CPTR - NIAID 2017 JOINT WORKSHOP

EVOLUTION OF A DATA DRIVEN PRECLINICAL ROADMAP FOR NOVEL TB REGIMENS: EMPHASIS ON ANIMAL MODELS AND PHARMOCOMETRICS FOR SELECTION OF EFFICIENT, RATIONAL SEQUENTIAL TB TREATMENT REGIMENS.

September 11-12, 2017

National Institute of Allergy and Infectious Diseases (NIAID)| Rockville, MD

BACKGROUND

TB treatment continues to be challenging and currently requires a long duration of therapy with multiple drugs, especially in MDR and XDR disease. The incidence of TB that is resistant to the frontline drugs is increasing, further complicating treatment and adding to costs. TB drug regimen development is lengthy, complicated, expensive and risky since clinical trials are prolonged and complex while uncertainty remains about how preclinical data should be used and whether they provide reliable information for key clinical development decisions such as whether new drugs, when dosed in combinations, are able to result in shorter treatment duration and non-relapsing cure. With the recent increases in new drug candidates, the number of new chemical entities that could be combined with each other or with existing anti-infective drugs is increasing. As an example, one of the challenges TB drug regimen developers face is that *e.g.* 14 drug candidates would generate about 1300 hypothetical three and four drug combinations options. Selecting the most suitable and promising combinations to take into clinical studies will be dependent on solid preclinical data and a realistic assessment of when combination efficacy can no longer be modelled in animals but requires human clinical trials.

The TB drug development community must take full advantage of pharmacometric principles and disease model data to accelerate the selection and development of new regimens with the greatest chance of delivering the treatment goals. Furthermore, we need to develop methods to assess when drug combinations are no longer maximally effective during treatment and could be switched to a different set of drugs to limit the change for resistance development and adverse events, thus allowing the development of chemical entities with a safety profile that supports administration for weeks rather than months as part of a more complex treatment regimens.

OBJECTIVE

The TB drug development community is collectively working towards the goal of advancing entirely novel TB drug regimens containing new and existing antibiotic agents.

Agreement upon the most informative translational roadmap (including preclinical models and supporting datasets) to inform the selection of components for such a regimen, as well as, appropriate dose and rank ordering will be key enablers for this process.

While the primary goal of the workshop is to develop a roadmap to guide advancement of entirely novel regimens, we will also discuss how the principles of a rigorous, data-driven roadmap can contribute to the development of treatment courses that may include sequential combinations of existing and emerging drugs to lead to shorten treatment duration.

EXPECTED OUTCOMES

An expected outcome of this workshop will be an expanded translational roadmap (2014 CPTR/NIAID Workshop Manuscript) to deliver new preclinical TB drug regimens that are safer, simpler and shorter for the treatment of DS, MDR and XDR TB. Furthermore, best practices related to management of pre-clinical data and data sharing to accelerate regimen development is key.

Additionally, we are expecting input regarding the use of the roadmap to develop sequential combinations of current/novel antibiotics to arrive at a shorter course of treatment that has broad efficacy against DS and DR TB to expand the definition of "treatment regimens" for TB.

Proceedings from the workshop will be published in a peer-reviewed journal.

To achieve this directive, specific discussion topics to be addressed include:

- Distinguishing between the development and use of pre-clinical animal models and clinical data for research versus drug development decision-making purposes.
- Review contemporary activities ongoing to evaluate the predictive accuracy and applicability of murine models.
- Define gaps in data collection and application of murine models, emphasizing comparison of pharma and academic best practices and exploring areas for collaboration
- Identify and plan activities for evaluation of additional non-murine animal models of TB for predicting clinical efficacy, including analyses of strengths and weaknesses.
- Current and emerging tools, including quantitative in silico drug models, to leverage animal model data to enable selection of drug combinations, dose levels and duration for subsequent clinical evaluation.

The following topics will be outside of the scope of this meeting:

- Discussion of specific drug classes and specific regimens.
- Programmatic implementation of specific regimens.
- Head-to-head comparisons of animal models without considering their utility for preclinical decision making (i.e. animal models supporting research)
- Host-immune modulation therapies

MONDAY, SEPTEMBER 11, 2017

ROOM 1D13 | National Institute of Allergy and Infectious Diseases (NIAID)| Rockville, MD

8:15 *15 min*	**Welcome & Kick-off**	*Christine Sizemore* *Debra Hanna*
8:30 *30 min*	**Novel preclinical animal models being employed in active drug development programs** • Marmoset Imaging **Discussion:** • What are the study design, data collection and analysis considerations for translation to clinical study design? • How can these models be used to inform compound selection, clinical trial design and dose selection? • What is the industry perspective on these emerging animal models?	*Laura Via*
9:00 *45 min*	**Critical Path Translational Roadmap for regimen selection and development based on pre-clinical animal models: Aligning academic and drug developer best practices** • Review and discuss goals for the workshop • Review and discuss current state of the pre-clinical roadmap and potential gaps (tools or process) for accelerating the selection and study of candidate combinations	*Christine Sizemore* *Peter Warner* *Debra Hanna*
9:45 *75 min*	**Best application of established murine models in drug development decision-making and contemporary analyses of translation of pre-clinical models for clinical outcome** • Evidence-based predictive accuracy evaluation of the sterilizing mouse model (CPTR) • Retrospective analyses on design of ReMOX and Rifaquin (Fluoroquinolone containing regimens) and other rifamycin trials from the murine model • IMI/PreDiCT-TB mouse model translational efforts **Discussion:** • What do these efforts tell us about best implementation of data from murine models? • How predictive are mouse model data for clinical outcomes? • What data management systems are utilized for data collection, aggregation and analysis? • What gaps have been identified in these data sets that are critical for consideration in future study design? • How are we sharing data across these organizations to ensure we are not recapitulating these analyses?	*Eric Nuermberger* *Rada Savic* *Gerry Davies*
11:00 *20 min*	***Break***	
11:20 30 min	**Novel preclinical animal models being employed in active drug development programs (continued)** • Kramnik Mouse	*Anne Lenaerts*

	Discussion: • What are the study design, data collection and analysis considerations for translation to clinical study design? • How can these models be used to inform compound selection, clinical trial design and dose selection? • What is the industry perspective on these emerging animal models?	
11:50 *55 min*	**Facilitated Discussion (1): Identification and approaches to managing sources of variability and uncertainty in the translation between *in vivo* animal and human studies** • How are findings from detailed *in vitro* and *in vivo* preclinical studies currently translated to support human clinical trial design? • What are those key sources of uncertainty in the translation of *in vivo* efficacy in animal models to inform selection of TB regimens for clinical assessment? • How best to model regimen efficacy against patients who are at highest risk of relapse?" • Do existing and emerging animal models and quantitative *in vitro* models support the contribution of Mtb sub-populations (i.e., drug resistant variants, persisters, and pathological niches) to treatment outcome? If not, is there a "worst case scenario" that is more relevant to model?	***Moderators*** *Klaus Romero* *Ada Zhuang*
12:45 *60 min*	***Lunch***	
1:45 *60 min*	**Facilitated Discussion (2): Use of *in vivo* animal models to inform decision making** • How are animal models currently used to inform decision making for TB drug / regimen development? • What are the animal model data that are currently most important for designing regimens, including drug selection and treatment durations? • How do data collection and data management systems for animal model studies currently influence placement in the decision-making process? • What are the approaches used to integrate *in vivo* animal model data with other models (i.e., *in vitro* and *in silico*) to inform decision making? • How will emerging information (i.e., predictive performance evaluations, translational variability and uncertainty) be used to inform placement within the decision-making process?	***Moderators*** *Gerry Davies* *Larry Geiter*
2:45 *15 min*	***Break***	
3:00 *60 min*	**Facilitated Discussion (3): How can we use information from translational pharmacology data, to make decisions about drugs in-hand? How do you know when a regimen or a drug in the regimen is maximally effective (preclinical)? How do you know when to switch to a different regimen (preclinical)?**	***Moderators*** *Bill Bishai* *Dikoe Makhene*

	• What preclinical endpoints / measurements should be captured for drugs and regimens to be assured they are maximally effective while maintaining an adequate safety profile in animals and humans? • How are the exposure-response profiles for efficacy and safety characterized in animal models for a given drug as single-agent and in the context of a combination regimen? • What exposure-response endpoints can be used to determine efficacy with regard to key bacterial sub-populations? • How do you assess consequences of losing individual drug efficacy in a combination regimen due to resistance?	
4:00 *45 min*	**Wrap Up Day 1**	*Christine Sizemore* *Debra Hanna*
4:45	***Adjourn Day 1***	

TUESDAY, SEPTEMBER 12, 2017

ROOM LD20 | National Institute of Allergy and Infectious Diseases (NIAID)| Rockville, MD

8:30 *10 min*	**Welcome & Review Agenda**	
8:40 *20 min*	**Recap Day 1 Discussions & Outcomes** • Review key discussion points • Open discussion	*Christine Sizemore* *Debra Hanna*
9:00 *120min*	**Regimen Development "Simulation" (Point/Counterpoint discussion)** **Stage 1: General Discussion (max. 60 min):** *Objective:* Using examples, construct a TB drug regimen development roadmap that will be pressure tested in Stage 2. • Identify a hypothetical regimen and create a preclinical development plan based on discussions from Day 1 – revised roadmap. The goal is to apply concepts/roadmap discussed during the workshop to a hypothetical regimen (with specific drugs) and determine whether available data or available plans are solid, produce data that indeed predict human clinical outcomes and identify areas of weakness that may require additional research, model development and/or data. **Stage 2: Debate (max. 60 min)** *Objective:* Pressure test the roadmap developed in Stage 1	***Moderators*** *Christine Sizemore* *Mark Goldberger*

	• Justify the proposed data/models included in the development plan in the context of providing biologically relevant information to move into clinical trials **Team 1** – Project team "selling" the preclinical approach to management to get the go-ahead for clinical development – goal is to provide data driven arguments to support the proposed plan) **Team 2** – Skeptical upper management (finding inconsistencies in the plan and identifying missing data – goal is to play devil's advocate. Must offer alternative suggestions.	*Self-appointed teams in audience*
11:00 *20 min*	**Break**	
11:20 *45 min*	**Facilitated Discussion (4): What data are needed from a regulatory perspective to support clinical testing of a regimen that changes during the duration of therapy (e.g. 3 drugs for 2 weeks, 3 different drugs for the next 4 weeks, etc.)?** • What are the general regulatory considerations for selection of methods for in vivo animal model translation to clinical trial design and regimen selection? • What is the regulatory perspective on the preclinical data required to understand the individual contributions of regimen components (i.e., single agents or combinations in sequence) within a novel regimen? • How are regimens consisting of sequential changes in drug combinations evaluated in other diseases (infectious/non-infectious)?	***Moderator*** *Joe Toerner* *Christine Sizemore*
12:05 *45 min*	**Workshop Summary and Identified Research and Data Gaps**	*Debra Hanna* *Christine Sizemore*
12:50 *25 min*	**Funders Perspectives: The Need for Innovations in the Roadmap**	*Peter Warner* *Christine Sizemore*
1:15	***Adjourn***	