

Speaker Abstracts

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Immunological endpoints in challenge studies

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Background

Controlled human infection models provide a useful experimental medicine model to demonstrate a biological signal of efficacy in humans, prior to undertaking large, expensive field efficacy trials. Necessarily, the primary endpoint in such studies is usually microbiological, to allow the demonstration of a reduction in pathogen burden with vaccination. However controlled human infection models also allow the identification of potential immune correlates of protection, which can subsequently be validated in field efficacy trials. For tuberculosis vaccine development, the identification of immune correlates of protection would be game changing. In developing a controlled human infection model for tuberculosis, it is not possible to ethically infect healthy volunteers with virulent *Mycobacterium tuberculosis*. However, using BCG as a model mycobacterial challenge agent which is licensed for human use, we have established controlled human infection models using intradermal and aerosol delivered BCG.

Experimental Approach

Using an intradermal infection model, we have identified gene expression signatures and cytokine profiles that correlated with mycobacterial growth. We have also used an in vitro mycobacterial growth inhibition assay to demonstrate that it is possible to detect the same vaccine response using in vivo and in vitro challenge assays.

An additional potential use of controlled human infection models is to interrogate the immunobiology of a controlled time point infection. Such studies complement field studies where it is not possible to precisely time infection. Using an aerosol BCG infection model, we are currently using bronchoalveolar lavage fluid, lung biopsies and blood taken at different time points post-infection to define the immunobiology of mycobacterial infection in humans. Parallel studies in non-human primates allow us to use these immunological outcomes to bridge to efficacy and furthermore to confirm the relevance of such animal models.

