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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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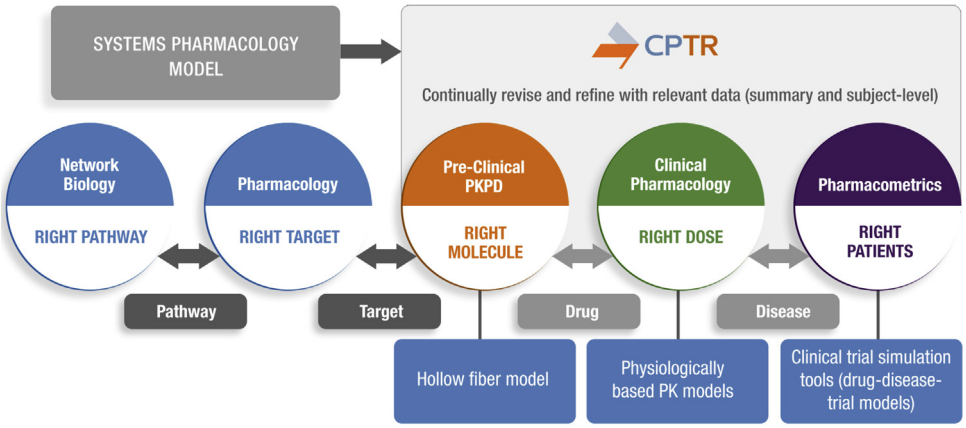

Figure 1. CPTR comprehensive approach to optimizing translational understanding of new TB drugs and regimens.

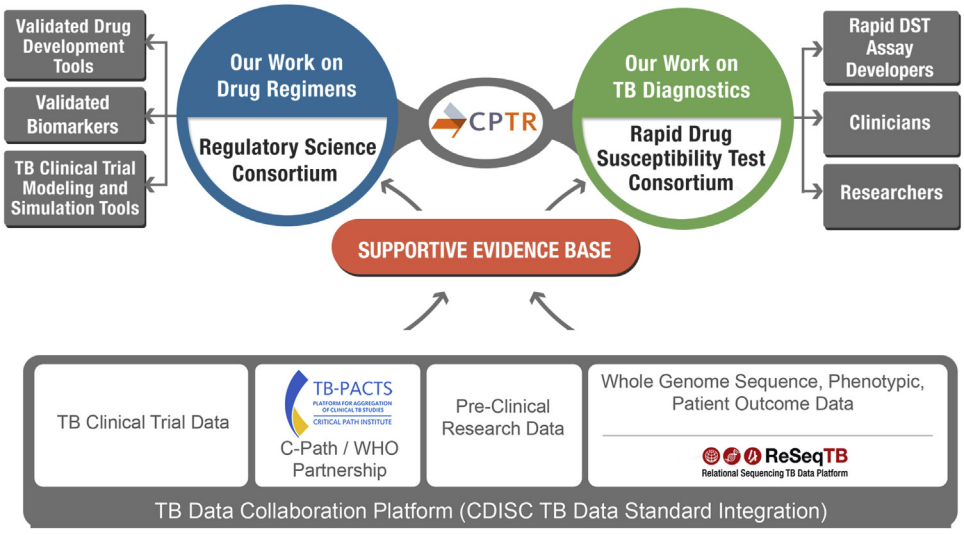

Figure 2. CPTR data collaboration platform.

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