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## Early immune responses to the Live vaccine strain and SchuS4 infection in cynomolgus macaques

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**Aim:** The early host response to pulmonary infection with *Francisella tularensis* was characterized in non-human primates.

**Methods:** Cynomolgus macaques received either  $1 \times 10^5$  cfu of the Live vaccine strain (LVS) or 1100 cfu of the SchuS4 strain of *F. tularensis* by pulmonary instillation and the bacterial growth, dissemination, cell recruitment, cytokine responses, and histology were examined 1, 4 and 7 days after infection.

**Results:** No growth of LVS in the lungs was detected post inoculation. LVS was detected in draining lung associated lymph nodes (LALN) on day 1 with an increase in LVS colonies found on days 4 and 7 post inoculation with clearance by day 28. No LVS colonies were detected in blood, spleen, or liver at any time points. In contrast, SchuS4 demonstrated an increase of up to 6 logs within 7 days in the lungs, LALN, spleen, and liver. LVS induced a robust mononuclear infiltrate, consisting of lymphocytes, monocytes, and dendritic cells expressing MHC class II in lungs and LALN. The LVS-induced cytokine profile consisted predominantly of increased levels of chemokines. The cellular infiltrate associated with SchuS4 inoculation was similar qualitatively but was decreased quantitatively as compared to LVS and there were additional increases in TNF $\alpha$  and IL-2. Histopathology comparisons on days 1, 4 and 7 demonstrated that LVS inoculation induced a mild, multifocal, granulomatous bronchiolitis and bronchopneumonia with infiltrates consisting primarily of epithelioid macrophages and lymphocytes. The pathology at identical time points associated with SchuS4 infection demonstrated a moderate to severe, multifocal to coalescing, necrotizing and pyogranulomatous bronchitis, bronchiolitis, and bronchopneumonia.

**Conclusions:** Understanding the basis for the difference in host response to the attenuated LVS strain versus the SchuS4 strain may provide insight into the impact that SchuS4 virulence factors have on the host immune response.

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