approach is that efavirenz is teratogenic (and at least half of treated patients are women). Also, there is no fixed-dose combination with stavudine and lamivudine, and efavirenz-based treatment is more expensive. There has been debate about whether the dose of efavirenz should be 600 mg or 800 mg daily,[4] although results of a study done in Thailand[6] show that plasma concentrations and virological outcomes are equally good at the 600 mg dose in patients with tuberculosis and a median bodyweight of 50 kg.

Other options, such as substituting rifabutin for rifampicin (rifabutin is a less potent inducer of CYP450) or using triple NRTIs—eg, zidovudine, lamivudine, and abacavir—are not feasible because of cost. Other concerns for triple NRTI regimens are antiviral potency, limited data in patients with tuberculosis, and monitoring for hypersensitivity reactions due to abacavir. There is some evidence[4] that although nevirapine concentrations are reduced by rifampicin they are still in the effective range. Further studies on the safety, pharmacokinetics, and efficacy of concomitant nevirapine and rifampicin are urgently needed.

The initiation of HAART during treatment for tuberculosis can lead to immune reconstitution syndrome, manifested as a worsening of symptoms and signs or the appearance of new tuberculosis lesions.[7] This problem arises most frequently when HAART is started early in the course of treatment for tuberculosis (such as in the first 2 months) and when the patient has a low CD4-lymphocyte count ($<100\times10^6$ cells/L). The most common features are fever, lymphadenopathy, and worsening respiratory symptoms and signs.[7] The illness is generally managed with anti-inflammatory drugs, including corticosteroids in severe cases.

Development of active tuberculosis has also been reported in 20% of patients who start HAART,[8] is being increasingly documented during scale-up of HAART in resource-poor countries, and, in Africa, is associated with a previous episode of tuberculosis.[9] One possible explanation is that active tuberculosis is simply not being diagnosed before HAART is started. The development of simple and effective diagnostic methods for tuberculosis is needed to limit such oversight.

Conflict of interest statement

We declare that we have no conflict of interest.

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Tuberculosis drug development pipeline: progress and hope

Melvin Spigelman, Stephen Gillespie

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 needed[2] 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.[3] 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

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	Development stage	Sponsor/coordinator
Gatifloxacin	Phase III	European Commission/OFLOTUB consortium, Institut de Recherche pour le Développement, WHO TDR, Lupin
Moxifloxacin	Phase II/III	Bayer, TB Alliance, Centers for Disease Control and Prevention, University College London, Johns Hopkins University
TMC 207 (previously R207910)	Early bactericidal activity	Johnson and Johnson (Tibotec)
OPC-67683	Early bactericidal activity	Otsuka Pharmaceutical
PA-824	Phase I	TB Alliance
LL-3858	Phase I	Lupin

Table: **Tuberculosis drug clinical development pipeline**

pulmonary cavities, empyema, or extrapulmonary locations, or had novel mechanisms of action that were active against infections that are either sensitive or resistant to current drugs. Drugs with long half-lives, allowing for simplification of therapy, are needed, as are those able to target tubercle bacilli in a dormant state, which many think are responsible for late relapse disease and latency. Treatment regimens that can be used safely concurrently with the commonly prescribed protease inhibitors and non-nucleoside reverse transcriptase inhibitors used in highly-active antiretroviral therapy for HIV are also an urgent research priority.

The decline in incidence of tuberculosis in the developed world has been accompanied by a fall in the commercial incentive for pharmaceutical companies to invest in antituberculosis drug research and development. This lack of investment over the past 30 years has resulted in a paucity of new drugs. Unanticipated by most, the explosive AIDS epidemic and deteriorating socioeconomic circumstances in many of the world's poorest nations has fuelled a worsening of the global tuberculosis epidemic. In response, 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.[5] 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).[6–10] The moxifloxacin programme, about to enter phase III, is being undertaken under an umbrella agreement between the TB Alliance and Bayer Pharmceutical, 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.[6]

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.

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Progress and hindrances in tuberculosis vaccine development

T Mark Doherty, Graham Rook

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[3] or worsen pathology by affecting toxicity of TNFα.[3] Raised concentrations of interleukin 4 are noted in patients from both developing and developed countries,[4,5] suggesting that *M tuberculosis* itself drives the interleukin 4/Th2 response.[6] This theory would explain why healthy individuals with latent infection that does not progress express increased levels of interleukin 4δ2, 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[3] and its raised expression in PBMC and bronchoalveolar lavage from patients with tuberculosis.[4,7]

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

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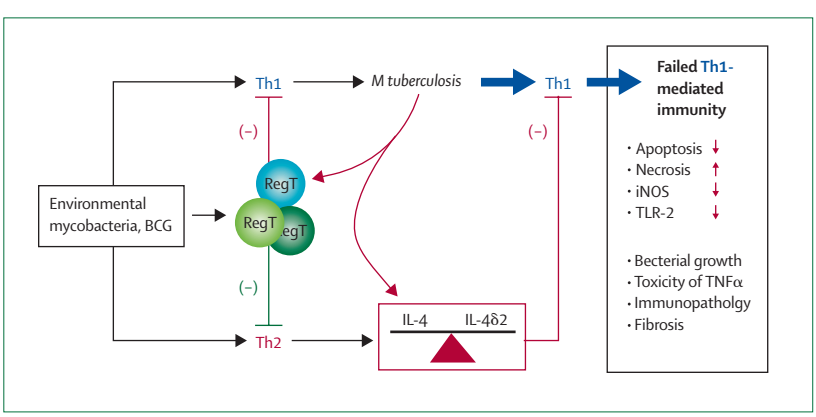

Figure: **Hypothetical sequence of events leading to short and variable duration of protection after BCG vaccination**

Contact with cross-reactive environmental mycobacteria primes and maintains a variable mixture of Th1, Th2 (particularly in developing countries), interleukin (IL) 4δ2, 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 Beijing 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.