Reference: 04/JE

Project Title: Isolation of broadly neutralising antibodies from porcine reproductive and respiratory syndrome vaccinated pigs to identify conserved epitopes for improved vaccine design.

Supervisors: Dr Jane Edwards and Prof Simon Graham Research group: PRRS Immunology

Project Summary: Porcine reproductive and respiratory syndrome (PRRS) is arguably the most economically important disease of pigs globally. The causative agents are rapidly mutating RNA viruses: PRRS virus 1 (PRRSV-1) which is endemic across Europe, and PRRSV-2 which is prevalent across the Americas and Asia. The rapid evolution of PRRS viruses has meant the circulation of a huge diversity of strains, which poses a major challenge to control through vaccination.

Live attenuated virus vaccines are available commercially and are widely used. Whilst these vaccines can provide protection against closely related strains, they are far less effective against more divergent strains. Consequently, these vaccines are failing to help control the PRRSV panzootic and there is an urgent requirement to explore alternative approaches to vaccine development.

Like other viruses, the PRRSV neutralising antibody response is an important correlate of protection. Transfer of neutralising antibodies from immune pigs to naïve pigs confers complete protection against PRRSV infection, strongly suggesting that vaccine strategies which induce neutralising antibodies would be protective. However, to be effective in the field, these vaccines need to stimulate antibodies capable of broadly neutralising PRRSV. The primary aim of this project is to isolate and characterise broadly neutralising monoclonal antibodies (mAbs) from immune pigs. These mAbs can then be deployed to identify highly conserved targets on PRRSV, which would provide a basis for the development of a more broadly protective vaccine.

Further Details*:* To isolate broadly neutralising mAbs, we aim to take a two-pronged approach; firstly to exploit B lymphocytes cryopreserved from pigs which had been experimentally challenged with diverse PRRSV-1 and -2 strains, that resulted in strong and cross-neutralising antibody response. In parallel to this, we will screen sows from UK pig farms to identify animals with broadly neutralising antibodies.

Using both approaches, we will immortalise B cells using a retroviral vector expressing Bcl-6 and Bcl-xL which serves to prevent terminal differentiation and apoptosis. We will then select B cells based on their ability to bind both PRRSV-1 and -2 and isolate these cells using single cell FACSorting. B cells will then be cultured and the mAbs they secrete screened for PRRSV specificity and neutralisation. Specific mAbs will then be characterised and used to help identify broadly neutralising epitopes that will inform future vaccine development.

References for Suggested Reading:

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- Robinson, S. R., Li, J., Nelson, E. A., Murtaugh, M. P. (2015) Broadly neutralizing antibodies against the rapidly evolving porcine reproductive and respiratory syndrome virus. *Virus Res* 4:203:56-65
- Young J. E., Dvorak C., M., T., Graham S. P., Murtaugh, M.P. (2021) Isolation of Porcine Reproductive and Respiratory Syndrome Virus GP5-Specific, Neutralizing Monoclonal Antibodies from Hyperimmune Sows. *Front Immunol* 12:63849

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