Tuberculosis drug development pipeline: progress and hope

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More than 50 years after the introduction of effective chemotherapy for tuberculosis,1 the disease remains unconquered and in many resource-poor countries, especially those blighted by HIV, alarmingly unstable. Although multidrug regimens are available that cure 95% of patients with active, drug-sensitive pulmonary tuberculosis, newer and better drugs are needed2 because of poor compliance with the 6 months of treatment, interactions with antiretroviral drugs, and the emerging issue of drug resistance.

Of these problems, the long duration of therapy is the most important to overcome, since shorter regimens would increase the proportion of patients who complete treatment, reduce the number who relapse, and improve the overall effectiveness of tuberculosis control programmes. Causes of non-compliance with complex treatment regimens include feeling well long before drugs can be safely set aside and the difficult conditions in most developing countries. In part because of these difficulties, WHO introduced their DOTS strategy in 1993. One of the crucial components of this strategy is the direct observation by trained personnel of patients taking their medications to ensure compliance and help prevent the emergence of drug resistance. Although important for treatment success, this strategy greatly increases the cost of delivering care. That said, regimens to treat multidrug-resistant tuberculosis (MDR-TB) are badly tolerated, expensive, relatively ineffective, and must be taken for up to 2 years.4

Other than by shortening treatment time, new agents would be considered an advance if they were able to penetrate sites that are difficult to treat, such as
developing new therapies for tuberculosis. continued or initiated work aimed at finding and developing new therapies for tuberculosis. The Tuberculosis Trials Consortium (TBTC) sponsored by the US National Institutes of Health (NIH), the Special Programme for Research and Training in Tropical Medicine and Malaria, the World Health Organization (WHO), and the Rockefeller Foundation convened a meeting in 2000, in Cape Town, South Africa, to investigate ways to stimulate drug development. From more than 120 attending organisations came the recommendation to form a not-for-profit public-private partnership—the Global Alliance for TB Drug Development (TB Alliance)—responsible for the development of improved and affordable therapies.1 Coincident with the growth of the TB Alliance, three major pharmaceutical companies—AstraZeneca, GlaxoSmithKline, and Novartis—formed or developed discovery research units focused on tuberculosis. In the meantime, other companies and organisations, including Otsuka Pharmaceutical, Johnson and Johnson, Lupin, Sequella, the US National Institutes of Health (NIH), the Special Programme for Research and Training in Tropical Diseases (TDR) sponsored by WHO, and the Tuberculosis Trials Consortium (TBTC) sponsored by the US Centers for Disease Control and Prevention continued or initiated work aimed at finding and developing new therapies for tuberculosis.

This renewed interest in drug discovery and development has transformed a bleak picture into one of cautious optimism. There are now potentially useful agents at every stage of the development pipeline with multiple organisations doing clinical trials (table).4–10 The moxifloxacin programme, about to enter phase III, is being undertaken under an umbrella agreement between the TB Alliance and Bayer Pharmaceutical, and is investigating the potential for shortening treatment duration by substituting moxifloxacin, in the current first-line regimen, for either ethambutol or isoniazid. Studies to investigate the treatment shortening potential of substituting gatifloxacin for ethambutol are also being done by a product development team supported by TDR and the European Commission. And there are compounds in preclinical development too.4 Although this development pipeline is extremely encouraging, there remain many challenges. Development of a new drug active against Mycobacterium tuberculosis is only the start. As was discovered decades ago, the pathology of the disease and the biology of the causative organism mean that treatment with multidrug therapy is required. Thus, the role of new agents must be identified in the context of a treatment regimen. The fact that we now have several potential new agents in clinical trials means that we will soon need a complex series of studies to find the optimum treatment-shortening regimen. We need to devise innovative techniques to approach this challenge. The capacity to do large trials to high clinical-practice standards has diminished during the years of decline, and the infrastructure needed for rapid testing of new drugs needs to be re-established in high-burden countries. Finally, resources are needed, both financial and human, to allow us to take full advantage of and extend the progress made over the past few years.

Conflict of interest statement
We declare that we have no conflict of interest.

References
Progress and hindrances in tuberculosis vaccine development

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BCG, introduced as a prophylactic vaccine in 1921 by Calmette and Guérin, initially proved a resounding success, reducing mortality from tuberculosis by about 90% in vaccinated children. 1 Unfortunately, though, the vaccine has little effect on pulmonary tuberculosis, which is most common in young adults in regions where tuberculosis is endemic. 1 Furthermore, attempts to extend the period of protection of the vaccine by giving a second dose have been fruitless. A possible reason for this lack of effect is that the low level of immunity induced by environmental mycobacteria or previous vaccination is sufficient to inhibit the growth of BCG, blocking its boosting effect, but has only a small effect on the more virulent Mycobacterium tuberculosis. 1 However, this theory does not explain the lack of long-term protection afforded by neonatal vaccination, especially given the cross-reactivity that prevents the use of BCG in adults, which might be expected to boost the effect of BCG vaccination in infants. Here we discuss an alternative hypothesis: waning immunity might not be due to induction of insufficient T-helper (Th)1 activity, but rather to the presence of other mechanisms that undermine the efficacy of the Th1 response—specifically, inappropriate Th2 responses or regulatory T-cell activity, or both (figure). An understanding of the evolution of the immune response will be the key to the design of vaccines with longer-lasting efficacy.

Immunity to M. tuberculosis depends on a robust Th1 cell-mediated response and, in particular, continued production of interleukin 12, interferon gamma, and tumour necrosis factor (TNF) α; however, by themselves, high concentrations of interferon gamma are not predictive of efficacy. 2,3 So what other factors might play a part? Results of studies in patients indicate that raised expression of interleukin 4 in peripheral blood 4 and in the infected lung 5 is associated with progressive tuberculosis. Excessive concentrations of interleukin 4 might impair Th1-mediated effector mechanisms by downregulating inducible nitric oxide synthase (iNOS) and apoptosis of macrophages 6 or worsen pathology by affecting toxicity of TNFα. 7 Raised concentrations of interleukin 4 are noted in patients from both developing and developed countries, 8 suggesting that M. tuberculosis itself drives the interleukin 4/Th2 response. 8 This theory would explain why healthy individuals with latent infection that does not progress express increased levels of interleukin 482, an antagonistic splice variant of interleukin 4; long-term control of latent M. tuberculosis infection might require inhibition of interleukin 4 activity. 4 Thus, although an effective vaccine must induce a lasting Th1 memory response, 2 over the longer term it might also need to inhibit the development of a Th2 response, or downregulate it if already present. Other mechanisms might also undermine immunity. Patients with severe tuberculosis often become anergic, reverting to negative in tuberculin skin tests, and the lymphoproliferative or interferon gamma response of peripheral blood mononuclear cells (PBMC) to M. tuberculosis can be depressed. These types of anergy are associated with release of interleukin 10 and its raised expression in PBMC and bronchoalveolar lavage from patients with tuberculosis. 9,10

These data suggest that even if a Th1 response is induced by vaccination, its long-term efficacy is not assured; this assumption leads inevitably to regulatory T cells, because it is these cells that control the

Figure: Hypothetical sequence of events leading to short and variable duration of protection after BCG vaccination

Contact with cross-reactive environmental mycobacteria primes and maintains a variable mixture of Th1, Th2 (particularly in developing countries), interleukin (IL) 482, and regulatory T-cell activity (RegT). On the one hand RegT might be potentially beneficial if it limits Th2 or immunopathology, whereas on the other hand it might limit efficacy of Th1 response. The pattern seen will depend on local mycobacterial flora and exposure. Subsequent infection with M. tuberculosis can drive further RegT activity or Th2 (particularly after high-dose challenge or Bejing strains). These various pathways might compromise the efficacy of the dominant Th1 response, and result in immunopathology. Effective vaccines might need to modulate RegT and Th2, in addition to enhancing Th1.

