Accelerating Innovation in Tuberculosis Drug & Diagnostic Development: The Continued Case for Collaboration Enabled by CPTR

The Critical Path to TB Drug Regimens (CPTR) is a cross-sector initiative that aims to speed the development of safer and shorter duration anti-tuberculosis (TB) drug regimens and rapid drug susceptibility tests. This collaboration of leading international pharmaceutical and diagnostic companies, public health experts, civil society organizations, and regulatory authorities from around the world has continued to prove more necessary and productive since its launch in 2010. Given the complexity of combination drug testing, clinical trial design, and the need for multiple, global regulatory approvals and processes, CPTR provides a collaborative platform to facilitate partnership and to identify and advance the most promising combinations of new TB drugs and diagnostics, regardless of the sponsor. CPTR also drives solutions-oriented, data-driven dialogue to bridge critical knowledge gaps that impede the acceleration of drug development strategies and the establishment of regulatory pathways to overcome obstacles.

**TOOLS TO BENEFIT TB RESEARCH AND TREATMENT**

Although CPTR tackles a broad array of issues relevant to TB drug regimen development and deployment, our teams have a strong focus on improved collaborative testing methodologies, which require shared data platforms. The data platforms enable the development of these methodologies and drug development tools to support effective decision making in the TB regimen development process, as well as help to ensure the effective and sustainable implementation of newly-developed anti-TB treatments.
NEW TB DRUG REGIMENS AND DIAGNOSTICS ARE URGENTLY NEEDED

TB and drug-resistant TB are major threats to global health. TB is the world’s deadliest infectious disease, and harder-to-treat forms of drug-resistant TB are also on the rise. Despite this crisis, the tools to diagnose and treat TB today are antiquated and inadequate.

Today’s TB therapies are more than 40 years old and take an unacceptably long time to cure. The current treatment regimen for drug-sensitive TB takes six months or longer, and many patients experience harsh side effects. These shortcomings may cause patients to default on their treatment, which can lead to further illness, drug resistance, or even death.

Treatment for MDR-TB and XDR-TB is extremely complex and expensive. Therapy can last two years or longer, with daily injections for the first six months. The drugs used are more toxic, and can be up to 475 times more expensive than first-line therapies. The cost and resources required to treat MDR-TB and XDR-TB are prohibitive in many regions, and therefore most who suffer from these forms of TB are unable to access treatment. Only about 50% of MDR-TB patients and 30% of XDR-TB patients have favorable outcomes. Identifying those most in need of new TB drugs and drug regimens is critical to increase their chance of survival.

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CRITICAL PATH TO TB DRUG REGIMENS

<table>
<thead>
<tr>
<th>RESEARCH RESOURCES</th>
<th>REGULATORY SCIENCE</th>
<th>RAPID DRUG SUSCEPTIBILITY TESTING</th>
<th>DRUG DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Led by the Critical Path Institute</td>
<td>Led by the Critical Path Institute</td>
<td>Led by the Critical Path Institute</td>
<td>Led by the TB Alliance</td>
</tr>
<tr>
<td>• Stakeholder &amp; Community Engagement • Global Regulatory Pathways</td>
<td>• Modeling &amp; Simulation • Preclinical &amp; Clinical Science • Biomarkers &amp; Clinical Endpoints • Data Standards &amp; Integration • Health Authorities Submissions</td>
<td>• Enabling Science • Next Generation Sequencing • Surveillance • ReSeqTB Data Sharing Platform</td>
<td>• Drug and Combination Testing &amp; Development</td>
</tr>
</tbody>
</table>

FOCUS

HOW CPTR WORKS: OUR STRUCTURE AND AREAS OF FOCUS

CPTR is organized as four operational components, which are adaptive in structure to quickly react to evolving challenges in the field. Each component is comprised of workgroup teams, each with a targeted mission and project management plan to implement CPTR’s broader goals. These efforts are supplemented and enhanced by input from collaborative partners and an expert Advisory Panel, which provides guidance across the comprehensive initiative.

DRUG DEVELOPMENT COALITION

Led by the TB Alliance, the Drug Development Coalition consists of drug developers who contribute their TB drug candidates to be tested in combination, with the goal of assembling the most effective TB drug regimens – regardless of sponsor. The Drug Development Coalition is responsible for selecting promising combinations, conducting the appropriate clinical trials to evaluate them, and bringing such regimens forth for registration. CPTR is enhancing its partnership with the TB Drug Accelerator effort as well as informing the translation of new potential drugs from the early discovery into early combination testing phases.

REGULATORY SCIENCE CONSORTIUM

Led by the Critical Path Institute, the Regulatory Science Consortium participants are leading scientists from industry, regulatory authorities, and academia. This arm focuses on establishing and improving the framework for combination drug development, which includes advancing innovative drug development tools such as data standards, data platforms, biomarkers, clinical endpoints, and disease progression models. These teams establish scientific consensus on and seek regulatory endorsement – such as qualification – of preferred tools for developing TB drug regimens.

RAPID DRUG SUSCEPTIBILITY TESTING (RDST) CONSORTIUM

Led by the Critical Path Institute, the RDST Consortium’s partners collaborate to facilitate development of new diagnostic tools to complement novel drug regimens. Treating TB patients with appropriate drugs (to which their bacteria are susceptible) is integral to improving patient outcomes, slowing the development of drug resistance, and maximizing the impact and life of new TB regimens. For these reasons, the development of new TB cures and corresponding diagnostics must be synergized. The RDST advances the diagnostic field through the development of innovative tools, like the Relational Sequencing TB Data Platform (ReSeqTB), which standardizes and curates drug-resistance and other meta-data to advance diagnostic assays and assist in the clinical interpretation of genetic polymorphisms. The RDST also partners in the development and optimization of novel culture-based testing, such as the microtiter plate format, which is standardized, faster, more informative, and more affordable than existing standard drug susceptibility testing.

RESEARCH RESOURCES GROUP

Led by the Critical Path Institute, the Research Resources Group works to create the framework and infrastructure that will support the development of novel TB regimens. This arm is responsible for increasing clinical trial capacity, promoting understanding of the potential ethical challenges along the path to TB drug development, expanding regulatory guidance globally, providing relevant information on TB drug markets, and ensuring effective and appropriate stakeholder and community engagement.
CPTR’S IMPACT: KEY INNOVATIONS

CPTR has spearheaded several important advances to innovate TB regimen and rapid DST development.

- CPTR’s combination development model is the established gold standard for TB drug development programs and clinical trials. Traditional drug development models substituted or added one drug at a time to an existing regimen, meaning the path to a completely novel regimen would take decades. Since the launch of CPTR, several trials testing multiple novel drugs together have been conducted, unlocking the potential to introduce more broadly effective TB cures much more quickly. These advances have been made possible in part by the development of clinical pharmacology models to support such innovative research.

- CPTR has created the Relational Sequencing TB Data Platform (ReSeqTB) to integrate and standardize global TB patient data dispersed among multiple private and public databases, providing a tool to help identify correlations between Mycobacterium tuberculosis (M.tb) mutations and clinically relevant resistance. This will aid the development of new rapid drug susceptibility tests, facilitate international research and collaboration, and, ultimately, directly enable interpretation of sequencing data for personalized patient care. CPTR has partnered with the Translational Genomics Research Institute’s (TGen’s) Pathogen Genomics Division to sequence isolates with critical patient-outcome data to help bridge knowledge gaps in identifying TB drug-resistance patterns across the globe.

- Collaborations between the Critical Path Institute and the Special Programme for Research and Training in Tropical Diseases (hosted at the World Health Organization), enabled by CPTR, have developed the TB Platform for Clinical Trials (TB-PACTS) to integrate and synthesize data from completed Phase III TB drug trials. This tool provides a robust and complete set of data from which drug developers can study and evolve concepts such as biomarkers, predictability of earlier stage clinical data, and clinical trial design.

- In partnership with Critical Path Institute and CDISC, CPTR finalized version 2.0 of the CDISC TB Therapeutic Area User guide, which includes all necessary terminology required to support Rapid Drug Susceptibility testing and pediatric information.

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**SPOTLIGHT ON RESEQTB**

C-Path has 10 years of experience with the design and implementation of global data platforms in nine major disease areas, representing data from more than 30,000 patients and growing.

Over the past 12 years, FIND collaborations have led to the delivery of 11 new diagnostic tools, created an enabling environment for countless more through specimen banks, reagent development and increased market visibility, and supported scale-up of diagnostics through quality assurance and lab strengthening.

The WHO Global TB Programme aims to advance universal access to TB prevention, care and control, guide the global response to threats, and promote innovation.

The mission of the CDC Division of Tuberculosis Elimination (DTBE) is to promote health and quality of life by preventing, controlling, and eventually eliminating tuberculosis from the United States by collaborating with other countries and international partners in controlling global tuberculosis.

As a Stop TB Partnership working group, the New Diagnostics Working Group (NDWG) is a network of global experts representing academia, governmental and technical agencies, NGOs, diagnostic manufacturers, national TB programmes and the patient community. The mission of the NDWG is to foster development and evaluation of new TB diagnostics by serving as a coordination, communication, and advocacy platform for effective collaboration of all stakeholders in TB diagnostic research and development.

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases.
CPTR’s work led to the regulatory endorsement of the in vitro hollow fiber system of tuberculosis (HFS-TB) – a preclinical model to evaluate TB drugs individually or in combination – by leading regulatory authorities, including the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA).

CPTR, in partnership with Simcyp, has developed a Physiologically-Based Pharmacokinetic (PBPK) TB-specific set of models and compound files 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 4 drugs. This collection of models is comprised of 1) a comprehensive PBPK model of the TB-infected lung, which includes relevant aspects of drug distribution into granulomatous lesions; 2) a compound library for standard-of-care and recently approved drugs (with metabolites); and 3) a virtual South-African population, which captures relevant genetic variants and TB-related physiologic changes that affect drug distribution in this population. With these components integrated into Simcyp version 16 (an already recognized 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 studies. CPTR has engaged in dialogue with EMA on the potential for the qualification of this novel PBPK methodology.

CPTR, in partnership with Simcyp scientists, developed a model-based cardiovascular risk-stratification algorithm to optimize predictions of clinically-observed electrophysiological effects of existing and novel TB drugs. This platform integrates preclinical ion channel activity data with drug exposure information to predict the potential risk of drug-induced Torsade de pointes (TdP). With a user-friendly interface, all members of preclinical and clinical development teams can use this tool to create a common, quantitative-based set of estimates to inform the drug and regimen development process for TB.

CPTR and the WHO have partnered to sponsor a model-based meta-analysis of the Phase III quinolone-containing trials in order to further critical learnings from the REMoxTB, RIFAQUIN, and OFLOTUB trials through the aggregated data set provided by TB-PACTS. This analysis, termed as TB Reanalysis of Fluoroquinolone Executed Clinical Trials (TB-ReFLECT), is led by University of California San Francisco, and will help the community understand the drivers for study outcomes as well as influence future TB trial design.

In partnership with Otsuka, CPTR is advancing dialogue with regulators on a potential new pharmacodynamic biomarker for TB clinical trials. The lipoarabinomannan project seeks to improve the speed and agility of decision making within the course of complex TB combination studies.

“The degree to which we can bring together parties who might otherwise never come together is the degree to which we will produce truly transformative interventions.”

– Jim Gallarda, Bill & Melinda Gates Foundation
ACHIEVING INNOVATION THROUGH PARTNERSHIP

Co-founded by Bill & Melinda Gates Foundation, Critical Path Institute, and TB Alliance, the spirit of partnership and collaboration fuels the success of CPTTR. Initiative members come together to contribute their expertise, resources, and commitment to innovation. The CPTTR framework enables the brokering of partnerships that can be otherwise difficult to achieve – the formation of a drug regimen, which includes drugs from multiple sponsors, for example.

HOW TO GET INVOLVED

CPTTR initiative welcomes participation from any company or research organization with a promising TB drug candidate or diagnostic in development, as well as other groups providing the technical expertise or resources to help develop new TB drug regimens and diagnostics. Contact information is available at www.cptrinitiative.org.

MEMBERS AND PARTNERS

The CPTTR Initiative is made possible by the in-kind contributions of partners representing eight pharmaceutical developers, 18 diagnostic industry partners, 26 academic institutions, 20 non-governmental organizations, and five government bodies from around the world. A current and comprehensive list of members and partners can be found here: www.cptrinitiative.org/partners.