A New Era in Tuberculosis Treatment: What Does the Future Hold?

Ken Duncan

Global Health Discovery, Bill & Melinda Gates Foundation, Seattle, Wash., USA

Abstract

Antituberculosis drug discovery and development have increased dramatically over the last 2 decades following the declaration by the World Health Organization that tuberculosis (TB) was a 'global health emergency'. It is now clear that the current short-course 6-month regimen is not short enough or robust enough to contain the dual threat of HIV-influenced TB and multidrug-resistant TB. In the efforts to develop new drugs and regimens, the interplay between host and pathogen must be recognized and the role of the body's immune system explored in containing TB, but, possibly, at the same time encouraging features of persistence and thus complicating chemotherapy. Despite the potential pitfalls that lie ahead, the publication of the genome sequence of *Mycobacterium tuberculosis* and partnerships between pharmaceutical companies, biotechnology industries and academia are paving the way towards the development of new anti-TB drugs and regimens and give reason for cautious optimism.

The papers in this volume of *Progress in Respiratory Research* provide a comprehensive retrospective analysis of the medicines available today for treating tuberculosis (TB), as well as a glimpse of what the future may hold. The landscape has evolved dramatically since the dark days of the early 1990s when the global TB epidemic was increasing in intensity and the emergence of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* raised the spectre of a world in which TB would once again be an untreatable disease, leading the World Health Organization to declare TB 'a global health emergency' and to start developing programmes for the control of TB [1].

At that time there was very little activity in TB drug discovery and development. The world had been satisfied in the early 1970s when rifampicin was added to the TB drug armamentarium and the 'short-course' regimen we are familiar with today was introduced. It was assumed that the tools that had been created would be sufficient to control TB. This coincided with a period in which it was believed that infectious diseases had been conquered, following on from US Surgeon General William H. Stewart's reported statement in 1967 that we could 'close the book on infectious disease' [2]. It did not help that TB is a disease of poverty and had largely been controlled in countries that constitute the major markets for pharmaceuticals, and the drug industry concentrated its resources on more financially lucrative conditions. A further consequence of these factors was that many young researchers were actively discouraged from following a career in TB research of any kind. The only significant innovations to follow were development and widespread implementation of directly observed therapy, short course, which brought some order to the delivery of medicines and improved compliance and treatment completion rates, and the introduction of fixed-dose combinations, which ensured drug quality and guarded against monotherapy that can lead to drug resistance.

How wrong could we be to suppose that these tools would be sufficient to treat TB in all its forms? Coupled with the lack of an effective vaccine that protects adults from developing active pulmonary disease and the lack of selective and specific point-of-care diagnostic tests, the number of incident TB cases continues to rise, although in recent years mortality has begun to fall [3]. Co-infection with HIV has also had a devastating effect on the epidemic, particularly in sub-Saharan Africa [4]. MDR-TB continues to be a problem in many parts of the world [5], and although it can be treated with second-
line agents, these are not always available, are expensive and cause significant side effects. The existence of even more broadly resistant ('extremely drug-resistant', XDR) TB strains highlights the need for new treatment options [6].

The greatest impediment to improving TB treatment outcome is surely the time it takes to cure a patient with active disease. The current complex multidrug regimen is highly effective with high cure rates, under well-defined conditions such as those encountered in well-managed programmes or under clinical trial conditions. But it takes a minimum of 6 months (the 'short' course) to achieve cure, and in general use, compliance cannot be assured and therefore treatment failure is common. The future of TB therapy must be one in which treatment time is reduced to only a few months or, better still, a few weeks. Why is this so difficult to achieve when we can cure other bacterial infections in a matter of days or weeks? The reasons are numerous and relate to the biology of the organism, the host response to infection and the properties of the available drugs [7].

**Barriers to Treatment Shortening**

*M. tuberculosis* is slow-growing with a doubling time of around 20 h, in contrast to most bacterial pathogens, which divide much more rapidly. It would not be unreasonable to assume that, since antibiotics primarily work on cells that are actively dividing, the overall duration of therapy might somehow correlate with the length of the growth cycle. This raises doubt that a significantly faster cure might ever be achieved. During treatment we observe rapid initial reduction of bacterial numbers in sputum during the first few weeks of chemotherapy until bacteria can no longer be cultured, yet treatment must be continued because of 'persistence', an ill-defined phenomenon that describes the remaining bacilli that cause recurrence of disease.

The interplay between host and pathogen is a critical factor that cannot be ignored. *M. tuberculosis* is adept at escaping host defence mechanisms in macrophages, and the immune response to infection results in the formation of granulomatous lesions that become caseous and hypoxic, conditions in which the drugs are unable to penetrate or be effective. It is unclear whether chemotherapy helps the host clear the infection by killing the few damaged bacteria that remain after drug treatment, or hinders it by forcing the bacterium into a state in which it is not susceptible to drugs.

The 6-month treatment period represents a significant improvement over the 18–24 months it took to cure a patient when TB drugs were first introduced. In some respects it is not surprising that it still takes this long when the regimen comprises 4 'first-generation' agents. Although some efforts were made to improve current agents, no second-generation drugs were ever introduced. Contrast this with HIV therapy: the first agents introduced had poor pharmacokinetics, had to be dosed several times daily and had significant side effects limiting their acceptability. Today, many new medicines derived from those first agents, as well as drugs in new chemical classes, are available targeting multiple mechanisms and in fixed-dose combinations such that once-daily therapy can be tailored taking into account the drug resistance pattern in the infecting viral strain.

**The Present**

Through the efforts of the pharmaceutical and biotechnology industries and academia, and supported by product development partnerships such as the Global Alliance for TB Drug Development (www.tballiance.org), there is a substantial pipeline of new drug candidates [8]. In preclinical studies, the potential to reduce the duration of chemotherapy has been demonstrated, and several drug candidates have been assessed in murine models of infection [9–11]. Recognizing that there needs to be a new regimen and that achieving this goal will take decades if it follows the established path of replacing and testing one drug sequentially in the current regimen, groups have come together to launch a broad effort, the Critical Path to TB Drug Regimens (www.c-path.org/cptr.cfm) to test new drug combinations at an earlier stage in clinical development than would normally be considered. Partnership with the US Food and Drug Administration is helping to develop regulatory science and define new guidelines for evaluating the safety and effectiveness of new combination products.

If we take an optimistic view of the current pipeline, there are sufficient candidates to ensure that a new combination regimen will be developed, and that this regimen will be able to shorten chemotherapy by 2, or perhaps 3, months. It should be noted, however, that the current drug candidates fall into relatively few drug classes and we should anticipate that due to attrition several drug candidates will fail to reach registration. Thus, the more pessimistic view is that the current pipeline is insufficient to meet our goal and we must continue efforts to replenish it. Fortunately, the drugs in development all show activity against MDR-and XDR-TB strains and should provide new options for treatment of patients infected with such strains, even if they
fail to shorten the duration as would be required to change first-line therapy.

Our understanding of *M. tuberculosis* improved greatly with the publication of the genome sequence in 1998 [12] but this of itself is only one tool with which to advance drug discovery; although we know the primary sequence of every gene, we do not know which of the approximately 4,000 genes are the most vulnerable to inhibition, other than those that are the targets of today’s drugs. Through genetic approaches, those genes that are essential for the viability of *M. tuberculosis* have been identified [13] but this only provides a starting point and further work is needed to validate potential drug targets. The promise of target-directed rational drug design was not fulfilled in other areas of antibacterial drug discovery [14], an important lesson for the TB community. New approaches that start with compounds having whole-cell activity against the pathogen have greatest promise but conversely provide the most difficult path to optimization. Fortunately we are now well positioned to take whole-cell hits, identify their targets rapidly and then deploy the full suite of structure-based design tools at our disposal to ensure success.

A feature of recent drug discovery efforts, particularly those aimed at solving the more intractable problems of persistence and latent TB, has been the formation of international, multidisciplinary partnerships between researchers in academia and industry, leveraging funds provided by governments and philanthropic donors. These consortia have succeeded in bringing together the diverse skills of researchers in academia with expertise found only in industry. An example of this aimed at identifying a new first-line drug is the ‘New Medicines for Tuberculosis’ programme (www.nm4tb.org), a consortium of European researchers funded by the European Commission 6th Framework Programme, in partnership with AstraZeneca scientists based in Bangalore, India. This team has identified and validated a number of drug targets, but its biggest success to date was the discovery of a new class of anti-TB agents, the benzothiazinones, and identification of the major target, decaprenylphosphoryl-β-d-ribose 2’-epimerase [15]. Another example is a consortium established to solve one of the ‘Grand Challenges in Global Health’ (www.gcgh.org), namely finding a more potent and rapidly acting treatment for latent TB. This consortium, funded jointly by the Bill & Melinda Gates Foundation and the Wellcome Trust, comprised academic groups from around the globe led by a team based at Imperial College, London, working in partnership with the Novartis Institute for Tropical Diseases, Singapore. Exploring the hypothesis that latent *M. tuberculosis* resides in hypoxic lesions, and that *M. tuberculosis* adapts its metabolism to cope with this environment, the team hopes to find agents that are effective under these conditions and thus can be used to eliminate latent infection, and it also aims to develop new tools and approaches needed for rapid evaluation of drugs in latently infected humans [16].

In spite of successes over the past decade, the paradox remains that if we continue to conduct TB drug discovery the way we always have, we risk only finding more of the same and not the breakthrough that we really need. In other words, current efforts may yield incremental improvement on therapy duration – which will nonetheless be welcomed with drugs that are easier to take and that combat MDR-TB – but will not provide a truly transformational medicine. With this in mind, the Bill & Melinda Gates Foundation embarked on a programme to address mycobacterial persistence. Various hypotheses were put forward to explain persistence, such as that the bacterium resides in a compartment where it responds to its micro-environment by altering its metabolism, thus remaining unaffected by current drugs, or that persistence is a stochastic phenomenon, that is at any one time a small fraction of bacteria are quiescent or dormant and not dividing and thus refractory to treatment. In a programme known as the ‘TB Drug Accelerator’, grants were made to investigate the underlying causes of persistence and to characterize the persistent organism in vivo, to generate robust and scalable whole-cell assays that mimic the conditions encountered by the persistent bacterium in the host, to generate new tools that would permit deconvolution of whole-cell active compounds to reveal their targets and thus engage the full suite of drug discovery tools, to determine which of the current animal models best predicts the ability of a drug to shorten therapy, and finally to apply state-of-the-art tools and technologies widely used elsewhere to facilitate preclinical discovery and clinical development, such as advances in imaging to monitor bacterial load in situ and in real time. At the time of writing, the programme is now generating data and tools that are opening new avenues of drug discovery in collaboration with a number of pharmaceutical companies.

**The Future**

We can be optimistic that during the next decade new drugs will be registered and introduced that will augment or replace those that are currently in use. However, we must not be complacent and should strive to discover and develop a transformational therapy that will improve the outlook for
newly diagnosed patients such that they are facing a course of treatment that lasts only a few weeks. We must increase the number and quality of drug candidates to ensure success and we must challenge the current paradigm of drug discovery to find agents working through new mechanisms. Finally, greater investment is required to understand the role played by the human immune system in order to identify ways in which this powerful weapon can be deployed with greater effect. To do all of this will require sustained financial and scientific commitment as there will surely be failures along the way, but we are well placed to achieve the breakthrough in therapy that will at last provide tools to control this disease more effectively.

Ken Duncan
Deputy Director, Global Health Discovery
Bill & Melinda Gates Foundation
PO Box 23350, Seattle, WA 98102 (USA)
Tel. +1 206 709 3705, E-Mail ken.duncan@gatesfoundation.org