Working Group on new TB Vaccines

STBVAC

Welcome to the Working Group on New TB Vaccines

TB vaccines

BCG

The only vaccine currently available for immunisation against tuberculosis (TB) infections is the so-called Bacille Calmette-Guerin (BCG). BCG is the most widely used of all childhood vaccines and has been available since the 1920s. Delivered at or near birth, it has been shown consistently to provide significant protection against severe childhood forms of disease, including the often fatal tuberculous meningitis. It also provides appreciable protection against leprosy. However, it has failed to protect consistently against the main problem of infection with Mycobacterium tuberculosis, i.e. adolescent and adult pulmonary TB in endemic countries in the South.

During the long time BCG has been used, numerous sub-strains have evolved from the original strain and have been used for vaccine production. Not surprisingly, in view of the diversity of sub-strains, manufacturing processes, immunisation schedules and levels of exposure to environmental mycobacteria and virulent *Mycobacterium tuberculosis* infection, BCG vaccines different levels of protective efficacy of BCG vaccines in adult populations have been reported.

In view of both the low efficacy of BCG as well as its diversity, it is obvious that new approaches to protect against TB would be highly desirable. However, the long history of BCG use, its satisfactory safety record and the fact that it provides some protection against extra-pulmonary TB during childhood and leprosy have been used as arguments to improve BCG rather than replace it. Two main lines of research build on such an approach: (a) attempts to improve BCG itself through genetic manipulation and (b) development of prime-boost vaccination paradigms with BCG as the priming component and entirely novel vaccines to boost the BCG-induced immunity.

New TB Vaccines

What is needed is probably not one, but more likely two or even three new TB vaccine types with different profiles:

- "Priming vaccines", i.e. vaccines intended to replace BCG early in life and before exposure to Mycobacterium tuberculosis,
- Vaccines to boost anti-mycobacterial immune responses induced by BCG (or its replacement), either early in life (infancy) or later (adolescence/adulthood) when latent TB is/may be installed,
- a therapeutic vaccine against active TB.

It may possible that a vaccine can be identified which covers several of these functional profiles, but this will not be automatically the case for all vaccine candidates. Thus, it is known that live BCG does not boost anti-TB immunity in latently infected or previously BCG-immunized human individuals or animals.

Priming vaccines: This type of TB vaccine, of which BCG is the prime example, is intended for use in newborns or young infants, i.e. at a timepoint when the individual's immune system has not yet been exposed to natural infection with Mtb or other mycobacteria. Current thinking implies that live TB vaccines such as 'old' BCG, improved BCG or rationally attenuated Mtb would be used as 'first contact' vaccines.

Booster TB vaccines: Booster doses of one of the new adjuvanted subunit or virus-vectored vaccines. Early booster vaccines would be given during the first year of life, ideally in combination with other childhood vaccines, such as DTP or measles vaccine. Late booster vaccines, which are sometimes also referred to as 'post-exposure vaccines' are vaccines that can be given at a post-infancy timepoint in life, typically to school children, adolescents or adults, when the individual has either been vaccinated, .e. g. with 'old' or 'improved' BCG, or latently infected with Mtb (or other mycobacteria) or both. These vaccines, which are to be used against firmly established latent TB may require a different set of antigens than the ones that are expected to be active against primary infection in newborns and the type of immune response induced may differ.

Therapeutic TB vaccines: Therapeutic vaccines, i.e. those that are to be given to individuals with active TB, represent a special case of the above-mentioned post-exposure vaccines. The general idea is not to use these vaccines as stand-alone agents, but rather as adjunct to antibiotic treatment, with the aim of shortening the duration of anti-TB chemotherapy. Inactivated

mycobacteria as well as a DNA subunit vaccine encoding for a mycobacterial heat-shock protein are being proposed for this purpose.