Project: Mapping cross-reactive neutralising epitopes in the conserved N-terminus of foot-and-mouth disease virus capsid protein VP2 (Ref: PIR1)

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Research Group: Picornavirus Molecular Biology

Project Summary:

Foot-and-mouth disease virus (FMDV) causes an economically devastating disease of livestock. The virus evolves rapidly resulting in high levels of variability between virus strains. Current vaccines are often not able to provide protection against these multiple different strains of FMDV and this is a major problem hindering control of the disease. However, not all parts of the virus are variable. Several broadly cross-reactive monoclonal antibodies against the highly conserved N-terminus of capsid protein VP2 (VP2N) have been previously identified; some are neutralising but most are non-neutralising, suggesting that neutralising epitope(s) in VP2N are masked by immunodominant non-neutralising epitopes. This project aims to map the location of epitopes in VP2N that will induce neutralising antibodies against all strains of the virus and explore recombinant approaches for efficiently presenting such epitopes to the immune system. This project will be supervised by Dr Amin Asfor who has 7 years' experience mapping FMDV antigenicity and Dr Toby Tuthill who has a long standing interest in conserved capsid structures as targets for controlling picornaviruses.

Details:

The picornavirus family includes important viruses of animals and humans, e.g. foot-and-mouth disease virus (FMDV), poliovirus and rhinovirus. These viruses are small and simple, comprising a single-stranded RNA genome within a non-enveloped protein capsid. During virus infection, antibodies are generated which recognise the viral capsid. Neutralising antibodies can block viral entry by recognizing epitopes on the capsid required for cell entry.

In contrast, non-neutralizing antibodies often fail to block infection because they recognize epitopes that are not critical for viral entry. Conserved internal components of the capsid (the N terminus of VP4 and the N-terminus of VP1) have been extensively studied in poliovirus and rhinovirus, are transiently exposed at the surface of the virus (a process known as 'breathing') and are irreversibly externalised during entry to become involved in membrane interactions for the delivery of the genome into the cytoplasm. We and others have shown that these conserved capsid components have potential as linear epitopes for the induction of broadly reactive neutralising antibodies. In FMDV, the equivalent processes are less well understood but are thought to involve highly conserved sequences in VP4 and the N-terminus of VP2 (VP2N). This project will:

- Map linear epitopes in VP2N by using a panel of short overlapping peptides to screen for antibody reactivity in infected animal sera by ELISA.
- Discriminate between neutralising and non-neutralising epitopes by affinity purifying antibodies from the sera (using peptide-affinity) and assessing ability of the antibodies to neutralise virus.
- Test antibody cross-reactivity against viruses of multiple serotypes.
- Present peptide epitopes coupled to KLH (or engineered into a hepatitis B core virus-like particle epitope display system) to raise neutralising antisera for testing against viruses *in vitro.*

Training and guidance will be provided by the supervisors and additional members of the group. The student will gain experience of molecular biology, cell culture, immunological assays, and working with viruses at high containment. Over the time of the project they will be expected to increase their independence in the lab, to report on progress in group meetings and attend external scientific meetings.

References for Suggested Reading:

- Tuthill *et al*. Curr Top Microbiol Immunol. 2010; 343: 43–89
- B. Freiberg *et al.* Journal of Virological Methods 2001; 92: 199–205
- Zhao *et al*. BMC Microbiology 2013, 13:287