CRITICAL PATH INSTITUTE

CPTR 2017 Workshop: Day 2 – March 21, 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 2 of the 2017 CPTR Workshop is provided below.

AGENDA

8:15 – 8:30 am	**Welcoming Remarks** *Mel Spigelman (TB Alliance)*
Driving Progress Through Regulatory Innovation – Learnings from Oncology and Translatability to TB Regimen Development ***Moderators: Martha Brumfield (Critical Path Institute) and Debra Hanna (Critical Path Institute)***	
8:30 – 10:00 am	**Interview and Q&A** *Richard Pazdur (Food and Drug Administration)* *Edward Cox (Food and Drug Administration)*
TB Patient Perspectives ***Moderators: Debra Hanna (Critical Path Institute) and Erica Lessem (Treatment Action Group)***	
10:00 – 11:00 am	**Interview and Q&A** *Steve Bradley (TB Alert)* *Phumeza Tisile (TB Proof)*
11:00 – 11:15 am	**Break**

TB Drug Co-Development Roundtable ***Moderator: Carl Mendel (TB Alliance)***	
11:15 – 11:25 am	**Session Introduction** *Carl Mendel (TB Alliance)*
11:25 am – 1:15 pm	**Brief Industry Updates** *Jeffrey Hafkin (Otsuka)* *Tine De Marez (Janssen)* *Dan Everitt (TB Alliance)* *Charles Wells (Sanofi)* *June Kim (Qurient)* *Norbert Heinrich (University of Munich)* *Bern-Thomas Nyang'wa (TB-PRACTECAL)* *Alison Webster (GlaxoSmithKline)* **Panel Discussion**
1:15 – 2:15 pm	**Lunch**
Topical Breakout Sessions	
2:15 – 3:30 pm	**Demo and Training: Physiologically-based Pharmacokinetic (PBPK) Model and QT Prolongation Module** *Chairs: Iain Gardner (Certara) and Klaus Romero (Critical Path Institute)* **Demo and Training: Relational Sequencing TB Data Platform (ReSeqTB)** *Chair: Amanda Borens (Critical Path Institute)* **Stakeholder & Community Engagement Workgroup: Applying Community Outreach and Engagement Strategies to Inform Trial Design** *Chair: Steve Wandiga (Kenya Medical Research Institute)* **Progressing the Preclinical Roadmap – Next Steps in Evaluating in vivo Models and Other Drug Development Tools** *Chairs: Debra Hanna (Critical Path Institute) and Eric Nuermberger (Johns Hopkins University)*
3:30 – 3:45 pm	**Break**

Next Generation Sequencing for TB Diagnostics: Advances, Opportunities and Necessary Steps ***Moderator: Angela Starks (Centers for Disease Control and Prevention)***	
3:45 – 3:50 pm	**Session Introduction** *Angela Starks (Centers for Disease Control and Prevention*
3:50 – 4:00 pm	**Target Product Profiles for TB Diagnostics** *Tim Rodwell (FIND)*
4:00 – 4:15 pm	**The Role of Genome Sequencing in Global Surveillance of Anti-tuberculosis Drug Resistance** *Matteo Zignol (World Health Organization)*
4:15 – 4:30 pm	**Advances in Targeted Sequencing** *Dave Engelthaler (Translational Genomics Research Institute)*
4:30 – 4:45 pm	**Microdilution Based MIC Detection for Old and New Anti-TB Drugs: Preliminary Evaluation of the Layout Proposed for the Cryptic Project** *Daniela Cirillo (San Raffaele Scientific Institute)*
4:45 – 5:15 pm	**Panel Discussion** *Moderator: Angela Starks (Centers for Disease Control and Prevention)* *Panelists: Tim Rodwell (FIND), Matteo Zignol (World Health Organization), Dave Engelthaler (Translational Genomics Research Institute), Daniela Cirillo (San Raffaele Scientific Institute), Richard Compton (Nanopore), Joshua Trotta (Thermofisher)*
5:15 pm	**Closing Remarks** *Marco Schito (Critical Path Institute)*
5:20 pm	**Adjourn**

Welcoming Remarks

Mel Spigelman (TB Alliance)

Mel Spigelman opened the second day of the workshop by introducing the day's agenda and drawing attention to the personal stories of TB patients, reinforcing the driving force behind CPTR and all TB research and development efforts.

- Video

Driving Progress Through Regulatory Innovation – Learnings from Oncology and Translatability to TB Regimen Development

Moderators: Martha Brumfield (Critical Path Institute) and Debra Hanna (Critical Path Institute)

Richard Pazdur (Food and Drug Administration)

Edward Cox (Food and Drug Administration)

This session focused on extrapolating regulatory learnings from other fields for use in TB. Richard Pazdur discussed the evolution of oncology drugs and the explosion of new drugs and how drug development strategies popular in oncology may relate to TB. Martha Brumfield identified the development of biomarkers a gamechanger for oncology research and treatment, noting similar advances could do the same for TB. Pazdur noted a lack of coordination in biomarker development in oncology – this is something CPTR is helping address in TB. He remarked that oncology represents both the best and worst in pharma – great progress and innovation, but lack of coordination because competition trumps cooperation. Edward Cox emphasized that this is a potential strength of CPTR, as cooperation can enable the limited resources for TB research to be used most effectively and efficiently.

- Video (Session Intro)
- Video (Richard Pazdur)
- Video (Edward Cox)
- Video (Q&A)

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TB Patient Perspectives

Moderators: Debra Hanna (Critical Path Institute) and Erica Lessem (Treatment Action Group)

Steve Bradley (TB Alert)

Phumeza Tisile (TB Proof)

This session offered an opportunity to hear perspectives from two TB patients and survivors, Phumeza Tisile and Steve Bradley. Erica Lessem (Treatment Action Group) provided introductory remarks for the session.

Phumeza Tisile shared her harrowing story being treated for TB, MDR-TB, pre-XDR-TB, and finally XDR-TB. Her treatment lasted almost four years total. Tisile was taking 20 – 30 pills daily, plus injections for a substantial length of time. She lost her hearing while sick, but was ultimately able to regain it with cochlear implants years later. Tisile was ultimately cured with the help of an unapproved TB drug – linezolid – which is now undergoing additional development. Tisile has since dedicated herself to advocating for better treatments for TB, more investment, and greater inclusion of the patient perspective in the research process. She delivered a strong message about ensuring new treatments reach those in need – asking what good are new and improved therapies if those suffering can't afford them?

Steve Bradley shared his story, which included lengthy delay in getting accurately diagnosed with TB and terrible side effects of TB therapy. Bradley lost his sight and experienced permanent reduced sensitivity in his legs due to complications with first line treatment. Bradley spoke of the devastating effects of loss of independence and ability to work, as well as the terrible neglect of TB and stigma associated with it. He continues to share his story to raise awareness for TB and research, and remains optimistic that breakthroughs to improve therapy may be on the horizon.

- Video (Session Intro)
- Video (Phumeza Tisile)
- Video (Steve Bradley)
- Video (Q&A)

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TB Drug Co-Development Roundtable

Moderator: Carl Mendel (TB Alliance)

One of the signature sessions of the annual workshop, The TB Drug-Co-Development Roundtable was introduced the by Carl Mendel, who drew specific attention to the CTB2 database as an important new resource in the field.

- Video
- Presentation

Jeffrey Hafkin (Otsuka)

Jeffrey Hafkin delivered an update on Otsuka's programs to provide access to delamanid. The drug is currently available through the Global Drug Facility, and an access program in South Africa was unveiled on World TB Day, 2017. Efforts to expand access in several additional countries in Asia are ongoing. Overall, treatment has been provided for more than 2,400 patients in 45 countries. Additionally, the pediatric delamanid program has been expanded, following a WHO endorsement of use of delamanid in certain pediatric populations in October of 2016. Hafkin also provided an update on the ongoing development of the OPC-167832 compound.

- Video
- Presentation

Tine De Marez (Janssen)

Tine De Marez presented on the latest in the bedaquiline clinical development program. Areas covered included post-marketing commitments – a phase 3 study and pediatric study. De Marez covered locations where bedaquiline has already received approval and where submissions for approval have been completed. The update also noted that the pediatric trial of bedaquiline is underway, specifying that adolescents in the trial receive adult tablets and younger children receive a pediatric formulation of the drug. De Marez closed by providing an update on additional studies that include bedaquiline within drug combinations.

- Video
- Presentation

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Dan Everitt (TB Alliance)

Dan Everitt gave an overview TB Alliance's clinical portfolio. New and promising compounds discussed included TBAJ-587, a second generation diarylquinolone, and TBI-223 an oxazolidione that shows increased safety and a favorable efficacy profile in mice. Everitt also gave an encouraging update on the Nix-TB trial, which treats patients with XDR-TB or who have failed MDR-TB therapy with a fully novel regimen. As of the presentation, 31 patients had completed therapy and six months of follow-up. Interim results are quite promising. Finally, Everitt presented plans for TB Alliances upcoming NC-007 combination trial.

- Video
- Presentation

Charles Wells (Sanofi)

Charles Wells presented on the status of rifapentine, which was WHO prequalified in 2017. Registration has been achieved in Asia, with additional applications for approval submitted in several other regions. Wells gave updates on the TBTC Study 31 update, assessing a shortened regimen for active TB, and on the studies dedicated to rifapentine as part of fixed dose combinations. Wells also identified two recent preclinical drug candidates discovered by Sanofi.

June Kim (Qurient)

June Kim offered info on Qurient's drug candidate, Q203. Kim reviewed the compound's key attributes and noted that it is scheduled to enter an EBA study later in 2017. Development is continuing with a partner; Phase 1 has taken place in Russia.

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- Presentation

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Norbert Heinrich (University of Munich)

Norbert Heinrich presented an update on the drug candidate, BTZ2043. Heinrich provided background on the compound and summarized Phase 1 and 2 development plans, plus presented the slated trial design for an upcoming Phase 2a study.

- Video
- Presentation

Bern-Thomas Nyang'wa (TB-PRACTECAL)

Bern-Thomas Nyang'wa presented plans and goals for an ongoing late stage trial treating drug-resistant patients using combinations of bedaquiline, pretomanid, linezolid, moxifloxacin, and clofazimine. The trial consists of two stages. Patients will be observed after 8 weeks, and those who received regimens that do not perform up to standard will discontinue experimental treatment and receive standard therapy, while better performing regimens will be continued for six months and follow-up, seeking cure. The trial commenced in January of 2017. Nyang'wa articulated plans to expand the trial to additional sites.

- Video
- Presentation

Alison Webster (GlaxoSmithKline)

Alison Webster provided a concise overview of GSK's TB drug portfolio. Webster discussed the organization's strategies and approaches to drug discovery and development, including the role of beta-lactams. She also presented on GSK's newest anti-TB compound, GSK070.

- Video
- Presentation

Panel Discussion

- Video

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Topical Breakout Sessions

The 2017 CPTR Workshop included topical breakout sessions on a range of topics, including interactive training demonstrations on several tools developed through CPTR partnerships.

Demo and Training: Physiologically-based Pharmacokinetic (PBPK) Model and QT Prolongation Module

Chairs: Iain Gardner (Certara) and Klaus Romero (Critical Path Institute)

Attendees participated in a hands-on demo using the CPTR PBPK model in TB drug development scenarios. Following a short introduction to the PBPK model, attendees created a compound file for moxifloxacin and used this to simulate plasma and lung concentrations of the drug. The results were compared to available clinical data. The PBPK model for moxifloxacin will be refined by incorporation of P-glycoprotein transport data and the effects on the local drug concentration in the lung examined. In the last part of the session a demonstration of how the PBPK model can be coupled with the Cardiac Safety Simulator to predict QT prolongation was given. Using Moxifloxacin as an example, session chairs will discuss the use of QSAR models and in vitro ion channel data together with plasma/tissue concentration data from the PBPK model to predict changes in ionic currents and ultimately QT prolongation caused by drugs.

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Demo and Training: Relational Sequencing TB Data Platform (ReSeqTB)

Chair: Amanda Borens (Critical Path Institute)

In this training session, CPTR reviewed the Data Browser and common tasks associated with online data exploration. CPTR highlighted the architecture of the underlying data for exploration and download, reviewed the terms and conditions for accessing the data, and discussed summary statistics for existing data in the repository. The new Visual Browser tools were reviewed, showing existing functionality as well as features in development. After the initial training overview, future enhancements and known challenges were discussed, and participants were given an opportunity to provide feedback.

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Stakeholder & Community Engagement Workgroup: Applying Community Outreach and Engagement Strategies to Inform Trial Design

Chair: Steve Wandiga (Kenya Medical Research Institute)

Attendees received a briefing from the Stakeholder & Community Engagement Workgroup (SCE-WG) on work planned to examine the correlation of implementing outreach strategies for recruiting TB patients to ultimate retention throughout the trial. One goal of this work includes generating recommended best practices, or a template guide, for recruitment for TB trials. Attendees shares their perspectives and suggestions for additional areas—from clinical trials to diagnosis and delivery of care—that could benefit from enhanced community and stakeholder engagement.

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Progressing the Preclinical Roadmap – Next Steps in Evaluating *in vivo* Models and Other Drug Development Tools

Chairs: Debra Hanna (Critical Path Institute) and Eric Nuermberger (Johns Hopkins University)

Attendees discussed currently available and emerging efficacy-based models for clinical trial design for TB regimen development, identified next steps needed to progress the preclinical roadmap, identified data gaps and needs, and prioritized animal models, other than the sterilizing mouse model to examine for evidence-based decisions for TB drug regimen development and qualification. The group also discussed and addressed the dichotomy in the field regarding employing in vivo models for preclinical and drug development purposes.

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Next Generation Sequencing for TB Diagnostics: Advances, Opportunities and Necessary Steps

Moderator: Angela Starks (Centers for Disease Control and Prevention)

Introductory Remarks

Angela Starks (Centers for Disease Control and Prevention)

- Video

Target Product Profiles for TB Diagnostics

Tim Rodwell (FIND)

Tim Rodwell discussed the need for new diagnostics and features important for them to possess to support technical and operational needs for use in low income settings considering new and upcoming TB drug regimens.

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The Role of Genome Sequencing in Global Surveillance of Anti-tuberculosis Drug Resistance

Matteo Zignol (World Health Organization)

Matteo Zignol discussed efforts to use genomic sequencing in surveilling global TB drug resistance. Zignol explained the operations of the program and associated challenges and solutions. Surveillance is performed using Xpert, and often smear microscopy, but the transportation of samples remains a challenge, losing up to 20% of samples in the process. Sequencing was posed as a solution to the loss of samples due to transportation. Zignol presented the results of using sequencing data for surveillance. Suboptimal sensitivity remains an issue, and there are ongoing efforts to develop models to adjust for misclassification. In particular, moxifloxacin is prone to sensitivity issues under sequencing methods. The first such project was successful; additional studies are ongoing and planning for later in 2017.

- Video
- Presentation

Advances in Targeted Sequencing

Dave Engelthaler (Translational Genomics Research Institute)

Dave Engelthaler discussed the novel methods in which sequencing-based assays can be implemented to address clinical questions. This included points on for identifying minor drug resistant subpopulations using nested amplicon next generation sequencing and interpretation. Engelthaler discussed the potential of these strategies to potentially identify early cases of drug resistance while addressing the needs to lower rates of sequencing error.

Microdilution Based MIC Detection for Old and New Anti-TB Drugs: Preliminary Evaluation of the Layout Proposed for the Cryptic Project

Daniela Cirillo (San Raffaele Scientific Institute)

Daniela Cirillo presented the work performed by the CRyPTIC consortium on evaluating a new microtiter plate designed to contain existing, new and repurposed TB drugs. The topics discussed included a validation study regarding reproducibility by assessing percentage of interpretable plates by reading day and by drug, agreement between readers and reading method. Various plate reading methods were also assessed and future work is planned on evaluating machine learning algorithms.

Panel Discussion

- Video

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