CPTR Newsletter – December 2018

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In the Spotlight

TB-ReFLECT meta-analysis published in Nature Medicine

The TB Reanalysis of Fluoroquinolone Executed Clinical Trials (TB-ReFLECT) project, a meta-analysis of individual patient-level data from the REMox-TB, OFLOTUB and RIFAQUIN clinical trials, achieved a major milestone with publication of the meta-analysis results in the journal *Nature Medicine*. This manuscript represents the culmination of TB-ReFLECT efficacy analyses and, given the extensive readership

and high-impact of *Nature Medicine*, highlights the potentially significant impact of this analysis on patient care and the design of future clinical trials in pulmonary TB.

Results highlighted in the manuscript demonstrate the importance of multiple factors that influence long-term outcome, including patient-specific characteristics at baseline and while on treatment, as well as the strong influence of dosing frequency and adherence. Dr. Rada Savic, who led the TB-ReFLECT project, notes this work emphasizes the need to shift away from a "one-size-fits-all" approach towards more pragmatic strategies for stratified clinical trials and patient care. As an example, compared with conventional approaches, stratified medicine trials are expected to enable benefits such as ultra-short course therapy options (1-2 months for drug-sensitive, and 2-4 months for drug-resistant). Another key finding noted by Dr. Savic is the importance of adherence on treatment success, which is actively being translated into numerous adherence interventions by domestic and international organizations.

The manuscript, titled "*A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis,*" is available via open access at the following link: https://doi.org/10.1038/s41591-018-0224-2.

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Updates to the TB-PACTS Clinical Trial Data Repository

CPTR continues to support the TB research community as a strong partner in data sharing through the expansion and updating of the Platform for Aggregation of Clinical TB Studies (TB-PACTS). TB-PACTS contains curated and standardized clinical trial datasets and enables access to data that helps researchers to address key questions in TB. This includes supporting high-impact analyses such as TB-ReFLECT and enabling the development of quantitative, translational drug development tool.

Recent updates to TB-PACTS includes the expansion of the depth and breadth of available clinical trial datasets. As of December 2018, CPTR has evaluated, standardized, and integrated 17 clinical data sets, which have been made available in TB-PACTS. This includes aggregated data from 12,234 subjects, from Phase 2 and Phase 3 clinical trials. CPTR continues to work on expanding the number of standardized clinical trial datasets, and where possible will make these analyses available to the broader community.

CPTR has also initiated activities to develop a graphical web-based interface which will give researchers an intuitive and user-friendly method of exploring the datasets within TB-PACTS. This will allow high-level exploration of database offerings to allow researchers to determine if the available data can support specific research questions before applying for access to the database. The interface is being designed to provide insight into the data tables, fields and structure, with features including data filtering, visualizations (e.g., histograms, bar charts, scatter plots) and descriptive statistical summaries. Additionally, C-Path is developing a query terminal to allow deeper, more meaningful interrogation of the database for approved users who have existing knowledge and familiarity with the database.

A tabular listing of the available clinical trial datasets, including references, is available here: TB-PACTS Data Table. Researchers can request access to TB-PACTS via the following link: https://c-path.org/programs/tb-pacts/codr-database/.

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Other Project Highlights

Application of the Hollow Fiber System for TB to Inform Regimen Development Programs

The Hollow Fiber System for Tuberculosis (HFS-TB) is a powerful *in vitro* tool that can be used to determine pharmacokinetic/pharmacodynamic (PK/PD) relationships for anti-TB drugs and regimens. The resulting PK/PD parameters can be used by researchers to inform the potential clinical use of the drugs and combinations (e.g., dose selection based on target PK/PD indices identified in the HFS-TB).

Following qualification by the European Medicines Agency in 2015 as a drug development tool, and compounded by the increasing number of drugs and regimens in development, interest in the application of the HFS-TB to inform regimen development in TB has risen significantly. Given the limited number of labs which have implemented the HFS-TB, CPTR continues to encourage laboratories with suitable infrastructure and experience to implement the HFS-TB. To help increase HFS-TB capacity, a lab manual detailing the design and conduct of HFS-TB experiments has been developed. The manual is a valuable resource for investigators who wish to implement the HFS-TB as a tool within their own laboratories and is available for download at the following link: HFS-TB Lab Manual.

In addition to increasing overall capacity for HFS-TB experiments, CPTR is supporting research conducted at Baylor University that applies the HFS-TB to determine the characteristics of high-interest anti-TB compounds and regimens. The scope of the experiments, which constitute Stage II of the HFS-TB project, includes the evaluation of 11 different anti-TB compounds and combinations under log-phase, intracellular, and semi-dormant (acidic) growth conditions. Stage II efforts are ongoing, with multiple experiments completed for several compounds and regimens of interest; for example, a set of experiments comparing the performance of oxazolidinones was recently completed. CPTR and Baylor University plan to publish the results of these experiments as the project progresses, with Stage II work expected to be ongoing through May 2019.

ReSeqTB Program Updates

Collaboration to Expand ReSeqTB Clinical Data Sets

C-Path partnered with the Translational Genomics Institute (TGen) to identify, acquire, and sequence additional TB isolates with clinical data to enhance the ReSeqTB knowledgebase. To date, more than 5,000 isolates have been sequenced, and the team is on track to exceed the target of sequencing 8,420 isolates by the end of April 2019. Work is proceeding to curate the corresponding phenotypic data, which includes data from several past clinical trials.

ReSeqTB Platform – Current Statistics	
Total Data Points	9,215 individual isolates • 7,608 with matching phenotypic data
Data Sources	17 data contributors
Geographic representation	33 countries

Supporting Global Surveillance of TB Resistance

The Bill & Melinda Gates Foundation funded C-Path to provide the first-ever data platform for global surveillance of tuberculosis resistance based upon genomic sequencing data. This effort, led in partnership with the World Health Organization (WHO) and Foundation for Innovative New Diagnostics (FIND), will leverage the technology behind the Relational Sequencing TB Data Platform (ReSeqTB) to support the Global TB Surveillance group at the WHO. C-Path has automated the bioinformatics pipeline and optimized the database infrastructure and will build an instance of the infrastructure and technology in early 2019. This instance will be located near and managed by the WHO. Additionally, C-Path has begun to process the historical laboratory data from WHO to consolidate their surveillance data management tools. This work is expected to lead to better policies for managing drug-resistant TB on a global scale.

Sequencing Collaboration Progress	
Total Data Sequenced	5,316 isolates • 1,204 uploaded to platform, remainder being mapped
Data Sources	32 data contributors
Geographic representation	24 countries

For more information on ReSeqTB, or to apply for access to the platform, visit: https://platform.reseqtb.org/.

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Progress with Regulatory Authorities

LAM Biomarker

CPTR met with EMA's Scientific Advice Working Party (SAWP) on Oct. 29, 2018, to receive qualification advice from the Agency for lipoarabinomannan (LAM) as a pharmacodynamic (PD) biomarker for measurement of bacterial load in sputum for assessing treatment response in early TB drug development. Sputum LAM, as a PD biomarker, is proposed as a novel methodology that will provide a closer to "real-time" measure of changes in response to treatment in mycobacterial burden within the lung during clinical trials of TB drugs/regimens. This would enable more efficient clinical trial designs (e.g., adaptive designs) to compare potential anti-TB regimens containing novel agents.

The CPTR team received valuable feedback from the Agency that will be incorporated into the statistical analysis plan. Once these analyses are completed, CPTR will present the results to SAWP in a follow-up Scientific Advice procedure (3-4Q 2019) to help guide subsequent submission for a Qualification Opinion on LAM as a pharmacodynamic or response biomarker.

CPTR continues to advance regulatory efforts with the U.S. FDA in parallel. The LAM biomarker was accepted into FDA's DDT Biomarker Qualification Program on Oct. 31, 2017 (DDTBMQ 000070). CPTR will submit a Qualification Plan to FDA in mid-2019, which will address questions and comments previously received from FDA in their response to the Letter of Intent.

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Notes from Recent Meetings

Grand Challenges

Berlin, Germany, 15-18 October: Representatives from the CPTR Initiative were invited to participate in the 2018 Grand Challenges Annual Meeting. This meeting, which was held in conjunction with the World Health Summit, featured scientific track sessions representing a range of global challenges, including "Optimizing Drug Discovery and Translation." A session titled "PBPK/PD models as an integrated translational approach in early drug development," chaired by Dr. Jeff Barrett from the Gates Medical Research Institute, focused on how challenges in the application of mechanistic *in silico* drug development tools may be addressed. This session included panelists representing industry, academia and regulatory authorities, and included a presentation from CPTR which highlighted the application of the TB physiologically-based pharmacokinetics (PBPK) platform in the development of novel drugs and regimens for TB.

International Consortium for Trials of Chemotherapeutic Agents in TB (InterTB)

London, England, 22 October: The 2018 International Consortium for Trials of Chemotherapeutic Agents in TB (InterTB) meeting was held at St. George's, University of London. The CPTR initiative partners and contributors were represented among the speakers and included presentations on novel clinical trial designs and biomarkers, with CPTR Initiative partners and contributors well represented amongst the speakers. Of note, this year's meeting was held in honor of the late Professor Denis Mitchison, whose scientific contributions in TB research were instrumental in defining the current standard of care regimens used worldwide.

Advancing TB research through data science and informatics for public heath impact satellite meeting

The Hague, Netherlands, 25 October: In collaboration with the Office of Cyber Infrastructure and Computational Biology (OCICB) at the National Institutes of Health, CPTR led a satellite meeting at the Union World Conference on Lung Health to capture stakeholder challenges and opportunities for bringing in big data informatics to address public health issues in TB. A number of speakers were invited to provide their

perspectives on the ethics of big data, model-informed drug development, informatics in clinical trials, and the challenges of incorporating next-generation sequencing (NGS) for use in global surveillance. As an outcome of this meeting, a whitepaper is being developed that will highlight the challenges, opportunities, and lessons learned from the workshop as a call to action for increased funding to incorporate big data to facilitate the translation to an effective public health response.

ReSeqTB contributor satellite meeting

The Hague, Netherlands, 25 October: A small, focused satellite meeting at the Union World Conference on Lung Health provided ReSeqTB contributors the opportunity to discuss challenges in analyzing WGS data for TB, as well as programmatic and policy updates. Attendees shared perspectives on necessary steps to standardize bioinformatic pipelines for valid comparisons of results between laboratories. Establishing sequencing standards was a key point of discussion, and there was consensus that a standard validation protocol will be needed to adequately compare pipeline outputs for the purpose of clinical decision-making.

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Next issue preview

- Progress on Adaptive Trial Design project evaluating traditional and adaptive Phase 2 clinical development strategies via clinical trial simulation
- Performance of the TB-specific PBPK platform in predicting drug concentrations in lung tissue, epithelial lining fluid and granuloma tissue

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