Ref: 12/MM
Project Title: Role of antibody-mediated opsonisation of FMD virus in FMD vaccine-induced protection

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Project Summary:
Foot-and-mouth disease virus (FMDV) causes an important disease of cloven-hoofed livestock in many countries around the world. Vaccines against FMDV have been developed and the antibody response generated by vaccination is thought to be a crucial determinant of protection from disease by preventing the virus binding to its cognate receptor (virus neutralisation). However, an additional function of antibodies, known as opsonisation, is not measured by traditional assays and is thought to play a role in FMDV protection. Non-neutralising antibodies can "tag" viruses for recognition and processing by the host immune system in order to generate a more effective response. This project will investigate the contribution of opsonising antibodies, in the serum of FMDV vaccinated and infected animals, to the total antibody response.

Details:
Foot-and mouth-disease (FMD) is an economically devastating disease of cloven-hoofed animals with a global distribution. It stunts livestock development in developing countries by limiting access to world markets, and outbreaks in countries normally designated as FMD-free cost billions of pounds in control measures and trade losses (e.g. outbreaks in UK, 2001 and 2007, Japan, 2010, and Korea, 2010 and 2011). The causative agent, FMD virus (FMDV), is a single-stranded positive sense RNA virus belonging to the genus *Aphthovirus* in the family *Picornaviridae*. It has a high mutation rate and exists as seven serotypes (O, A, C, Asia 1, SAT1, SAT2 and SAT3), and numerous subtypes and constantly evolving strains showing a spectrum of antigenic diversity. Vaccination is an important means to control FMD, however is constrained by the lack of cross-protection between serotypes as well as incomplete protection between some subtypes and strains, necessitating constant monitoring to anticipate the need for new vaccine development and the maintenance and selection amongst multiple vaccine strains.

The humoral immune response is thought to be an important component in vaccinal protection to FMDV as there is a strong correlation between antibody titer and protection against virus generalization in cattle challenged at 21 days after vaccination. This holds true whether antibody titers are calculated based on *in vitro* virus neutralization tests (VNT) or binding assays (ELISA). Further, adoptive transfer of immune anti-FMDV serum or mAbs prior to challenge with FMDV can confer protection to mice and guinea pigs. As observed with numerous other viral infections, the precise mechanism of *in vivo* protection remains largely unknown, although it has been speculated that opsonization of free virus may be involved, since protection occurs at dilutions of antibodies below that needed for *in vitro* neutralization. If so, then antibodies that merely bind as well as those that are neutralizing *in vitro* may have a role in protection. Therefore, serological tests using post-vaccinal serum (BVS) can provide very useful information in terms of cross-reactivity of the vaccine.

The amount of anti-capsid antibody present in the BVS correlates well with clinical protection whereas low levels of antibody may or may not be protective. Despite this, there are reports where some animals are protected without detectable level of antibodies and vice versa. These *in vitro* serological tests quantify the ability of BVS to neutralize or bind field strains of FMDV, but this may not accurately reflect what happens *in vivo*. Cellular immunity such as antibody-mediated opsonisation and phagocytosis of the pathogen also play a role *in vivo*. In this project a transformed murine macrophage cell line (RAW264.7) will be used to measure the role played by opsonising antibodies to improve the correlation between *in vitro* cross-reactivity and *in vivo* cross-protection. These cells are not susceptible to FMDV infection unless the virus forms an immune complex in association with an antibody. Successful opsonisation and uptake will be measured in terms of cell death by flow cytometry. This cell line can detect opsonizing antibodies at sensitivity clearly above a serum neutralization titer (10-100 times higher).

These studies will provide the student with well-rounded experience of general virology, bioimaging techniques and data analysis as well as a unique opportunity to work with SAPO4 level pathogens at high containment. The student will be encouraged to participate in wider group lab meetings, student club and seminars.

References for Suggested Reading:

Lannes N et al. (2012). Vet Res. **30**; 43-64.
McCullough, K. C., et al. (1987). Virol **157**(2): 516-525.
McCullough, K. C., et al. (1992). J. Virol **66**(4): 1835-1840.
McCullough, K. C., et al. (1988). Immun **65**(2): 187-191.
Pay, T. W. F. and P. J. Hingley (1992). Vacc **10**(10): 707-713.

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Closing date to apply: 31.01.20