REF: 01/AS/CW/SB

Project Title: Developing a hand-held test to assess foot and mouth disease virus vaccine integrity

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Research group: Picornavirus molecular biology; Translational science

Project Summary:
Foot and mouth disease (FMD), caused by FMD virus (FMDV), is among the most infectious diseases of cloven hoofed livestock in the world, resulting in severe trade restrictions as well as loss of production. In regions where FMDV is endemic, outbreaks are controlled using vaccination. However, high quality inactivated vaccines are crucial for an effective vaccination campaign. In turn, the quality of an FMDV vaccine is dependent on the quality of the FMDV particles from which it is made.

Along with a molecule of RNA, mature, intact FMDV particles (referred to as 146S) each contain 60 copies of four proteins: VP1-VP4. Whilst immunogenic, 146S capsids are unstable and disassemble at low pH and/or raised temperatures, yielding capsid subunits (pentamers, 12S) comprising only VP1-VP3. Importantly, in contrast to 146S particles, 12S pentamers have greatly reduced immunogenicity. Given the lack of VP4 in 12S pentamers, an assay which is able to detect its presence or absence will provide a quantitative indication of vaccine quality. An antibody named 5B6 has been isolated that targets a conserved epitope on the VP4 protein of every FMDV serotype and strain. This 5B6 antibody therefore provides an ideal candidate reagent for developing assays to assess FMDV vaccine quality, regardless of strain.

Details:
In conjunction with a universal trapping agent, 5B6 has been incorporated into an enzyme-linked immunosorbent assay (ELISA), thus permitting laboratory testing of particle integrity at all stages of vaccine production for any FMDV serotype or strain. However, an exciting prospect is to transfer the assay onto a lateral flow device (LFD), the same technology as that used for a pregnancy test. Importantly, an LFD assay requires no training and will decentralise the assay from well-equipped laboratories to the field, for example on a farm in an endemic country. This allows a vaccine to be checked, prior to use, for any drop in quality between manufacture and point of use, e.g. as a result of cold chain failure. In addition to 5B6, an additional panel of antibodies, which may contain an even better candidate, will be assessed.

This placement will involve the development and evaluation of an LFD assay according to the following steps.

1. Use ELISA to assess which antibody is the best for taking forward into a LFD format. If 5B6 (IgM isotype) proves to be the best antibody, clone into an IgG context.
2. Produce stocks of the antibody and formulate into LFDs. This will be performed by the collaborating company Mologic.
3. Determine assay range, sensitivity and specificity. Parameters such as sample concentration or dilution methods will be explored and the optimal buffer formulation identified.

This project will provide the student with the opportunity to learn and use molecular biology methods whilst contributing to a real-world solution to an enduring problem in FMDV vaccination programmes. Performing this project will be immensely useful to the programme at a wider level. However, its very nature means that this will become a package of work that a student can drive and claim as their own. Lastly, this placement will provide the student with experience of working with pathogenic viruses within a high containment environment.

Reference for Suggested Reading:
Malik N, Kotecha A, Gold S, Asfor A, Ren J, Huiskonen JT, Tuthill TJ, Fry EE, Stuart DI. (2017) Structures of foot and mouth disease virus pentamers: Insight into capsid dissociation and unexpected pentamer reassociation. PLoS Pathog. 13(9):e1006607. doi: 10.1371/journal.ppat.1006607