Discussion

Best application of established murine models in drug development decision-making and contemporary analyses of translation of pre-clinical models for clinical outcome

• 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?
Novel preclinical animal models being employed in active drug development programs

• 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?
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?
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 sharing and evaluation efforts currently influence study design and interpretation of animal model studies?

• 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?
How can we use information from translational pharmacology data, to make decisions about drugs in-hand?

- 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?
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)?