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Novel live vaccine candidates against airborne *Francisella tularensis*

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Francisella tularensis LVS remains the sole vaccine shown to have efficacy in humans against systemic or airborne challenge with the type A subspecies of the pathogen. In an attempt to produce a better-defined and more efficacious vaccine than LVS, we have been producing targeted deletion mutants of the virulent type A strain, Schu S4. Until recently, we had made deletion mutants that were either at least as attenuated as or as effective as LVS, but not both in a murine intradermal (ID) vaccination and aerosol challenge model. However, deleting the *clpB* gene alone or both the *FTT0918* and *capB* gene has generated mutants that fulfill or surpass both criteria. In BALB/c mice, ID inoculation of LVS generates protective immunity against a subsequent challenge via the same route with $> 10^3$ LD_{50} of Schu S4. However, in our hands, the same vaccination regimen only prolongs life by a couple of days in mice challenged with an aerosol of Schu S4. In contrast, the two new deletion mutants elicited significantly longer survival times ($P < 0.05$) following aerosol challenge. To try and determine the basis for this enhanced survival, we have been comparing various immune responses in mice following immunization with LVS or Schu S4 Δ*FTT0918*Δ*capB* or Schu S4 Δ*clpB* or following immunization and aerosol challenge. Immunoproteomic analysis revealed distinct patterns of serum antibody response, and FACS and multiplex cytokine and chemokine analysis revealed distinct patterns of cell-mediated responses in the lungs, spleen and serum. The implications of these findings for defining mechanisms and correlates of live vaccine-induced protection will be presented along with a brief overview of progress with other vaccine efforts within the tularemia field.
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