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.

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 BCG 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 mucosal 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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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. gltA1=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

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 the 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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