Discussion

Critical Path to TB Drug Regimens

NIH National Institute of Allergy and Infectious Diseases

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?

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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)

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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)

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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?

Facilitated Discussion (3)

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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)

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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)?