The collaborative work of the CPTR Initiative has contributed to the development of the first new drugs for TB in over 40 years, and has solidified a drug regimen development pipeline in TB.

**CPTR: Revitalizing the Pipeline**

In the United States, tuberculosis (TB) is easily thought of as a disease of the past. In 2018, the U.S. saw only 9,029 total cases of TB and 542 deaths. Globally, however, an estimated 10 million people fell ill and 1.4 million died from TB. TB is the world’s leading cause of death from a single infectious agent. While there are encouraging trends in the global incidence and death rates (a reduction of 9% and 14%, respectively, over the last five years), TB remains a significant global health problem.

In 2010, first-line treatment of TB generally included a multidrug regimen of isoniazid, pyrazinamide, ethambutol and rifampin. Several alternative second line drugs were also in use; however, most were associated with significant adverse events, including permanent loss of hearing. Of the drugs available to treat TB, most were older and had been in use for many decades. For example, rifampin, the most recently approved at that time by the U.S. Food and Drug Administration (FDA) for use in TB, was approved in 1971. Despite the World Health Organization declaring TB a global public health emergency in 1993, it had been more than 40 years since any new drugs were available to treat TB.

At the same time, drug resistant, multidrug resistant (MDR), and extensive drug resistant (XDR) strains of TB were becoming increasingly problematic. Factors leading to drug resistance are complex and multifactorial. Treatment of TB is lengthy, often required to be at least six months in duration. The treatment course can be complicated in nature, generally consisting of a four-drug regimen for two months, followed by a longer phase of two drugs. The TB mycobacteria itself can lay dormant in the lungs, regrowing and causing reinfection despite lengthy treatment. Populations likely to be infected are from poor and rural countries with limited access to healthcare. These factors, and others, all contribute to the emergence of drug-resistant strains of TB that make treating infections even harder.

An urgent need existed for novel drug regimens with improved efficacy and safety profiles, as well as shorter treatment duration, to address the global health crisis in tuberculosis.
To help meet this need, the Critical Path to Tuberculosis Drug Regimens (CPTTR) Initiative was launched in March 2010 by Critical Path Institute (C-Path), Bill & Melinda Gates Foundation and Global Alliance for TB Drug Development. CPTTR is a public-private partnership that includes the pharmaceutical industry, academic researchers, patient advocates, and national and global regulatory and public health agencies. CPTTR has worked over the last 10 years to reinvigorate the drug regimen development pipeline in TB at a time when many pharmaceutical companies were leaving the anti-infective space.

The results and impact from CPTTR’s work have been broad and far-reaching. In partnership with the Clinical Data Interchange Standards Consortium (CDISC), CPTTR has developed standardized terminology to support TB clinical trials, including pediatric information. CPTTR has also received regulatory endorsement of the hollow fiber system of TB, a preclinical model to evaluate dosing requirements for TB drugs used individually or in combination. CPTTR-ReFLECT, a model-based analyses of several previously completed TB trials, has enabled learnings that will help the community understand study outcomes and improve the design of future clinical trials. In partnership with Simcyp™ scientists, CPTTR has developed a TB-specific set of physiologically-based pharmacokinetic models and compound files that will inform first-in-human clinical studies. CPTTR has also partnered with the Translational Genomics Research Institute’s (T-Gen’s) Pathogen Genomics Division to whole genome sequence TB isolates with clinical and culture-based drug sensitivity data. This data was incorporated with similar data from the global community and able to identify drug resistance patterns across the globe. Incredibly, this is an incomplete list of CPTTR’s successes to date.

In 2012, bedaquiline was approved by FDA for use as part of combination therapy for MDR TB. In 2019, pretomanid received FDA approval for use as part of a combination regimen with bedaquiline and linezolid for the treatment of XDR and MDR TB. After more than 40 years of stagnation, patients around the globe have the first new drug regimens for TB. The years of collaborative work of the CPTTR initiative has contributed to these approvals, and most importantly, helped solidify a drug regimen development pipeline to meet the needs of TB patients everywhere.

Access Citations

https://c-path.org/programs/cptr/