Reference: 01/MT

Project Title: Evaluation of a live attenuated virus vaccine genetically engineered to boost immune responses in piglets

Supervisors: Dr Michelle Thom and Prof Simon Graham **Research group:** PRRS Immunology

Project Summary: Porcine reproductive and respiratory syndrome viruses (PRRSV) are responsible for huge losses in the global pig industry. PRRSV cause reproductive failure, post-weaning respiratory disease and can lead to secondary infections with bacteria, necessitating antibiotics.

The PRRSV exists as two distinct species: PRRSV-1 and PRRSV-2, with both demonstrating a high mutation rate that has resulted in the emergence of highly pathogenic PRRSV-2 strains spreading across Southeast Asia and highly virulent PRRSV-1 strains identified within Europe. Vaccination is an important component of PRRS control and although there are several commercial vaccines available, they do not provide high levels of protection.

To try to protect herds from PRRS, producers have traditionally vaccinated pigs around 3 to 4 weeks of age, when maternally derived antibodies (MDA) are typically low enough not to interfere with the vaccine's ability to trigger the desired immune response. MDA play a short-lived but critical role in protecting piglets against infectious disease in the early stages of life. However, MDA can also impair vaccination by dampening host immune responses, neutralising live attenuated vaccines and inhibiting neonatal B cell responses, thus leaving the immunised piglets vulnerable to pathogens once MDA wanes.

We are investigating ways to overcome MDA interference, enabling earlier and long-lasting immune protection. One possible strategy to boost neonatal immune responses of vaccination is to transiently block natural immune system regulators using immune checkpoint inhibitors (ICIs). The objective of this project is to evaluate whether genetically engineering a live attenuated PRRS vaccine to express peptide-based ICIs will potentiate immune responses of MDA-positive (MDA+) piglets, resulting in enhanced protection.

Further Details: Depending on progress, the successful student may undertake the following in the duration of the research project:

1. The safety, immunogenicity, and efficacy of these recombinant PRRSV vaccines will be assessed by a vaccination trial in MDA+ piglets. The student will play a key role in these studies. This will involve detailed analysis of PRRSV-specific immune responses: both antibody (ELISA and virus neutralisation assays) and T cell responses (IFN-gamma ELISpot assay and flow cytometry), as well as assessing protection by measurement of virus loads (in secretions, blood and in tissues collected post-mortem) by quantitative RT-PCR.
2. In addition, there will be scope and time for the student to take the lead on part of the project. Whereby they would be encouraged to research, design and set up *in vitro* assays to determine the biological activities of these peptide-ICIs on T cells from different livestock species (cattle and chicken).

The successful student will be embedded in the PRRS Immunology Group and will receive support and guidance from the Group Leader Professor Simon Graham, and will work in partnership with the project research scientist Michelle Thom. Support will be also provided by other postdocs and students within the group. This exciting new project is well suited to students with interests in immunology, virology and vaccines.

References for Suggested Reading:

1. Lunney JK, Fang Y, Ladinig A, Chen N, Li Y, Rowland B, Renukaradhya GJ. 2016. Porcine Reproductive and Respiratory Syndrome Virus (PRRSV): Pathogenesis and Interaction with the Immune System. Annu Rev Anim Biosci. 4:129-54.
2. Vu HLX, Pattnaik AK, Osorio FA. Strategies to broaden the cross-protective efficacy of vaccines against porcine reproductive and respiratory syndrome virus. Vet Microbiol. 206:29-34
3. Darvin, P., Toor, S.M., Sasidharan Nair, V. et al. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med 50, 1–11 (2018). https://doi.org/10.1038/s12276-018-0191-1

To Apply:

Please email your CV (no more than two sides of A4) and a covering letter, detailing why you would like to undertake the placement and the knowledge and skills that you will bring to the Institute, to studentship@pirbright.ac.uk.

Closing date to apply: 09.00, 7th February 2022