RESEARCH ABSTRACT

SWINE HEALTH

Title: Development of a New Generation of Antisense Antiviral Drug against PRRSV – **NPB #06-168**

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Scientific Abstract:
The prevalence of PRRSV infection in swine herds is high and currently no effective strategies are available to control the infection. The current vaccines are unable to control PRRSV, and in some cases, even posed problems due to reversion of the modified live PRRSV vaccine to the pathogenic phenotype. Specific anti-PRRSV drugs are needed to complement other strategies in PRRS prevention and control. In this project, we proposed to continue our exploration of a new generation of molecular antiviral compounds, Phosphorodiamidate Morpholino Oligomer (PMO). PMOs are analogs of short DNA oligonucleotides with modified chemical structures, resulting in highly specific binding to target sequences and stable presence in the host. The PMOs are designed to specifically bind to PRRSV genomic RNA and block PRRSV replication. Two pairs of PMOs were identified to have enhanced suppression of PRRSV replication in cell culture, while individual constituent did not work under the same testing conditions. PMO 5UP1 that is complementary to 5' terminus of PRRSV genome was paired with 4P1 or 7P1 that are complementary to sequence in the translation initiation regions of ORFs 4 and 7, respectively. The PMO combination also inhibited replication of heterologous PRRSV strains in the North American genotype. We also examined in detail PMO-mediated inhibition of PRRSV replication in primary cultures of porcine pulmonary alveolar macrophages (PAM). Treatment of PAM with PMO 5UP2 resulted in protection from PRRSV-induced cell death for at least seven days, and produced no elevation in caspase activity. The virus titer in PAM was reduced by 99% in comparison with controls. In a preliminary test of in piglets, intranasal delivery of PMO 5UP2 reduced microscopic lung lesion that was induced by PRRSV infection. The piglets after PMO treatment had similar average daily weight gain to other control groups, indicating that the PMO compound had no detectable toxicity. These results indicate that the antiviral compounds are potential anti-PRRSV drugs to complement other strategies to control PRRS.