Journal of Infectious Diseases & Preventive Medicine

ISSN: 2329-8731

Antas, J Anc Dis Prev Rem 2013, 2:1
DOI: 10.4172/2329-8731.1000108

Short Commentary Open Access

Novel Recombinant BCG Vaccines: Do the Ordinary Platforms Matter?

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Abstract

Bacillus Calmette-Guerin (BCG) is the common name given to a family of vaccines against human tuberculosis. Created in 1921 by the in vitro attenuation of a virulent *Mycobacterium bovis* in France, the BCG vaccine continues to generate debate and confusion after nearly a century of use. Since the 1940s, significant sequence differences among the BCG strains have been reported. In addition, relationships between the recombinant BCG vaccines used in current clinical trials and their parental strains have been never fully delineated. In order to standardize and to clarify the subject regarding common BCG strains used to generate those novel vaccines, a sequential emergence of the parental strains and their matching recombinant strains was built. Hence, for a total of 16 BCG strains in worldwide circulation, 9 have been used to sustain one or more genetic alterations, resulting in around 21 novel recombinant BCG strains. Although it is an outstanding achievement, only 2 out of the 21 recombinant strains are from the most immunogenic group. Systematizing the novel BCG vaccines and their parental strains may facilitate our understanding of protection provided by BCG immunizations.

Tuberculosis (TB) is a major cause of illness and death worldwide. 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.

For TB protection, the live attenuated *M. bovis* BCG vaccine is employed earlier in life, and it is one of the most widely used vaccines. Actually, a large majority of the living population has been immunized with BCG, which is not a single organism, but comprises a number of strains (or substrains) that differ in genotypes and phenotypes [1]. Different factors have been responsible for the inconsistent efficacy of BCG vaccine against adult pulmonary TB, such as those related to the strain and the dose and method of administering the vaccine. Regarding the former, BCG has limited nitrogen metabolic capacity which may restrict multiplication and persistence of this live vaccine within the host [2]. Another reason is a waning of protection with age. BCG is clearly affected by still unknown host and/or environmental variables which alter the ability of certain groups of vaccines to respond successfully [3]. Despite being the most widely used vaccine in human history, the mechanisms by which this vaccine protects against TB and its effects on the immune system remain largely unknown. On the one hand, there are no comparative studies of the effectiveness of different BCG administration techniques. On the other hand, comparative genetic scrutiny of BCG strains worldwide has shown that the strains presently used are diverse [4].

Given the enormous burden of individuals chronically infected with *M. tuberculosis* and, therefore, at risk of developing reactivated TB, new prophylactic vaccines which might reduce that risk or which are used as an adjunct to chemotherapy could be very useful [3]. Any innovative vaccine candidate against TB, particularly those in subunit forms, should not only be studied in new regimens for newborns (e.g. prime-boost) but must be considered as a booster for these already BCG-immunized subjects. Actually, a major international research effort for the development of novel TB vaccines has been underway for several years.

Some experts in the field believe that advanced TB vaccines based upon a BCG platform, or novel approaches using BCG for priming or boosting protocols against adult forms of TB, will be invaluable in years to come. Thus, selections of viral, bacterial and parasitic antigens have been expressed in BCG and the ability of these recombinant mycobacteria to induce immune responses has been recognized. In 2008, our team published a review focused on the latest developments in the TB vaccine field for the understanding of the immune response required to control this pathogen [5]. At that time, major emphasis was devoted to the route of administration, either mucosa or parenteral, and it was hoped that progress in this area could lead to a more rational approach towards the improvement of the BCG vaccine. Since then, a concern has risen regarding differences in the parental strains of the recombinant BCG vaccines used in both pre-clinical and clinical trials. However, the issue still remains unresolved.

In order to clarify the central topic regarding published novel recombinant BCG vaccines, an illustration was prepared depicting the sequential emergence of the parental strains and their matching recombinant strains, if any (Figure 1). Hence, for a total of 16 BCG strains (excluding Copenhagen BCG) currently in circulation, roughly half (total of 9) have been used to sustain one or more genetic alterations, resulting in around 21 novel recombinant BCG strains. Of these, AERAS-407 has completed a phase I, whereas rBCG30 and VPM1002 are currently facing phase II clinical trials. Although it is an outstanding achievement, only 2 out of the 21 recombinant strains are from the most immunogenic group (Group I).

This under-representation of BCG strains with higher

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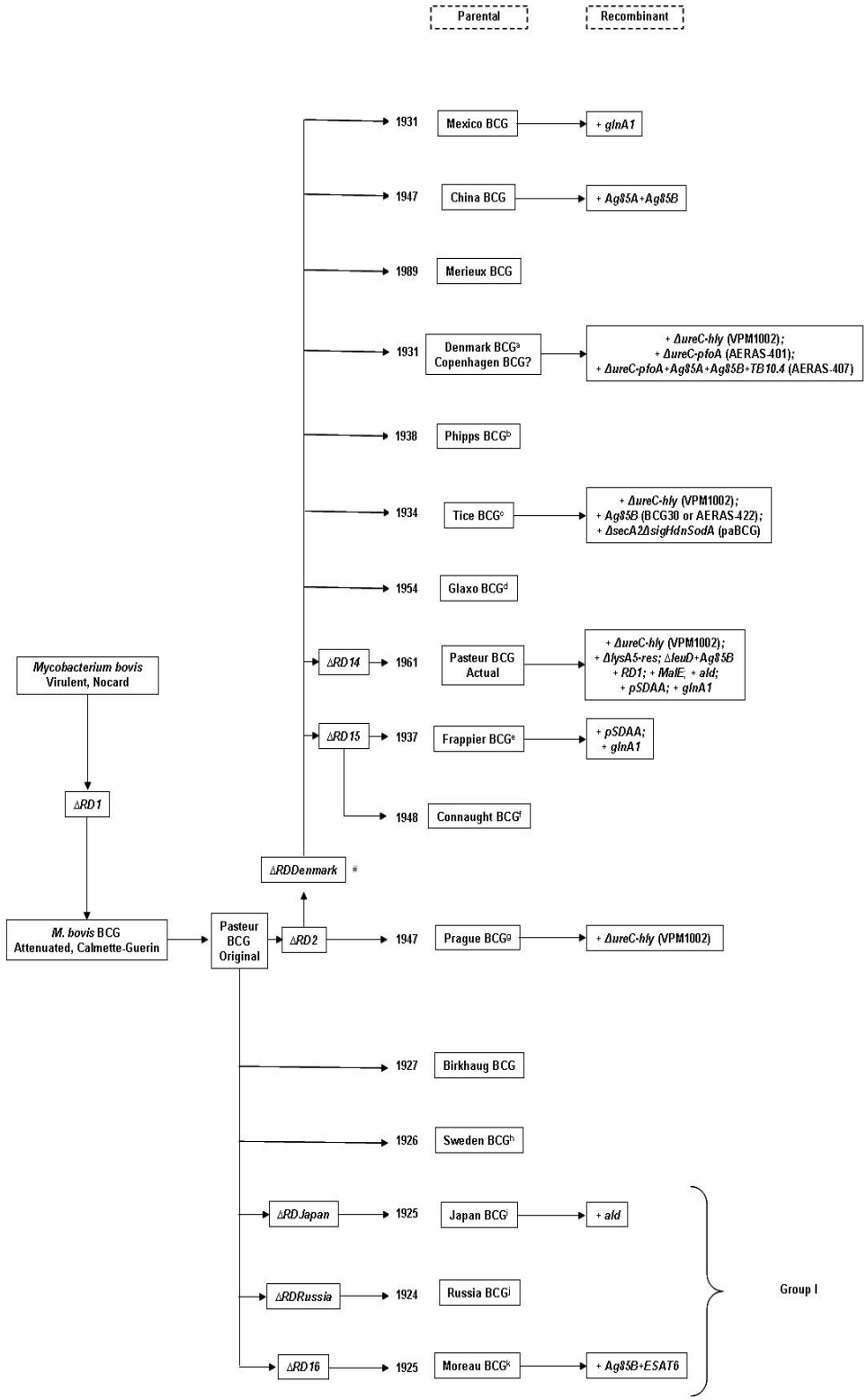
Received August 23, 2013; **Accepted** December 16, 2013; **Published** December 24, 2013

Citation: Antas PRZ (2013) Novel Recombinant BCG Vaccines: Do the Ordinary Platforms Matter? J Anc Dis Prev Rem 2: 108. doi: 10.4172/2329-8731.1000108



Common names of the BCG vaccine strains are as follows: a. Danish; b. Philadelphia; c. Chicago; d. London; e. Montreal; f. Toronto; g. Czech; h. Gothenburg; i. Tokyo; j. Moscow; k. Brazil. ald=L-alanine dehydrogenase gene. pSDAA=plasmid with L- serine deaminase gene. glnA1=glutamine synthetase gene. Not included the unpublished recombinant BCG strains expressing nadA and NMB1994 in both Moreau and Pasteur genetic background, available at: http://cordis.europa.eu/result/report/rcn/35633_en.html

or ΔRv1810, with a confirmation of the presence of tandem duplications [8]

Figure 1: Summary of all BCG vaccine strains, displaying the genealogy from the original ancestor strain *Mycobacterium bovis* (isolated in 1908) and the subsequent series of genomic deletions in the regions of difference (RD), ending up on the final parental and recombinant strains currently available.

immunogenicity may be limiting the efficacy of these recombinant vaccines by not taking advantage of previously established benefits of the strains from that group, despite virtually no surrogate marker has been available to predict vaccine efficacy [6]. For instance, in addition to safety records and other helpful characteristics, serious adverse events related to the BCG vaccine strains from the group I (Moreau, Russia and Japan) are rare, although they may include local complication. In addition, systemic complications and lethal dissemination are unusual as well, except in cases of cutaneous manifestations of disseminated BCG-induced diseases (BCGosis and BCGitis) in children with severe combined immunodeficiency [7]. Of note, the discrepancy in BCG vaccine infections may vary by BCG strain type, such as the Russia and Japan strains, although reports also include Pasteur, Glaxo and Copenhagen strains.

Nearly 90% of all vaccinations worldwide use the Pasteur, the Denmark, the Glaxo and the Japan strains. The BCG vaccine used in Brazil is exclusively from the Moreau-Rio De Janeiro (RDJ) strain, another member from the group I. Different BCG strains induce different immune responses in humans. The Moreau BCG strain induces a good DTH skin test response and rarely causes local or systemic adverse reactions. It remains to be determined if stable and compelling strain engineering would improve efficacy of the Moreau BCG strain. Alternatively, it has been shown that a given strain's performance may depend on the location of its usage, but there is no evidence that these phenotypic differences relate to differences in protective immunity between strains.

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.

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