Another Step Down the Development Pipeline for the Novel Tuberculosis Vaccine MVA-85A

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(See the article by Scriba et al, on pages 1832–43.)

The “Dose-Finding Study of the Novel Vaccine, MVA85A, in Healthy Bacille Calmette-Guérin [BCG]–Vaccinated Infants” by Scriba et al [1] in this issue of the Journal takes the development of this new vaccine candidate for tuberculosis a further step down its development pipeline. There are many new tuberculosis vaccines at different stages of development [2], but this vaccine is the first to be tested in children and infants. It has previously been shown to be both safe and immunogenic in South African children aged 2–7 years [3], and to move it into trials in younger children is an essential next step in its development. The infant immune system is immature [4, 5], with a bias towards Th2 cell polarization and low cytokine production, compared with that in adults [6]. Nevertheless, if BCG vaccine is administered shortly after birth, it induces strong Th1 cell responses, although the magnitude and quality of these can vary in different settings [7–9]. What is clear from the study by Scriba and colleagues is that BCG at birth induces responses to Ag85A that can be boosted by administration of MVA85A at 5–12 months of age. Boosting with MVA85A also induced long-lived polyfunctional T cells that were predominantly CD4+*. Interestingly, there were several differences in the immune signatures detected 28 days and 168 days after MVA85A boosting in these infants, compared with findings from earlier studies of older age groups, such as the detection of CD8 T-cell responses to Ag85A, the kinetics of the interleukin (IL)–17 response, and the lower frequencies of 85A-specific T cells that could be detected in BCG-vaccinated infants prior to MVA boosting. This shows the power of performing such detailed immunological assays in early vaccine trials.

It is interesting that infants had lower enzyme-linked immunosorbent spot (ELISPOT) responses to MVA85A than children aged 2–5 years, adolescents, or adults. This may reflect the boosting over time of Ag85A-specific responses by exposure to environmental mycobacteria because Ag85A homologues are present in all these nontuberculous mycobacteria [10]. Thus, either infants aged 5–12 months in this setting have not yet been exposed to such environmental mycobacteria, or the time period over which they were exposed was too short to induce higher Ag85A responses after vaccination. This comparison also illustrates another important and overlooked feature of vaccine trials—namely, that direct comparisons can only be made between results from different trials if identical protocols are used, which was the case here. Such direct comparisons greatly aid interpretation of the immunogenicity of different vaccines and vaccination regimens, although different assays may be needed when assaying the immunogenicity of different vaccines.

One objective of this study was to optimize the dose of MVA85A to use in infants. A clear dose-response relationship was, however, not detected, but one aspect that will deserve additional attention in the future is the number of infants that demonstrate interferon-γ responses to Early Secreted Antigenic Target-6 (ESAT-6). In group 1, which received the lowest MVA85A dose, 3 of 36 subjects experienced ESAT-6 conversion. This could be interpreted as showing not only that BCG given at birth fail to prevent such infants from Mycobacterium tuberculosis infection, but that boosting with MVA85A at the lowest dose also failed to induce complete protection. There are, however, several important caveats. First, the group sizes in this study, which was designed to demonstrate safety and...
immunogenicity, were low, and further larger studies are needed. Second, it is not clear whether ESAT-6 responses in such young children in this setting are always indicative of 
M. tuberculosis infection or whether exposure to other mycobacteria, such as Mycobacterium kansasii, that also express an ESAT-6 that is highly conserved with the 
M. tuberculosis protein [11–13], can induce IFN-γ responses to M. tuberculosis ESAT-6. Third, none of the children received a diagnosis of active disease, suggesting that vaccination may help contain infection.

The study illustrates other challenges that those designing such trials have to face. One issue is what comparison group to use. In this study, infants were offered Prevenar (Wyeth), a 7-valent polysaccharide pneumococcal vaccine conjugated to a nontoxic variant of diphtheria toxin; this should not have induced any antigen-specific cross-reactive T-cell responses, but any vaccine might induce nonspecific inflammatory responses that could, in turn, induce the nonspecific activation of other cells. In this instance, very low T-cell responses were observed in the control group given Prevenar, but with increasing interest in the innate immune response to M. tuberculosis [14], the choice of control vaccines may need further thought in the future. Secondly, conducting such studies in a setting such as South Africa illustrates the challenges of clearly identifying vaccine-related adverse events, because children at these ages experience many infectious disease episodes. However, no serious vaccine-related adverse events were identified.

So far, so good, and it is very reassuring that boosting with a key immunodominant antigen so soon after administration of BCG is not only safe, but induces increased numbers of antigen-specific T cells. At this stage, it is unclear what role multifunctional T cells making IFN-γ, IL-2, and tumor necrosis factor-α or T cells making IL-17 play in protection against tuberculosis.

Multifunctional T cells have been suggested to be key to protective immunity [15, 16], although in infants, the frequency of such cells 10 weeks after BCG vaccination does not correlate with subsequent protection against tuberculosis [17], and in adults with tuberculosis, they are associated with the development of disease rather than protection [18]. It is clear that CD4 Th1 responses and IFN-γ play a role in protection, but that other components are required in a protective biosignature; these may include components of the innate immune system. To move from immune signatures that indicate vaccine immunogenicity to signatures that indicate protective immunity is a challenging step that will require a trial of a protective vaccine for validation of these biosignatures. However, the inclusion of such detailed immunological assays in this and other early-stage trials of new candidate tuberculosis vaccines adds to our knowledge of mycobacterial immunity.

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References