2017 CPTR Workshop: Day 1 – March 20, 2017

The 8th Annual CPTR Initiative Workshop drew more than 150 participants to Washington, D.C. to learn and share information critical to the rapid advancement of new TB combination therapies, drug susceptibility tests (DST), and the tools and models necessary to develop and implement them. Participants represented a diverse group of global stakeholders, including product developers, regulators, health systems workers, and TB survivors and patient advocates. Detailed summaries and content from Day 1 of the 2017 CPTR Workshop is provided below.

AGENDA

8:00 – 8:05 am	**Welcoming Remarks** *Jan Gheuens (Bill & Melinda Gates Foundation)*
8:05 – 8:35 am	**Keynote Address: Perspectives of an Advocate** *Mark Harrington (Treatment Action Group)*
TB Drug Discovery Pipeline ***Moderator: Debra Hanna (Critical Path Institute)***	
8:35 – 9:15 am	**Overview of TB Drug Accelerator (TBDA) Activities and Portfolio** *Steve Berthel (New Venture Fund)*
Analysis and Lesson Learned from TB Re-analysis of Fluoroquinolone Executed Clinical Trials (TB ReFLECT) and Impact on the Future of TB Drug Development ***Moderator: Christian Lienhardt (World Health Organization)***	
9:15 – 9:35 am	**Session Introduction** *Christian Lienhardt (World Health Organization)* *Debra Hanna (Critical Path Institute)*

9:30 – 10:40 am	**Critical Collaborations: Update and future direction for TB Reflect and TB PACTS (Platform for the aggregation of Clinical Trials for TB)** *Rada Savic (University of California, San Francisco)*
10:40 – 10:55 am	**Break**
10:55 – 11:40 am	**Panel Discussion** *Moderator: Christian Lienhardt (World Health Organization)* *Panelists: Payam Nahid (University of California, San Francisco), Dave Hermann (Bill & Melinda Gates Foundation), Rada Savic (University of California, San Francisco), Patrick Phillips (UK Medical Research Council), Katherine Fielding (London School of Hygiene and Tropical Medicine), Amina Jindani (St. George's University)*
11:40 – 12:00 am	**Closing Session Remarks** *Debra Hanna (Critical Path Institute)*
12:00 – 1:00 pm	**Lunch**
Optimizing TB Drug Development Through Quantitative Platforms and Translational Pharmacology ***Moderator: Klaus Romero (Critical Path Institute)***	
1:00 – 1:10 pm	**Session Introduction** *Klaus Romero (Critical Path Institute)*
1:10 – 1:30 pm	**How to Maximize Lessons Learned into an Optimized Drug Development Process for TB** *Vikram Sinha (Merck)*
1:30 – 1:50 pm	**Quantitative Linkage Between TTP and Time to Culture Negative Status to Optimize Drug Development Decisions** *Nastya Kassir (Certara)*
1:50 – 2:10 pm	**A Systems Pharmacology Model for Tuberculosis: Understanding Bug-Host-Regimen Interplay** *Natasha Strydom (University of California, San Francisco)*

2:10 – 2:30 pm	**Reproducibility and Industrialization of the Hollow Fiber System Model** *Debra Hanna (Critical Path Institute)*
2:30 – 3:00 pm	**Panel Discussion** *Moderator: Klaus Romero* *Panelists: Nastya Kassir (Certara), Natasha Strydom (University of California, San Francisco), Tawanda Gumbo (Baylor University), Debra Hanna (Critical Path Institute), Paolo Denti (University of Cape Town), Vikram Sinha (Merck)*
3:00 – 3:15 pm	**Break**
Integration of Drug Development Tools and Strategic Regulatory Approaches to Accelerate TB Regimen Development ***Moderator: Larry Geiter (Otsuka)***	
3:15 – 3:20 pm	**Session Introduction** *Debra Hanna (Critical Path Institute)*
3:20 – 3:40 pm	**Examining the Predictive Accuracy of Sterilizing Mouse Efficacy Models** *Eric Nuermberger (Johns Hopkins University)*
3:40 – 4:00 pm	**Towards Regulatory Qualification of a PBPK model for use in TB Drug Research** *Iain Gardner (Certara)*
4:00 – 4:20 pm	**Lipoarabinomannan (LAM) as a Pharmacodynamic Biomarker and Potential TB Drug Development Tool** *Larry Geiter (Otsuka)*
4:20 – 4:40 pm	**21st Century Pathways to pan-TB Regimens** *Bob Wallis (Aurum Institute)*
4:40 – 5:00 pm	**Regulatory Pathways for CPTR Drug Development Tools and Methodologies** *Ann Robbins (Critical Path Institute Regulatory Consultant)*

5:00 – 5:30 pm	**Panel Discussion** *Moderator: Larry Geiter (Otsuka)* *Eric Nuermberger (Johns Hopkins University), Iain Gardner (Certara), Ann Robbins (Critical Path Institute Regulatory Consultant)*
5:30 pm	**Adjourn**

Welcoming Remarks

Jan Gheuens (Bill & Melinda Gates Foundation)

Jan Gheuens opened the event by reflecting on the growth and progress of the CPTR Initiative, as well as forward to its ongoing work. He stressed that the direction of CPTR is truly determined by those who participate it in, highlighting the community-driven nature of the Initiative. After his remarks, Gheuens was joined by Mel Spigelman of TB Alliance and Martha Brumfield and Debra Hanna of Critical Path Institute who honored him for his contributions to and leadership of CPTR.

- Video (Remarks)
- Video (Ceremony)

Keynote Address: Perspectives of an Advocate

Mark Harrington (Treatment Action Group)

Mark Harrington delivered a keynote address that offered many insights stemming from his extensive experience as an advocate, first in the HIV-AIDS space, and subsequently in other disease areas, including TB. Harrington cited the recent pull back in TB research funding, as well as the uncertain current political environment as challenges to progress. He called for renewed engagement and investment from industry and faster and greater growth of the early stage pipeline – noting that regimens can't be developed without a robust selection of new drug candidates. Harrington also noted encouraging successes in the field despite limited resources, referencing the promise and early successes of the NIX-TB trial/regimen, while raising associated questions related to new regimens around regulatory challenges and expanded access programs. Harrington closed by proclaiming that much has been done with little in the field of TB R&D and that he believes much more would be possible were adequate resources available. This underscores the importance of strong and effective advocacy efforts.

- Video

TB Drug Discovery Pipeline

Overview of TB Drug Accelerator (TBDA) Activities and Portfolio

Steve Berthel (New Venture Fund)

Steve Berthel provided an informative summary of the structure and goals of the TB Drug Accelerator (TBDA) Program, which functions as a key mechanism to help grow the pipeline of early stage TB drug research and accelerate such work. Particularly important is the ability of the TBDA, like CPTR, to bring together groups who are otherwise competitive in order to advance TB research efforts field-wide. He stated that the TBDA is committed to supporting a broad goal of a one-month point of care TB treatment regimen by 2024.

- Video
- Presentation
- Video (Q&A)

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Analysis and Lesson Learned from TB Re-analysis of Fluoroquinolone Executed Clinical Trials (TB ReFLECT) and Impact on the Future of TB Drug Development

Session Introduction

Christian Lienhardt (World Health Organization)

Debra Hanna (Critical Path Institute)

Debra Hanna and Christian Lienhardt began the session by providing an overview of the TB-ReFLECT program and its capabilities to provide improved understanding of factors responsible for variations in response to TB therapy, evaluation of endpoints and other trial design issues, and comparisons of results between regimens. Lienhardt explained the TB-PACTS database, highlighting its ability to modernize data analysis of past trials with current approaches, technologies, and resources.

- Video
- Presentation

Critical Collaborations: Update and future direction for TB Reflect and TB PACTS (Platform for the aggregation of Clinical Trials for TB)

Rada Savic (University of California, San Francisco)

Rada Savic presented an analysis of data from completed Phase 3 fluoroquinolone trials performed as part of TB-ReFLECT. Subjects covered included detailed analysis of patient subgroups in whom experimental therapy did and did not shorten time to cure, insight into predictors of successful treatment, and the importance of establishing universal definitions and procedures across trials and how TB-ReFLECT

addressed such data gaps on inconsistencies. Savic's presentation suggested that – at least until totally novel regimens are available – a single regimen of defined duration is likely not to be optimal for all patients.

- Video
- Presentation

Panel Discussion

Moderator: Christian Lienhardt (World Health Organization)

Panelists: Payam Nahid (University of California, San Francisco), Dave Hermann (Bill & Melinda Gates Foundation), Rada Savic (University of California, San Francisco), Patrick Phillips (UK Medical Research Council), Katherine Fielding (London School of Hygiene and Tropical Medicine), Amina Jindani (St. George's University)

The panel discussion delved further into key findings and implications of TB-ReFLECT data analysis. Calls were made to standardize research design and data collection. Additional discussion focused on the need and strategies to determine predictive endpoints for Phase 2 and 3 trials. An interesting topic debated was the possibility of stratifying patients by how difficult to treat their disease predicts to be, or for conducting trials in smaller numbers of the hardest to treat patients. This led to conversation around the potential benefits and drawbacks of that kind of approach.

- Video

Optimizing TB Drug Development Through Quantitative Platforms and Translational Pharmacology

Session Introduction

Klaus Romero (Critical Path Institute)

Klaus Romero opened the afternoon's program, noting that the upcoming sessions share a theme, which is the way newly developed tools are being used to enhance and improve current TB drug development efforts

- Video

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Quantitative Linkage Between TTP and Time to Culture Negative Status to Optimize Drug Development Decisions

Nastya Kassir (Certara)

Nastya Kassir focused on the need to evaluate TTP trajectory parameters with clinically relevant endpoints in Phase III studies. Kassir's work used data from the REMox TB study to analyze how the shape of the TTP model can be linked with response, and how changes in three key parameters can affect the rate of progression. Kassir hypothesized that these parameters could be used to predict results in Phase 3 studies. Further data presented suggested that these methods could provide valuable insight when extrapolating Phase 2 data to predict performance and outcome in Phase 3 and deciding whether to advance experimental regimens to the final and most expensive stage of development.

- Video
- Video (Question and Answer)
- Presentation

A Systems Pharmacology Model for Tuberculosis: Understanding Bug-Host-Regimen Interplay

Natasha Strydom (University of California, San Francisco)

Natasha Strydom explained the value of a systems pharmacology approach to understanding the relationships between *M.tb.* and the host. Strydom's presentation first detailed the systems pharmacology model. Data presented showed that immune response plays a role in efficacy of therapy, leading questions on how to make use of immune-status in TB therapy, especially in HIV co-infected patients.

- Video
- Video (Question and Answer)
- Presentation

Reproducibility and Industrialization of the Hollow Fiber System Model

Debra Hanna (Critical Path Institute)

Debra Hanna began by providing some background on the HFS-TB, including the pathway it took to receive regulatory endorsement. Hanna noted that HFS-TB is one of many possible tools that can be used to improve decision-making regarding specific types of drug development questions. She thoroughly explained the workings and capabilities of the tool and provided examples of the data already being collected by its use, as well as guidance for its use and discussion of opportunities to expand its use.

- Video
- Presentation

Panel Discussion

Moderator: Klaus Romero

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- Video

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Integration of Drug Development Tools and Strategic Regulatory Approaches to Accelerate TB Regimen Development

Session Introduction

Debra Hanna (Critical Path Institute)

- Video

Examining the Predictive Accuracy of Sterilizing Mouse Efficacy Models

Eric Nuermberger (Johns Hopkins University)

Eric Nuermberger delivered a progress report on the effort evaluate the sterilizing mouse model's predictive accuracy, with the intent of closing the translational gap to reduce late stage drug/regimen candidate attrition. Nuermberger stressed the need to develop and validate new tools, like the Hollow Fiber System model to assist in improving the predictive accuracy of early stage research.

- Video
- Presentation

Towards Regulatory Qualification of a PBPK model for use in TB Drug Research

Iain Gardner (Certara)

Iain Gardner discussed the PBPK model's capability to be applied for regulatory qualification, noting that the number of FDA submissions that incorporate PBPK is increasing. Gardner detailed the growing use of PBPK in decision-making, label claims, and regulatory guidance. Gardner went on the present about the workings of the model itself.

- Video
- Video (Question and Answer)
- Presentation

Lipoarabinomannan (LAM) as a Pharmacodynamic Biomarker and Potential TB Drug Development Tool

Larry Geiter (Otsuka)

Larry Geiter presented on Otsuka's attempt to develop a rapid assay for use as a drug development tool in conjunction with clinical trials, citing the huge unmet need for real-time measure of efficacy of treatment in a research setting. He went on to discuss challenges associated with EBA and culture-based tools, and to present data on LAM. Geiter remarked on his experiences meeting with regulatory agencies in pursuit of past projects, noting that discussions felt more productive when the associated research was bolstered by CPTR support.

- Video
- Video (Q&A)
- Presentation

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21st Century Pathways to pan-TB Regimens

Bob Wallis (Aurum Institute)

Bob Wallis laid out an alternative approach to TB regimen approval that could accelerate access to new therapies by starting with smaller groups of higher risk patients and expanding target population as evidence continues to accumulate. Such an approach would require approvals based on trials that include fewer patients.

Regulatory Pathways for CPTR Drug Development Tools and Methodologies

Ann Robbins (Critical Path Institute Regulatory Consultant)

Ann Robbins opened the session with a detailed presentation of FDA's regulatory processes and the qualification of biomarkers. Robbins explained that while seeking qualification is not a requirement, the data necessary to do so is generally required for ultimate regulatory approval. Therefore, by following the process of qualifying the tool, research more closely approaches "regulatory-ready" status. She then articulated some of the benefits of qualification and participating in the process.

- Video
- Presentation

Panel Discussion

Moderator: Larry Geiter (Otsuka)

Panelists: Eric Nuermberger (Johns Hopkins University), Iain Gardner (Certara), Ann Robbins (Critical Path Institute Regulatory Consultant)

- Video

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