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Advancing tuberculosis drug regimen development through innovative quantitative translational pharmacology methods and approaches

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SUMMARY

The development of novel tuberculosis (TB) multi-drug regimens that are more efficacious and of shorter duration requires a robust drug development pipeline. Advances in quantitative modeling and simulation can be used to maximize the utility of patient-level data from prior and contemporary clinical trials, thus optimizing study design for anti-TB regimens. This perspective article highlights the work of seven project teams developing first-in-class translational and quantitative methodologies that aim to inform drug development decision-making, dose selection, trial design, and safety assessments, in order to achieve shorter and safer therapies for patients in need. These tools offer the opportunity to evaluate multiple hypotheses and provide a means to identify, quantify, and understand relevant sources of variability, to optimize translation and clinical trial design. When incorporated into the broader regulatory sciences framework, these efforts have the potential to transform the development paradigm for TB combination development, as well as other areas of global health.

1. Introduction

In 2016, tuberculosis (TB) remains the leading worldwide cause of death due to an infectious disease. It is a condition that impacts one-third of the world's population and there are approximately 1.5 million TB-related deaths worldwide each year.[1] There is no question that a more efficacious and shorter duration therapeutic treatment for TB is needed, and that its development should be a global priority. However, the development of such a therapy is a tall order, given that the treatment of this disease requires a multi-drug regimen and that there are issues related to tolerability and the emergence of resistance for all TB drugs. Therefore, an entirely novel multi-drug regimen is required to overcome these barriers and improve the lives of patients suffering from this disease.

The development of this novel regimen will require a robust drug development pipeline, as well as an improved drug development process to advance the new therapeutic candidates. Such a process needs tools to inform critical decisions in the complex regimen development pathway. Two exciting new therapeutic advancements emerged in 2012 and 2014 with the accelerated conditional approvals of both bedaquiline[2] and delamanid. These novel drugs hold the promise of optimized therapies and outcomes for patients with the most challenging drug-resistant forms of the disease, but their utility could be jeopardized by combining them with older, less effective drugs. The TB community also has an opportunity to learn from and improve the design of complex multi-drug studies by leveraging the data from three phase III quinolone containing trials that failed to meet their expected endpoints.[3–5]

Since its inception in 2010, the Critical Path to TB Drug Regimens (CPTR) Initiative, a global public–private partnership, has keenly focused on accelerating the development of an entirely novel, shorter duration therapy for TB.[6] A core element of the CPTR strategy is the development, validation, and refinement of a suite of pre-clinical, translational methodologies and quantitative drug development platforms. These efforts are focused on optimizing the translation of novel TB drugs in development and informing the study design and enrichment of complex combination clinical trials (Figure 1). This holistic approach is designed to integrate learnings from experiment-level and patient-level contemporary data, including pre-clinical and clinical studies. These data are integrated using the Clinical Trial Data Interchange Standards Consortium (CDISC) Therapeutic Area Data Standard for TB, as described in Figure 2.[7] This figure also describes other components

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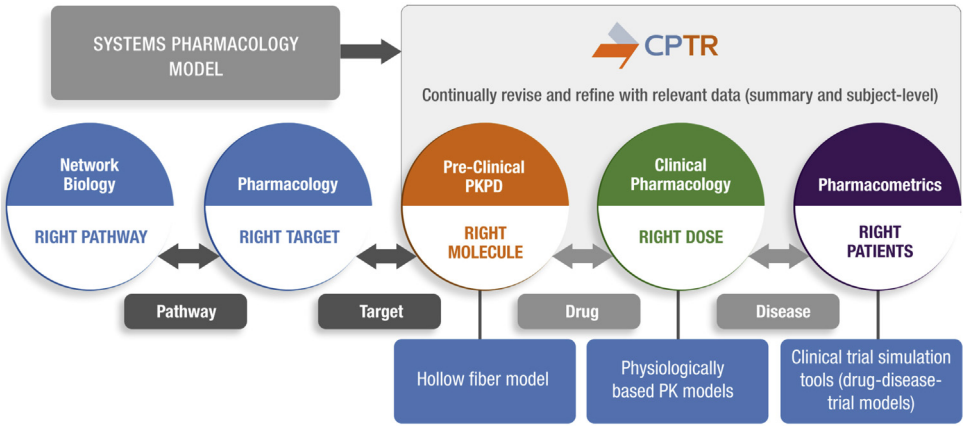

Figure 1. CPTR comprehensive approach to optimizing translational understanding of new TB drugs and regimens.

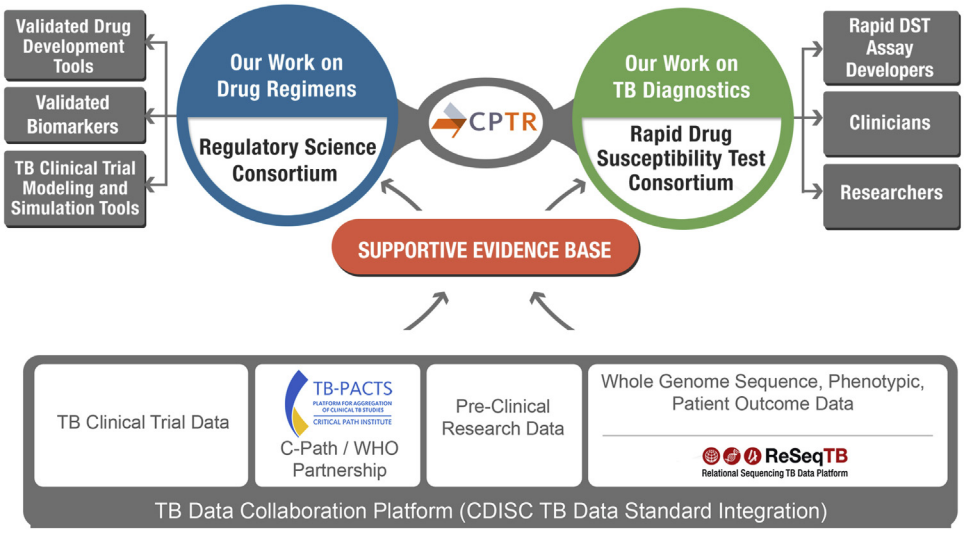

Figure 2. CPTR data collaboration platform.

of the CPTR data collaboration programs, including the Platform for the Aggregation of Clinical Trials (TB-PACTS) and TB Relational Sequencing Data Platform (ReSeqTB).[8,9] These integrated data are being used to develop first-in-class translational methodologies, represented by the seven project teams described below.

2. Learning from the collective TB drug development experience through the model-based meta-analysis of phase III quinolone clinical trials: informing the path forward

CPTR and the World Health Organization (WHO) Global TB Programme have convened leaders of recent major TB clinical trials and key subject matter experts. This team has reviewed key findings from the phase III trials of fluoroquinolone-containing shortened regimens for drug-susceptible TB (OFLOTUB, REMox, Rifaquin) that were conducted over the last decade, and integrated these findings into TB-PACTS. The intent is to extract key lessons from the TB-PACTS platform for future TB trial design, including the analysis of endpoints of treatment outcome for the selection of new regimens to be tested in phase III clinical trials, the statistical methods for assessment of non-inferiority, the incorporation of pharmacokinetic/pharmacodynamic (PK/PD) parameters into primary analyses, and the need for improved knowledge of the variability in patient response to treatment. The TB-PACTS database will also be used to determine whether there is a predictable linkage between pathogen load dynamics and clinically relevant endpoints in TB clinical trials. A framework for a regulatory-oriented disease progression modeling analysis that links pathogen dynamics over time (i.e., biomarker of drug response) with clinically relevant endpoints will be developed. The pathogen load dynamics model is being advanced to enable the addition of a drug biomarker model and its application for the development of new therapies against TB. The link to clinically relevant endpoints is aimed at optimizing drug development decisions.

3. Mechanistic systems pharmacology model to link target selection with mechanisms of action and immune response: improving discovery-to-development translation

Given the complexity of TB disease and drug treatment and the lack of optimal clinical endpoints, a translational systems pharmacology framework is being developed that integrates in silico models of TB disease progression with immune and drug response. This mechanistic model is based on non-clinical and clinical data, which are ultimately needed to inform TB treatment optimization and drug development. The objective of this work is to combine interdisciplinary systems biology and systems pharmacology models to formally characterize drug-host-bacteria-infected cell (four) interactions during TB infection–an essential step towards maximizing the efficacy and shortening the

treatment duration of novel TB regimens (Figure 2). The direct outcome of this project is the development of a translational TB drug development platform that will serve as a tool to optimize the study design of key pre-clinical and clinical trials, leading to a significantly shorter drug development time for new TB regimens.

4. Pre-clinical quantitative exposure–response modeling using the in vitro hollow fiber system for TB (HFS-TB) to improve translation

Selecting the drug and dose to advance from the pre-clinical study into early clinical studies is made more complex when including multiple new agents. The CPTR partnership successfully quantified the predictive accuracy of the HFS-TB for supporting early drug development and dosing, and qualified this tool with the European Medicines Agency (EMA) through a robust evidence-based methodology.[10–14] The partnership between the CPTR expert team and Baylor University is progressing work with the HFS-TB system to proactively assess the performance of novel TB drugs and drug regimens.

5. Physiologically based pharmacokinetic model for TB to understand the distribution of drug in the TB-infected lung

The Simcyp physiologically based pharmacokinetic (PBPK) platform,[15] a leading tool used widely by industry and regulators, is intended to optimize the design of clinical studies for multiple indications. CPTR, in partnership with Simcyp, developed a TB-specific set of models and compound files intended to inform the design of first-in-human studies that will simultaneously evaluate the exposure and efficacy of novel anti-TB combination regimens of up to four drugs, including their metabolites. This collection of models comprises a comprehensive PBPK model of the TB-infected lung (which includes relevant aspects of drug distribution into granulomatous lesions), a compound library for standard-of-care drugs (with metabolites) as well as recently approved drugs, and a virtual South African population, which captures relevant genetic variants and TB-related physiological changes that affect drug distribution in this population.[14] With the integration of these components into Simcyp version 16 (a recognized and best-in-class modeling and simulation platform), development teams and regulators evaluating novel TB regimens will have a robust tool to optimize clinical trial design for first-in-human as well as drug–drug interaction studies.

6. Cardiac risk assessment program to assess increased risk with TB drug regimen development

Drug-induced torsades de pointes (TdP) has been a major cause for the withdrawal of drugs approved for marketing.[16] The potential for cardiovascular risk is increased when multiple drugs must be combined in a complex TB drug regimen.[17] In order to optimize predictions of clinically observed electrophysiological effects of existing and novel TB drugs based on pre-clinical data on ion channel activity, CPTR has partnered with Simcyp scientists to develop a model-based risk-stratification algorithm with a user-friendly interface. This platform integrates ion channel activity data with drug exposure information, to predict the potential risk of drug-induced TdP that existing and novel TB drugs may pose. This tool is intended to optimize the safety decision-making process for TB drug development. An in silico modeling and simulation approach that integrates electrocardiogram changes beyond QT prolongation is now available as an actionable tool for optimizing the cardiac safety assessment of TB drugs and drugs for other indications.[18] This approach allows for the optimization of early screening as well as testing of clinical scenarios. Pre-clinical and clinical development teams can use this quantitative-based set of estimates to inform the safety of single drug and drug regimen development.

7. Liquid culture and quantitative assessment of time-to-positivity to support the development of a disease progression model and clinical trial simulation tool for TB

With the development of liquid media-based culture measures of pathogen load, the time-to-detection (TTD), also known as time-to-positivity (TTP), has emerged as an important assessment of patient progress during therapy. TTP represents the time to detectable growth of *Mycobacterium tuberculosis* in liquid media culture. TTP has several technical advantages over other methods, such as colony-forming unit (CFU) quantification from cultures in solid medium, including reduced variability and easier technical requirements. In a first stage, this project has developed a structural model that identifies and quantifies the most relevant sources of variability and interpretable parameters for the longitudinal trajectory of TTP. In a second stage, a model that links the interpretable parameters of TTP progression with clinically relevant endpoints in the REMox study is being developed. These models will provide a quantitative platform to inform decision-making when development teams are faced with choosing to advance novel regimens from phase II testing into phase III testing.

8. Population pharmacokinetic/pharmacodynamic (PK/PD) models for standard-of-care TB regimens

This project has explored PK/PD data, with therapeutic drug monitoring practiced in a 'real-world' clinical setting, in order to optimize dosing for first-line drugs in patients with active disease. An equivalent population PK/PD understanding for second-line drugs for patients with active disease will also be developed. These models will provide quantitative dosing recommendations for first- and second-line TB regimens.

9. Conclusions

Improving the translational performance of new TB drugs will be a foundational element to accelerate the development of an entirely novel, shorter-duration regimen for TB. The CPTR Initiative and its partners are committed to optimizing the design and execution of studies to evaluate novel TB regimens, by creating robust quantitative drug development platforms that are fully validated (Figure 3). These platforms are based on the integration of legacy and contemporary pre-clinical and clinical trial data. Each of the quantitative drug development platforms described, including a laboratory manual to support in vitro HFS-TB experimental design and execution, will be made publically and freely available to drug developers and to the TB research community.

The development of these quantitative drug development platforms, together with user-friendly interfaces, is envisioned to optimize individualized dosing, the design of studies, and mechanistic models of pathophysiological processes. With these tools, the TB drug development field can enter the twenty-first century and apply sophisticated technology and resources.

Modern drug development and medical practice, especially when it relates to global health issues, demands the optimal evidence for treatments, beyond limited empirical evidence provided by individual controlled trials. Evidence-based analysis must go further than the simplistic statistical inference for primary endpoints of individual trials and requires data aggregation and

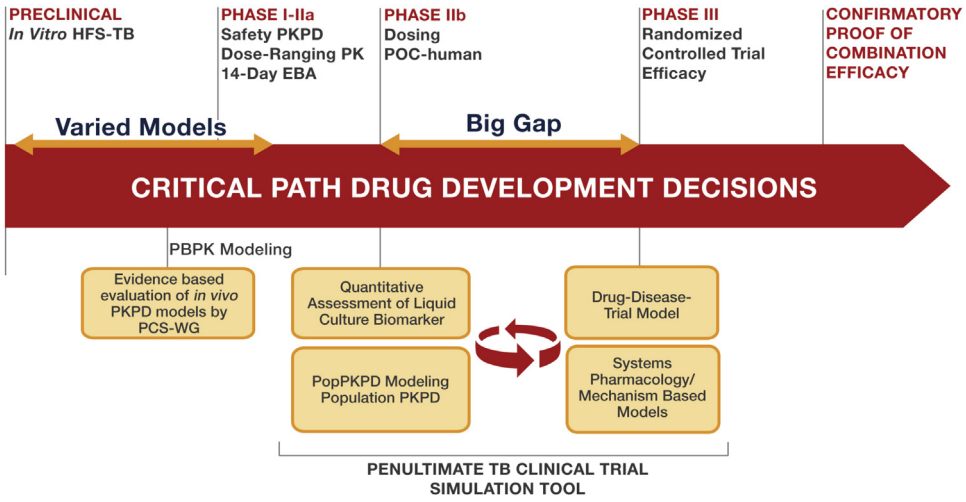

Figure 3. CPTR quantitative medicine approach to address key gaps in the TB drug development process.

corresponding analysis of multiple trials without the limitations imposed by systematic reviews. The tools described here offer the opportunity to evaluate multiple hypotheses and include a myriad of designs to evaluate such hypotheses. These platforms provide a means to identify, quantify, and understand relevant sources of variability, and to optimize translation and clinical trial design.

This effort, incorporated into a regulatory sciences framework that allows a rigorous and transparent regulatory review process, has the potential to transform the paradigm not just for TB combination drug development, but also for other areas of global health.

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