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Bill Denny is Director of the Auckland Cancer Society Research Centre, University of Auckland. Trained as a chemist, he has been closely involved bringing several drugs to clinical trial, including the tuberculosis drug TBA-354, which is being progressed by the Global Alliance for TB. He is a scientific co-founder of Proacta Inc. (hypoxia-activated prodrugs) and Pathway Therapeutics (kinase inhibitors), and a co-author on more than 600 papers and 100 published patents.

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Foreword

Advances in tuberculosis medicinal chemistry

William Denny & Michio Kurosu

Tuberculosis (TB), caused by infection with the bacterium *Mycobacterium tuberculosis* (*Mtb*), has remained one of the major causes of human morbidity and mortality. Several emerging global factors threaten TB control and prevention efforts. Chief among these are: the interaction between the human immunodeficiency virus (HIV) infection and TB pandemics, which poses exceptional challenges of tuberculosis control and emergence of multidrug resistant (MDR-) and extremely drug-resistant (XDR-) *Mtb*. *Mtb* can persist in host tissues for months to decades. The ability of *Mtb* to survive in host macrophages by entering a dormant state is one factor that requires the long duration of TB chemotherapy. These indications underscore the importance of the development of new antituberculosis drugs and efficacious TB chemotherapy regimens. Current TB drug regimens take too long to treat infections with even drug-sensitive strains of *Mtb*. Despite the growing resistance to current treatments for TB, only one new TB drug has been introduced into clinical use in recent years as a monotherapeutic agent. However, due to the resurgent interests of public and private partners in recent years, numerous antituberculosis compounds have been developed in order to improve current TB-chemotherapies. There are a growing number of candidate drugs in the pipeline, but further efforts in discovery are necessary to achieve optimum clinical outcomes. This book, focused on the medicinal chemistry of new drugs for tuberculosis, covers a wide range of topics around the development and deployment of what is hoped will be more effective drugs.

In Chapter 1, Denny discusses the design and properties of three new nitroimidazole-based drugs (PA-824, TBA-354 and delamanid) that are in or beginning clinical trial. A common mechanism of action is their reduction by the *Mtb* enzyme deazaflavin-dependent nitroreductase (Ddn), generating nitric oxide as the active species. All show activity against persistent TB and improved rates of bacterial killing in combination trials with standard agents. Palomino *et al.* (Chapter 2) discuss the growing field of drug repurposing as it applies to TB, reporting on both existing examples and on *in silico* methods of searching. In Chapter 3, Bach *et al.* discuss the secretion by *Mtb* of tyrosine phosphatase virulence factors within host macrophages, which interfere with host signal transduction pathways. These are discussed as potential drug targets, and 3D models of the binding of potential inhibitors to these enzymes are presented. A key to reducing treatment time for TB patients is the development of drugs effective against nonreplicating (dormant or persistent) *Mtb*. Kurosu (Chapter 4) reviews potential targets for these, based on bioinformatics and *in vitro* experimental data. In Chapter 5, Munro & McLean review and discuss the mode of action of the azole class of antifungal agents, which target a sterol demethylase cytochrome P450 enzyme. With the discovery of several P450 enzymes in *Mtb*, the azoles are of interest as potential drugs for TB. One of the reasons for the long time required to introduce new TB drugs into clinical practice is the need to decide their position in multidrug clinical regimens. In Chapter 6 Evangelopoulos & Waddell discuss the use of gene expression profiling to predict superior drug combination regimens and RNA-based assays for monitoring success. In Chapter 7, Protopopova discusses the ethylenediamine-based TB drugs ethambutol (a front-line agent) and the new analogue SQ109, which have different mechanisms of actions and pharmacological profiles despite their common pharmacophore.

The diarylquinoline bedaquiline is the most novel of the new drugs recently approved for clinical use. It specifically inhibits *Mtb* ATP synthase and is highly active against both drug-susceptible and MDR strains. In Chapter 8, Guillemont *et al.* review the development and observed structure–activity relationships which led to bedaquiline. Finally, in Chapter 9, Coffee reminds us that even as new and more effective TB drugs emerge from the laboratories, there are major ongoing obstacles to effective treatment in the developing countries, including sicker patients at presentation, both from advanced TB or co-infections, and difficulty in monitoring compliance to avoid the development of drug-resistant TB.

Overall, the chapters in this book point to a renewed pipeline of exciting new drugs for TB, but remind us of the huge difficulties in effectively combating this disease.

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