Introduction

This special issue of *Tuberculosis* focuses on key aspects of tuberculosis (TB) drug discovery and development. The urgent need for better TB therapies has recently been highlighted by the WHO/Stop TB Partnership's "Global MDR-TB and XDR-TB Response Plan 2007-2008" and "Anti-Tuberculosis Drug Resistance in the World; fourth global report".[1,2] Both documents point to the need for new drugs to help turn the tide of the global TB epidemic and halt the creation of increasing numbers of drug-resistant strains. The challenge for those working in TB drug research and development (R&D), however, goes beyond just the need to develop new drugs, for TB treatment requires combination therapy to prevent development of drug resistance. As a result, the eventual goal of TB drug R&D is to combine several drugs with differing mechanisms of action into safe and effective multidrug regimens that will shorten the duration of TB treatment and facilitate patient adherence to the full course of therapy. Optimally, such new regimens should be equally effective against strains resistant to today's drugs as against drug-sensitive strains of *M. tuberculosis*.

Present first-line TB treatment, as recommended by the WHO,[3] is highly effective when properly administered and fully adhered to. This four-drug regimen (two months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by four months of isoniazid and rifampicin) was arrived at through a series of trials led in large part by the British Medical Research Council beginning in the 1960s.[4] These trials were conducted in an earlier regulatory environment under conditions that in many respects would not be acceptable for drug registration by today's regulatory authorities. Nonetheless, these trials successfully decreased an initial TB treatment time for drug-sensitive disease from 12–24 months (with streptomycin, PAS and isoniazid) to the current six month, "short-course", treatment. Since the discovery of rifampicin in 1963 and the above-mentioned trials, no new classes of TB drugs have been developed and there have been no further advances in TB treatment-shortening.

This untenable public health situation is on the verge of changing. There are presently at least seven compounds in clinical development for TB, representing five different chemical classes (fluoroquinolones, nitro-imidazoles, diarylquinolines, pyrroles and diethylamines), and a significant number of discovery projects are being pursued by academic laboratories, government agencies, private sector companies, and not-for-profit organizations, including the TB Alliance, a public-private partnership focused solely on the discovery and development of improved, affordable treatments for TB. The challenges to TB drug R&D are significant, however.[5–7]

This issue of *Tuberculosis* aims to highlight some of the key facets of and challenges to this field through a series of review articles by leading contributors to this endeavor, with topics ranging from those pertinent to early discovery projects through some of the central issues facing those involved in human testing and drug registration (see Figure 1 for a diagram of the major phases in the drug R&D process).

The issue begins with an overview by Showalter and Denny of the drug development process from target identification through preclinical development, and a summary of several of the chemical classes currently in clinical development for TB. The next two articles deal with a key aspect of the drug discovery process: the identification of promising targets for drug action, and particularly those that may be vital to the "persistent" bacilli that are genetically sensitive, but relatively phenotypically resistant in the face of ultimately effective drug therapy. The review by Wei and Rubin describes molecular genetic approaches to identifying those genes whose products may be essential for *M. tuberculosis* survival, while the article by Nathan and colleagues proposes focusing on cellular processes that are particularly crucial for *M. tuberculosis* survival in the host and therefore may represent especially effective targets for attacking the "persistent" bacilli. The article by Basaraba addresses an area key to both the discovery and preclinical facets of TB drug R&D: animal models of TB, providing a comparison of tuberculous lesion morphologies and discussion of differences in host response seen in experimental TB infections in mouse, guinea pig, rabbit and monkey models. Franzblau and colleagues use development of the macrolide class of compounds to illustrate important issues in the lead optimization phase of TB drug development. In this stage, a promising pharmacophore is optimized relative to a set of desired drug features (often referred to as a "target product profile") through exploration of structure-activity and structure-toxicity relationships, followed by screening for best compounds via a set of relevant preselected assays.

Several crucial issues in TB drug clinical development are addressed in the final set of papers. Davies and
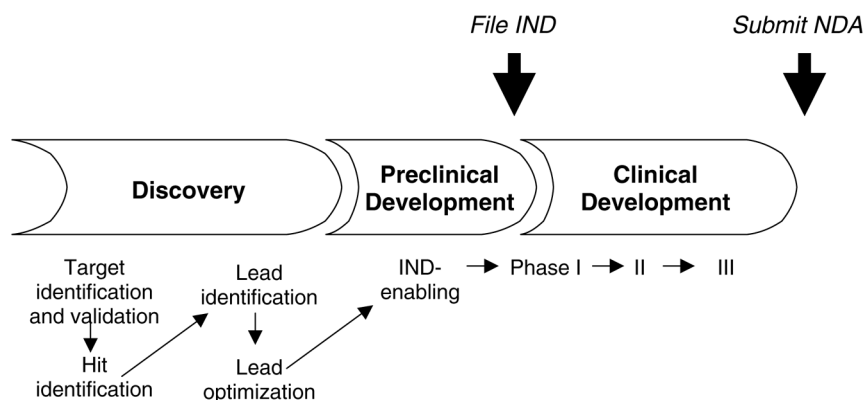
Figure 1 Schematic of typical drug R&D process.

Nuermberger discuss pharmacokinetic ("what the body does to the drug") and pharmacodynamic ("what the drug does to the body") issues relevant to TB drugs; Donald and Diacon provide a review of early bactericidal activity studies and their potential roles in demonstrating human "proof-of-concept" and dose-finding for new TB agents. Nunn, Phillips and Gillespie discuss the many challenges in designing pivotal safety and efficacy (Phase III) trials for new TB drugs, and Sacks and Berman complete this issue with a look from a regulatory perspective at some of the leading questions pertinent to registering new TB drugs, and the relative advantages that may accrue by first evaluating a new drug's safety and efficacy in MDR-TB patients.

The primary purpose of this special issue of *Tuberculosis* is to stimulate discussion, innovative thinking and further progress pertinent to TB drug discovery and development. The TB Alliance wishes to thank first and foremost the authors of these thoughtful and thought-provoking papers for their contributions; also the insightful peer reviewers who lent their expertise, and Doris Rouse and Rose Evans-Storms of RTI International, whose efficient efforts made this issue possible.

References

1. World Health Organization. 2007. The Global MDR-TB & XDR-TB Response Plan. Geneva: World Health Organization. Geneva, Switzerland: WHO (WHO/HTM/TB/2007.387).
2. World Health Organization. 2008. Anti-tuberculosis drug resistance in the world: fourth global report. Geneva, Switzerland: WHO (WHO/HTM/TB/2008.394).
3. World Health Organization. 2003. Treatment of tuberculosis: guidelines for national programmes. Geneva, Switzerland: WHO (WHO/TB/97.220).
4. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999;**3**: S231–S279.
5. Ginsberg AM, Spigelman M. Challenges in tuberculosis drug research and development. *Nature medicine* 2007;**13**: 290–294.
6. Williams KJ, Duncan K. Current strategies for identifying and validating targets for new treatment-shortening drugs for TB. *Current molecular medicine* 2007;**7**:297–307.
7. Laurenzi M, Ginsberg A, Spigelman M. Challenges associated with current and future TB treatment. *Infect Disord Drug Targets* 2007;**7**:105–119.

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