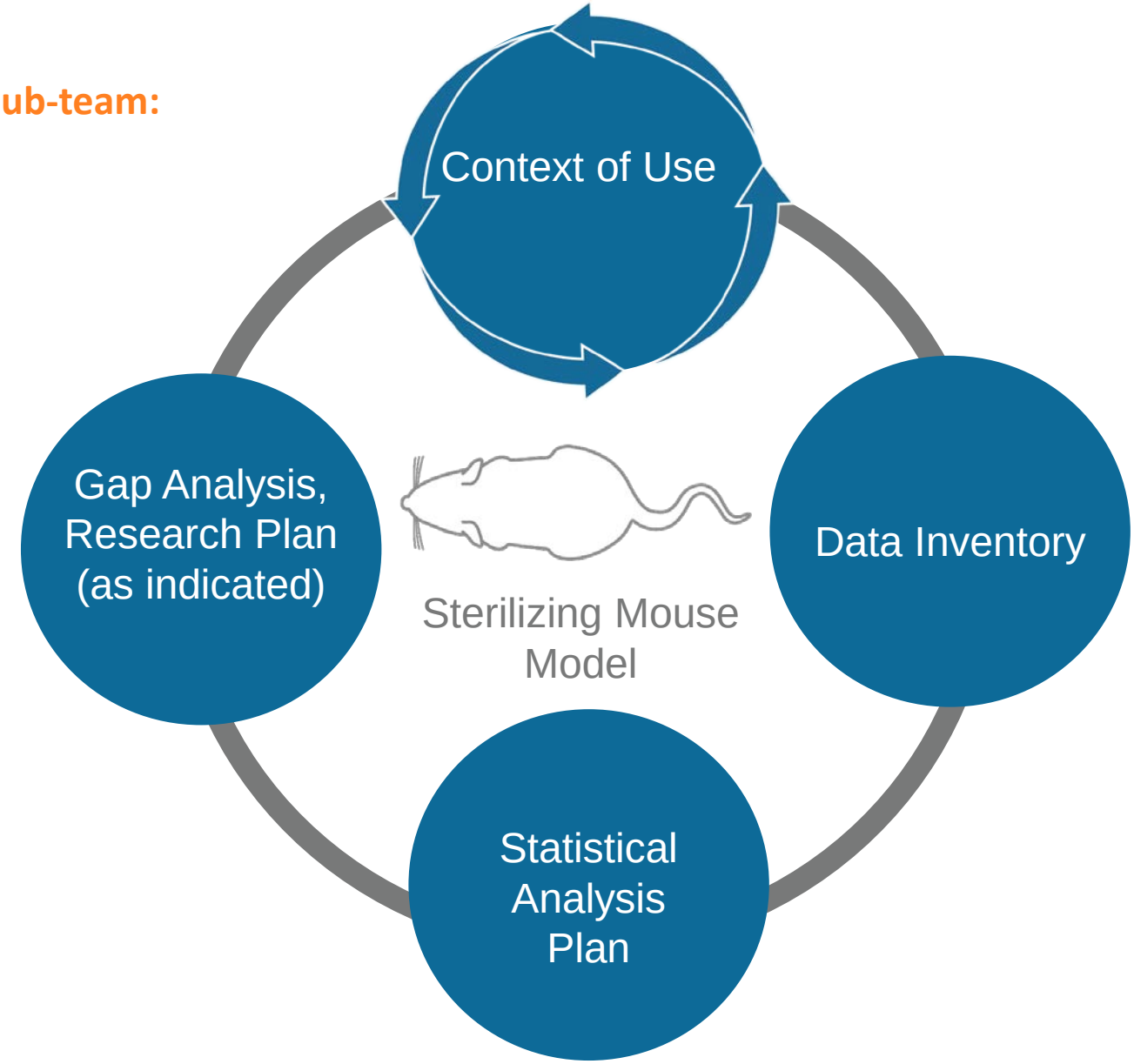
General Aim

- 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

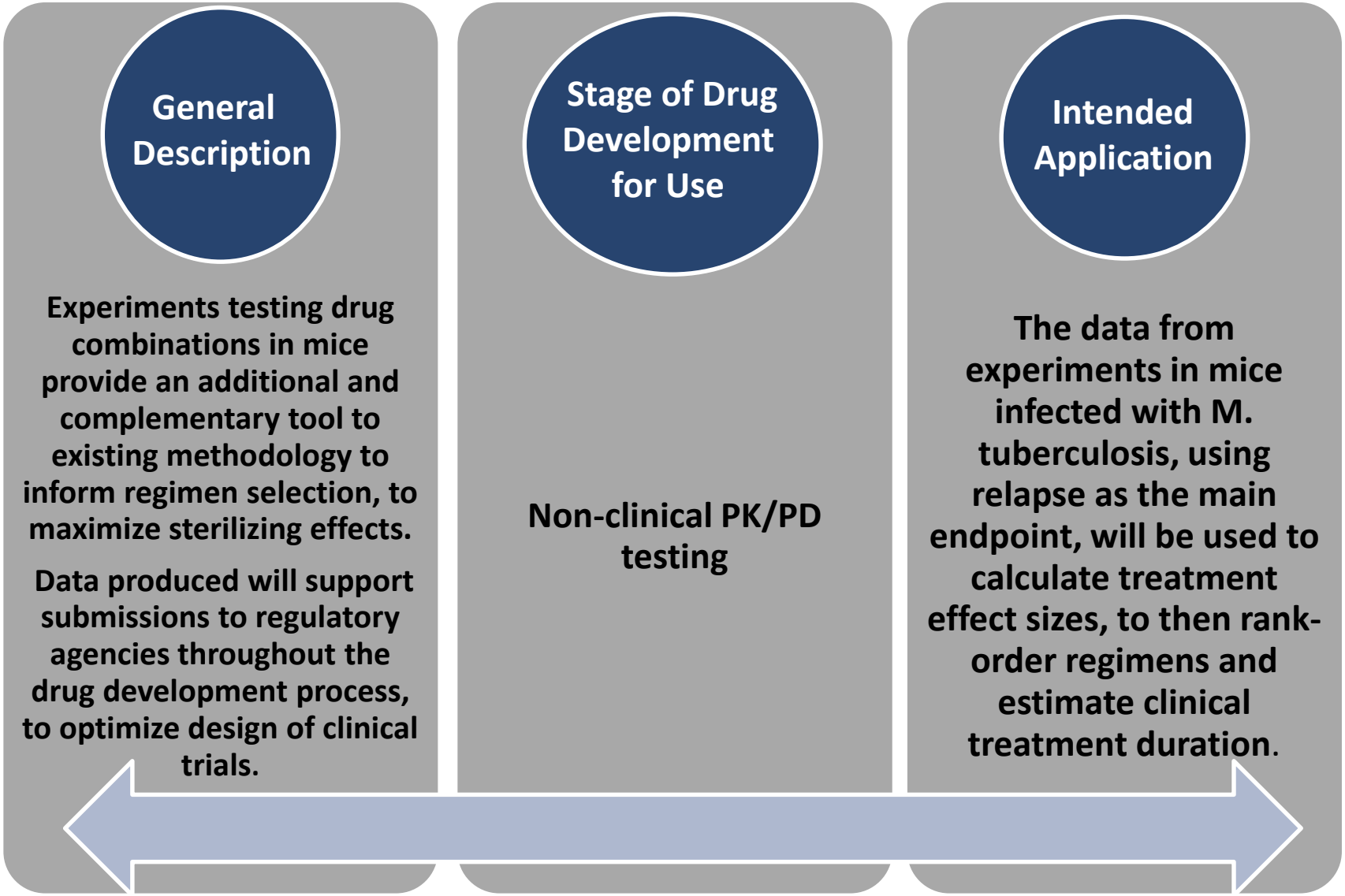
Workplan for evidence-based evaluation of sterilizing mouse model

CPTR PCS-WG Mouse Model Sub-team:

Dr. Nicole Ammerman
Dr. Al Berg
Dr. Dakshina Chilukuri
Dr. Geraint Davies
Dr. Geo Derimanov
Dr. Nader Fotouhi
Dr. Tawanda Gumbo
Dr. Debra Hanna
Dr. Karen Lacourciere
Dr. Barbara Laughon
Dr. Anne Lenaerts
Dr. Mike Lyons
Dr. Owen McMaster
Dr. Nader Fotouhi
Dr. Eric Nuermberger
Dr. Klaus Romero
Dr. Rada Savic
Dr. Christine Sizemore
Dr. Peter Warner
Lindsay Lehmann



COU Scenario 1: Treatment Duration and Rank-Ordering of Regimens



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

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
Comparing INH+RIF+PZA+EMB with PMD+MXF+PZA	PaMZ vs. HRZ(E)	8

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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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Dr. Debra Hanna (Critical Path Institute)

Dr. Karen Lacourciere

Dr. Barbara Laughon (National Institutes of Health)

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