ABSTRACT- Carlos Martin

Development of MTBVAC: roadmap to clinical evaluation of a new attenuated TB vaccine

Based upon the observation that *phoP* is an essential gene for *M. tuberculosis* virulence, we rationally attenuated the tubercle bacillus by inactivating *phoP* (Perez *et al,* Mol Micro 2001). The mutant was shown to be highly attenuated in cellular and animal models. The *phoP* mutant resulted more attenuated than BCG Pasteur in immunocompromised SCID mice and protected guinea pigs and non human primates against tuberculosis infection (Martin *et al* Vaccine 2006, Verreck *et al* PLoS ONE 2009). PhoP has been recently shown to be crucial for intricate virulence networks in *M. tuberculosis* (Gonzalo Asensio *et al* PLoS ONE 2008).

In order to develop a safe and more effective vaccine that could replace BCG, in collaboration with Prof. Brigitte Gicquel at Institut Pasteur Paris, we hve developed a new live vaccine, designated as MTBVAC, through the rational attenuation of a wild-type *M. tuberculosis* strain. MTBVAC is based on two stable independent deletions of two virulence genes *phoP* and *fadD26*; this second additional mutation in *fadD26* eliminates the synthesis of DIM, a family of lipids associated with *M. tuberculosis* virulence (Cox *et al.*, 1999; Camacho *et al*., 1999, Camacho *et al*., 2001). A major difference between MTBVAC and BCG, which is derived from the cattle pathogen *M. bovis*, and *M. bovis* has many deletions in its genome when compared to *M. tuberculosis*, and during the attenuation process BCG lost over a hundred additional genes from its genome. MTBVAC is the first live attenuated candidate vaccine developed fulfilling the Geneva consensus requirements for live mycobacterial vaccines (Kamath *et al* 2005, Walker *et al* 2010).

GMP (Good Manufacturing Practices) manufacturer and industrial partner BIOFABRI has finalised a GMP grade production process for freze dried MTBVAC live vaccine ready for clinical trials. GMP MTBVAC vaccine candidate has demonstrated excellent attenuation, safety and protective efficacy profile conferred by rigorous non-clinical studies in relevant animal models. Our plan of investigation is to progress the live attenuated MTBVAC vaccine candidate to first-in-human clinical evaluation that will be presented by Professor F Spertini.