RESEARCH ABSTRACT

SWINE HEALTH

Title: Rational design of attenuated foot-and-mouth disease virus strains for development of improved disease countermeasures – **NPB #11-005**

Investigator: Dr Teresa de los Santos

Institution: Plum Island Animal Disease Center, North Atlantic Area, Agricultural Research Service, United States Department of Agriculture, Orient Point, NY, 11957

Date Submitted: June 14th, 2012

Scientific Abstract: Foot-and-mouth disease virus (FMDV) leader proteinase (Lpro) cleaves itself from the viral polyprotein and cleaves the translation initiation factor eIF4G. As a result, host cell translation is inhibited, affecting the host innate immune response. We have demonstrated that Lpro is also associated with degradation of nuclear factor κB (NF-κB), a process that requires Lpro nuclear localization. Additionally, we reported that disruption of a conserved protein domain within the Lpro coding sequence, SAP mutation, prevented Lpro nuclear retention and degradation of NF-κB, resulting in *in vitro* attenuation. Here we report that inoculation of swine with this SAP mutant virus does not cause clinical signs of disease, viremia or virus shedding even when inoculated at doses 100-fold higher than those required to cause disease with wild type (WT) virus. Remarkably, SAP mutant virus inoculated animals developed a strong neutralizing antibody response and were completely protected against challenge with WT FMDV as early as 2 and for at least 21 days post inoculation. Early protection correlated with a distinct pattern in the serum levels of pro-inflammatory cytokines in comparison to animals inoculated with WT FMDV that developed disease. In addition, animals inoculated with the FMDV SAP mutant displayed a memory T cell response that resembled infection with WT virus. Our results suggest that Lpro plays a pivotal role in modulating several pathways of the immune response. Furthermore, manipulation of the Lpro coding region may serve as a viable strategy to derive live attenuated strains with potential for development as effective vaccines against FMD.