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Letter to the Editor

The Brazilian Experience on BCG Immunization and the Development of New Vaccines against Tuberculosis

Paulo R Z Antas*

[1]*Laboratório de Imunologia Clínica, Instituto Oswaldo Cruz, Fiocruz, Brazil*

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***Corresponding author**

Paulo R Z Antas, Lab. Imunologia Clínica, Instituto Oswaldo Cruz, Fiocruz, Av. Brasil, 4365 – Rio de Janeiro / RJ; Pav. Leônidas Deane – Room 409C, Tel: +55-21-3865-8152; Fax: +55-21-2290-0479; ZIP: 21040-900; Email: pzuquim@ioc.fiocruz.br

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The interruption of centuries of decline in case rates of Tuberculosis (TB) occurred, in most cases, in the late 1980s and involved industrialized countries due to increased poverty in urban settings and the immigration from TB high-burden countries. Thus, no sustainable control of TB epidemics can be reached in any setting without properly addressing the global epidemic.

A considerable rate of deaths from TB has been attributed to co-infection with *Mycobacterium tuberculosis* and Human Immunodeficiency Virus (TB-HIV). Immune deficient patients with HIV are at increased risk of latent *M. tuberculosis* infections (LTBI) progressing to active disease and being transmitted to others represents a considerable reservoir of bacilli. In addition, more than a half of the new TB cases are potentially MDR-TB "super strains" in the hot zones, such as the "BRICS" countries (Brazil, the Russian Federation, India, China and South Africa). MDR-TB strains, an airborne bacterium that is spread just as easily as drug-sensitive TB, are resistant to at least three of the four main drugs used to treat TB. Likewise, it has been reported the emergence of extensively drug-resistant (XDR) TB cases, defined as cases in persons with TB whose isolates are resistant to isoniazid and rifampicin (MDR-TB) as well as resistant to any one of the fluoroquinolone drugs and to at least one of the three injectable second-line drugs, Amikacin, Kanamycin or Capreomycin. XDR-TB is widespread raising the prospect of virtually incurable TB worldwide, such as the novel Total Drug-Resistant (TDR) TB strains found in India, Italy and Iran. The factors that most influence the emergence of drug-resistant strains include inappropriate treatment regimens, and patient noncompliance in completing the prescribed courses of therapy due to the lengthy standard "short-course" treatment or when the side effects become unbearable.

M. tuberculosis has been considered the world's most successful human pathogen. This bacillus can infect the host for decades without triggering clinical disease, with reactivation happening only when the immunity of the host is depressed. Much of its fortuity is also due to its ability to induce a pattern of host response that causes tissue damage in the lung. This eventually results in cavities in which infectious aerosols are generated, thereby enabling this pathogen to infect new hosts. It has been a highly successful strategy for the microbe, and has caused a lot of human misery. Vaccination with a live attenuated of *M. bovis* strain, Bacille Calmette-Guérin (BCG), induces protective immune responses in children against severe and fatal forms of TB.

However, the protection afforded against the most prevalent pulmonary form of TB in adults is highly variable. Therefore, more effective vaccines than the currently used BCG vaccine are needed to prevent TB development, especially in poor and developing countries. No human vaccine has produced more inconsistent results in controlled clinical trials than BCG. Following the failure of BCG in India, a theory was advanced that prior infection with environmental mycobacteria influences the subsequent efficacy of BCG vaccination. For instance, environmental mycobacteria evoke qualitatively different types of immune responses. A "Listeria-type" response was believed to augment BCG efficacy whereas a "Koch-type" response opposed BCG efficacy.

The "Koch-type" pattern of response was reminiscent of an observation reported by Robert Koch in his seminal experiments with *M. tuberculosis.* The "Listeria-type" was believed to depend more on immune cells, such as heat-killed *M. vaccae* immunotherapy, whereas the "Koch-type" response was viewed as a "double edged weapon" that while helping to contain infection, also damaged tissue. Very little is known about the microbiologic and immunologic basis for these two patterns of immune response.

TB is the classic model of cellular immunity. Protective host responses involve CD4+ T-cells secreting IFN-γ (Th1 cells) and activated macrophages producing ROS and RNI, whereas antibodies are unimportant by comparison. The CD8+ T-cells also appear to be important in the host containment of virulent *M. tuberculosis*. Disseminated disease can be often seen when TB is

accidentally introduced into naïve human populations, and still occurs in man, particularly in young children and in immunosuppressed persons. Clinical observations and studies in man provide insight into the components of true "containment". Th1 cell populations appear to be very important as HIV-infected persons with LTBI are at high risk of progressing to active TB, and frequently present with extra pulmonary or disseminated infection. Furthermore, treatment of TB-HIV co-infected persons with antiretroviral therapy often causes increased clinical and radiographic evidence of TB in the lung as the CD4+ count recovers – the so-called Immune-Reconstitution Inflammatory Syndrome (IRIS). This supports the animal model data and demonstrates that not only do CD4+ T-cells limit dissemination, but they also promote lung inflammation. CD8+ T-cell responses also appear to be important in man, particularly in maintaining LTBI from household contacts of TB index cases. In addition, the Brazilian experience in the field has shown growing evidence that apoptosis-associated cross priming might be involved. In this model, infected macrophages undergo apoptosis – this kills the bacillus and makes its antigens available for uptake by Dendritic Cells (DCs). DCs possess an endosome- to- cytosol transport mechanism and can present antigens via MHC Class I pathway as well. Thus, macrophage apoptosis is a host-beneficial response suggesting an interesting "two cell" mechanism for presenting antigens from macrophage pathogens: First, the macrophage commits suicide and kills the microorganism in the process – next, DC takes up the antigens and presents them via MHC Class I and II pathways. This mechanism has an advantage in that it protects the DC from microbe-mediated immune inhibition, which may be crucial as tubercle bacilli exhibit potent capacity for inhibiting the activation of macrophages and DCs.

It is thought that the presently available *M. bovis* BCG strains can be genetically modified in order to create new vaccines that will improve protection against TB. Thus, recombinant BCG over expressing key *M. tuberculosis* antigens or rationally over-attenuated *M. bovis* BCG strains can be specifically devised. One possible advantage of this strategy would be the vast clinical experience associated with the BCG vaccine, its known immunogenicity, and the safety profile of standard BCG strains. However, owing to problems related to the variable efficacy of BCG in some countries, as already advised here, studies for new BCG-based vaccines against TB should ideally employ the old strains of BCG, particularly the BCG Moreau strain currently used in Brazil. The latter strain is genetically closer to the original BCG Pasteur strain and is not associated with a high incidence of adverse effects.

Finally, it should be mentioned that the basic rationale underlying generation of novel TB vaccines is not to replace the current BCG vaccine, but to develop new vaccination strategies that can complement BCG's scope of action. Of special interest is the development of new live attenuated mycobacterial vaccine strains, which often provide a potent means to prevent several human diseases. In general, these vaccines are safe, efficient and induce both local and systemic immune responses. While stimulating both humoral and cell-mediated immune responses, live attenuated vaccines also activate the innate and adaptive branches of the immune system, which is an important advantage and confers a better protection for the host. In the context of live attenuated vaccines, auxotrophic strains of several intracellular bacteria that carry deletions in amino acid, purine or pyrimidine biosynthetic genes have demonstrated good protection levels in animal models of infection. The development of auxotrophic *M. tuberculosis* mutants that express all the antigens present in virulent mycobacteria (including many antigens deleted from BCG), but which cannot grow properly *in vivo* because the genes encoding metabolic enzymes necessary for survival are deleted, is a major goal in TB vaccine development. The advantage of attenuated *M. tuberculosis* strains as vaccines is that many hundreds of genes have been deleted from BCG, as a consequence of the progressive adaptation of BCG strains to laboratory conditions. Since these genes are still present in *M. tuberculosis*, this fact implies that live, more immunogenic strains can be obtained. Lately, many different experimental approaches have been developed for exploring this principle of targeted gene inactivation in both *M. tuberculosis* and *M. bovis*. The results are very encouraging, and this approach is currently considered one of the most modern technologies employed in the generation of attenuated *M. tuberculosis* strains that will serve as live vaccine candidates in the future.

In summary, TB remains a public health problem worldwide. This is a complex literature but evidences provide additional support for dissociation between protective T-cell responses and tissue damaging in TB. Thus new drugs and second generation vaccines are urgently required to control TB. However, the complex biology of *M. tuberculosis* has hindered the development of novel therapeutic tools. Genetic manipulation of *M. tuberculosis* is also difficult, but currently new, more efficient gene replacement techniques have allowed detailed studies of many mycobacterial genes. Although the complete genome sequencing of *M. tuberculosis* has been a landmark in mycobacterial research, the genetic determinants of *M. tuberculosis* virulence are not completely understood yet. Besides, new powerful bioengineering techniques allow for the development of rationally attenuated strains as potential vaccines to prevent the spread of TB.