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Novel vaccine strategies against tuberculosis: a road less travelled

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“CNS TB is the most serious form of TB, and predominantly affects young children. TB meningitis is universally fatal without treatment. Non-specific clinical presentation, poor diagnostics and delays in appropriate treatment complicate the management of TB meningitis.”

It has been more than 130 years since the discovery of *Mycobacterium tuberculosis*, the causative organism for tuberculosis (TB), yet it remains a formidable disease worldwide [1]. Major challenges include the lack of reliable diagnostics, requirement of prolonged treatment with multiple drugs to be taken daily, alarming increase in drug-resistant strains and the lack of an effective vaccine.

Bacillus Calmette–Guérin (BCG), a live-attenuated *Mycobacterium bovis* strain, is the only licensed vaccine against TB. While the exact mechanism of protection by BCG is not clearly understood, several studies demonstrate that BCG vaccination induces cellular immune responses that limit *M. tuberculosis* burden at the site of primary infection (lungs) [2–3]. This reduction in the bacterial burden, presumably, decreases extrapulmonary bacterial dissemination, and the subsequent risk of TB meningitis [4]. So, while BCG offers protection against disseminated forms of TB, it offers variable and limited protection against TB infection or pulmonary disease [5]. Therefore, significant efforts are being devoted to develop a new and efficacious TB vaccine. And while it is reassuring to note that several new TB vaccine candidates are in the pipeline, and many are being evaluated in clinical trials, several fundamental knowledge gaps, notably the lack of appropriate animal models and robust correlates of protection, are significant challenges in the search for a new TB vaccine [6]. In addition, the majority of TB vaccine candidates are focused on developing a better BCG vaccine (or boosting BCG-induced immunity), by enhancing cellular immunity

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against *M. tuberculosis* [7]. Since, antibody mediated mechanisms are the underlying basis for the majority of the approved vaccines against both extracellular and intracellular bacterial pathogens, the almost exclusive focus on enhancing cellular immunity, is yet another hurdle in the current efforts to develop an effective TB vaccine. A growing body of literature supports the critical role of humoral immune responses in protective immunity against TB, and these studies have been summarized in a recent review [8]. The failure of the Phase IIb study, the first in over 45 years, assessing a MVA85A vaccine designed to enhance the protective efficacy of BCG [9], has only added more fuel to this controversy.

CNS TB is the most serious form of TB [10], and predominantly affects young children. TB meningitis is universally fatal without treatment. Non-specific clinical presentation, poor diagnostics and delays in appropriate treatment complicate the management of TB meningitis. This leads to severe, irreversible neurological damage and high mortality, even when appropriate treatment is administered. Individuals co-infected with HIV are not only at an increased risk of developing CNS disease [11], but are also more likely to die of TB meningitis [12]. Management is even more challenging with disease due to drug-resistant strains, as several TB drugs have limited penetration into the CNS. Therefore, developing preventive strategies against TB meningitis should be a high priority.

Despite the fact that BCG provides variable and limited protection against adult pulmonary TB, it does offer protection against disseminated TB and meningitis in infants. Therefore, WHO recommends BCG administration to all (except those that are known to be HIV-infected) infants at birth in high TB burden countries [4]. This makes BCG one of the most widely used vaccines (administered to ~79% of the world's population). However, BCG has several major limitations. It is poorly defined (antigenically). The half a dozen different strains in circulation induce different levels of protection [13], and thought to contribute to the variable efficacy of BCG. In fact, protection offered by BCG against TB meningitis is also quite variable, with several studies showing protection of only 50–60% [14,15]. Moreover, BCG is a live vaccine, and therefore unsuitable for immunosuppressed infants especially in the setting of HIV [16]. Finally, BCG vaccination also confounds the interpretation of the tuberculin skin test that is widely used as a TB surveillance and diagnostic measure. For these reasons, a new, preferably acellular alternative to BCG would be ideal.

Much of the current understanding on the pathogenesis of CNS TB and subsequent meningitis comes from the meticulous work of Arnold Rich and Howard McCordock [17]. Rich postulated that bacteria gets deposited in the meninges and the brain parenchyma during the initial hematogenous 'bacteremic' phase. 'Rich foci' develop around these bacteria in the CNS, and later rupture into the subarachnoid space, causing diffuse, inflammatory meningitis. The fact that bacteria need to traverse the blood (or potentially the lymphatic) compartment before they can reach the CNS offers a unique opportunity to target bacteria in this compartment. Vaccine strategies that could neutralize the bacteria or surface expressed microbial virulence factors in the blood compartment, could therefore be utilized to prevent TB meningitis and other forms of disseminated TB. To this end, several acellular candidates exist, though none have explored the ability to prevent dissemination to the CNS and subsequent TB meningitis.

Since microbial virulence factors that promote CNS invasion are well described in numerous neuroinvasive pathogens [18], we focused on identifying virulence factors in *M. tuberculosis* associated with its dissemination to the CNS. We found protein kinase D (PknD), a surface expressed protein, to be an important mediator of *M. tuberculosis* invasion of the CNS, which could be neutralized by specific antisera, suggesting its potential role as a therapeutic target against TB meningitis [19]. We subsequently tested this in a guinea pig model of CNS TB and demonstrated that vaccination with the recombinant PknD subunit protein offered significant protection against *M. tuberculosis* dissemination to the brain. This protection was no different from BCG, even though PknD vaccinated animals had almost 100-fold higher pulmonary bacterial burdens [20]. Higher levels of PknD-specific IgG were also noted in animals immunized with PknD, but not in BCG-vaccinated or control animals. Furthermore, pre-incubation of *M. tuberculosis* with sera from PknD-vaccinated animals, but not with sera from BCG-vaccinated or control animals, significantly reduced bacterial invasion in a human blood–brain barrier model. Interestingly, based on gene sequence analyses, pathogenic strains of *M. tuberculosis* produce a full length PknD. However, a frame shift mutation was observed in the *pknD* homolog in BCG, resulting in a predicted truncated protein without the putative C-terminal sensor domain [21].

It is been observed that lungs are the predominant site for TB, and pulmonary disease is a potent route for required for TB transmission. Hence there is a perception in the TB research community that current resources should be exclusively channeled for the development of TB vaccines that prevent pulmonary infection or disease. In fact, a search on PubMed with the keywords ‘tuberculosis vaccine’ and ‘tuberculosis meningitis vaccine’ return 14,100 and 200 published (English) articles, respectively. Based on the title and available abstracts for these 200 articles, only three (including our prior publication) are focused on developing vaccines for TB meningitis or CNS TB [20,22,23]. Everyone agrees that meningitis is the most devastating form of TB, which disproportionately affects young children. Furthermore, more than half of all children afflicted with TB meningitis will either die or have significant neurological sequelae, even when appropriate treatment is administered [24]. BCG, widely used in high TB burden countries, primarily to prevent TB meningitis in young children, has several major limitations. So while robust efforts to develop TB vaccines against pulmonary infection and disease should continue, we should not forget an equally urgent and significant need for a better vaccine against TB meningitis and other serious forms of childhood TB.

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