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## Editorial

### Perceptions of Human Tuberculosis Vaccine: The Fiocruz Latest Contribution

Paulo RZ Antas\*

Laboratory of Clinical Immunology, Instituto Oswaldo Cruz, Fiocruz, Rio de Janeiro, Brazil

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As globally reported, tuberculosis (TB) is a major cause of illness and death worldwide, with increased burden mainly in developing countries. The Stop TB Partnership goals embrace dropping the global TB burden by half in 2015 and eliminating TB as a public health problem by 2050. As an ancient microbe highly adapted to the host, *Mycobacterium tuberculosis* infects humans through an oral route. TB can be caught by persons that inhale droplets containing the bacteria when an infected person coughs or sneezes. But the majority of these infected subjects will remain asymptomatic. In fact, this huge reservoir is blamed for the TB burden mainly in developing countries, causing the global resurgence of TB, which is further fueled by the HIV pandemic and the rise of *M. tuberculosis* multi (MDR)-, extremely (XDR)-, and totally (TDR)-drug resistant strains.

Importantly, vaccination is a key approach in reducing the frequency of TB. *M. bovis* bacillus Calmette–Guérin (BCG), the only licensed TB vaccine currently in use, was first administered orally in 1921, and since then many clinical trials in different parts of the world have evaluated the effectiveness of BCG in preventing TB disease. These trials demonstrate that BCG confers steady protection against extrapulmonary TB in children. However, BCG affords extremely inconsistent defense against pulmonary TB, which accounts for the major burden of global TB mortality and morbidity throughout the world. Therefore, a more successful vaccine is a major global health priority by governments. The Moreau BCG strain has been employed for some 70 years here in Brazil and lessons from its use should be taken in account for the development or improvement of new TB vaccines. In this venue, the challenges for the subsequent forthcoming years are obvious. It is improbable that any simple immunological correlate of protection will be recognized. Therefore, it is essential our understanding on how BCG confers protection. The vast majority of the current population has been vaccinated with BCG, with the possible requirement for a booster immunization in adulthood for TB protection. BCG Moreau strain also pro-

TECTS against leprosy, meningitis and extrapulmonary forms of TB. Factors related to differences in strain, dosage and BCG administering protocol have been responsible for the variable efficacy. This vaccine is clearly affected by, as yet unclear, host and/or environmental variables. Yet, little is known about the interaction of BCG with human monocytes. Also in preclinical studies, IFN $\gamma$  seems to be required but not sufficient for protection, and the magnitude of the immune response correlates with the degree of protection. However, any immunological correlate may be vaccine and disease-stage specific.

One of our central goals is to investigate the potential of BCG Moreau strain to induce in vitro specific cell-death in BCG-stimulated monocytes from healthy adults. There was a concomitant release of IL-1 $\beta$  and TNF- $\alpha$ , but not metalloproteinase (MMP)-9. In addition, there was an enhancement of monocytes necrosis, but not apoptosis, following BCG Moreau strain stimulation of umbilical vein cells from naïve, neonate population. This pattern was paralleled by different pro-inflammatory cytokine levels, as well as MMP-9 induction when compared to the adults. Those findings support the hypothesis that BCG induces distinct cell-death patterns during the maturation of the immune system and that this pattern might set the stage for a subsequent antimycobacterial immune response that might have profound effects during vaccination. In another small study, the in vitro Th1-immune response of neonates (IFN $\gamma$ ) was shown to be deficient when cells were placed in contact with recombinant antigens by an ELISPOT assay. In fact, the probable impairment was related to a non-specific immune response, since a potent mitogen assayed in parallel as an internal positive control yielded virtually no response in that group. Also, cells from vaccinated adult individuals in matching identical assays, yielded convincing data. The reasons behind this result are speculative; perhaps due to a higher amount of circulating immature immune cells or to a lack of exposure to mycobacterial antigens.

*M. tuberculosis* is an extremely well-adapted pathogen which has co-existed with the human host for millennia, and it has learned how to modulate potentially protective host responses to ensure its own survival. Therefore, tuberculosis currently presents distinctive challenges to vaccine development not faced in other diseases. In addition, the candidates for novel vaccines against TB based on diverse BCG platforms are valuable tools for TB control. The most promising ones in current clinical trials were derived from BCG strains. It hindsight, greater representation of BCG strains from the most immunogenic group may have led to candidates with higher efficacy than existing strains.

Finally, advances in the fields of immunology and molecular biology have stimulated research into new vaccination techniques for TB and alternative approaches are warranted in the next few years in order to develop more reliable tools to induce a protective immune response against this disease. In sum, series of quality articles inform and still convey our observational assessments in order to compile a message for those interested in the TB vaccinology. Therefore, our reputation in the field, the Fiocruz institutional history, and the relevance of tackle TB are our major focus. Particularly, the BCG vaccine, Moreau strain, is our main point of interest, and also the current relevance in public health at Fiocruz.