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Essential elements of protective immunity to *Francisella*K. L. Elkins¹¹Laboratory of Mycobacterial Diseases and Cellular Immunology, Center for Biologics Evaluation and Research, U.S. FDA, Bethesda, United States

Understanding the fundamental nature of mammalian immune responses to infections with virulent species of *Francisella* is of interest from both basic science and practical applications perspectives. Many types of different innate and adaptive immune responses to *Francisella* have been described through observations of disease and vaccination in humans, as well as studies in various animal models. Despite this, it remains challenging to discriminate between those that are critical to control of infection, those that contribute partially, and those that may only be epiphenomena. Here we focus on studies using parenteral vaccination of mice coupled with *in vivo* manipulations and *in vitro* studies to determine the most critical cell types and mediators, particularly with regard to development predictive correlates of vaccine-induced protection. Innate immune responses leading to production of TNF- α , Interferon- γ , and IL-12 p40, as well as processes requiring the cell-associated molecules MyD88 and CCR2, are critical, but none of these are useful individually in predicting protection. Because T cells are clearly crucial effector cells during adaptive responses, we have evaluated the utility of an *in vitro* co-culture assay that measures the ability of *Francisella*-immune T cells to control the intramacrophage growth of *Francisella* as a functional correlate of protection. T cells were obtained from mice vaccinated with a panel of qualitatively different *Francisella* vaccine candidates that provide strong protection, modest partial protection, and little to no protection. To date, there is excellent agreement between the magnitude and hierarchy of protection provided by this panel of *Francisella* vaccine candidates against *in vivo* LVS challenge, and the magnitude of *in vitro* activity of T cells obtained from vaccinated mice in controlling intramacrophage replication of *Francisella* LVS. Further, studies comparing gene expression between naive T cells and T cells primed by various vaccine candidates have defined a tentative panel of differentially upregulated gene products that track with *in vivo* protection, both quantitatively and qualitatively. Future studies will therefore explore the usefulness of both the functional assay and the panel in predicting survival of challenge with fully virulent *Francisella*, in other animal models, and human vaccination.