PhD Project Advertisement

Project title: Ruminating over host-parasite interaction models for fluke driven immune responses.
Project No: FBS2023-63-Wonfor-aq

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Project description:

Rumen fluke (RF), *Calicophoron daubneyi*, are trematode parasites that infect ruminant livestock and given a changing climate, are increasing in prevalence. Heavy infections with immature RF can result in animal morbidity and mortality. Due to the relatively recent emergence of RF infections compared to other more pathogenic gastrointestinal helminths, there is limited knowledge as to how the parasite interacts with the host, especially in terms of the host immune response. It is well known that related pathogenic helminths, such as liver fluke, have the ability to modulate host immune responses to their benefit, allowing longer survival in the host. One important mechanism that has been demonstrated in several parasitic species is the use of extracellular vesicles (EVs), which have the ability to transport parasite-derived cargo molecules, which are bioactive, and cause immunomodulatory changes in the host. Adult RF are known to produce and release EVs (Huson et al., 2018), containing proteins previously identified as immune modulators in related species and also have the ability to modulate bacterial populations within the rumen (Allen et al. 2021). However, the mechanism used by these EVs to modulate the host tissue immune responses is unknown.
In vitro models of animal diseases are desirable to develop an understanding of molecular host parasite interactions within a controlled experimental environment, allowing the reduction, refinement and replacement of animal studies. Cell culture models are commonly used *in vitro*, but do not account for multiple cell types within a tissue. As such, tissue explant models are a useful tool for providing *ex vivo* models. These explant models are also a novel method for helminth infections, yet have not yet been used or developed for helminth research.

To begin to elucidate the role of RF EVs on the host immune response, the present study aims to further establish *new in vitro* models that are relevant to RF predilection sites (ruminant gastrointestinal tract) and utilise established species-specific cell culture models to develop our understanding of RF immunomodulatory roles within the host. This project will complete key work to understand the host immune response to RF, which will be essential to understanding immune responses in co-infections with the more pathogenic liver fluke.

The hypotheses to be tested in this studentship are: 1. EVs produced by adult RF will modulate the host immune response in rumen tissue explants and epithelial cells, as well as an immune specific cell line of bovine macrophages. 2. Specific predicted immune related proteins identified in EVs will produce immunomodulatory responses like that observed in whole EV studies.
To investigate these hypotheses further, the following objectives will be completed:

1) Establish an *in vitro* explant tissue model of the bovine rumen for host-parasite interactions that can be maintained successfully and be stimulated with EVs from adult RF to assess immune responses in the tissue via protein secretion and polyomics (transcriptome and proteome profiling).
2) Verify results from objective 1 in a previously established model of rumen epithelial cells, and assess cell viability and metabolism in response to EV stimulation.
3) Synthesise key immune modulator proteins constitutively expressed by adult RF EVs to test in the rumen tissue explant/epithelial cell model and assess immune responses to better understand mechanisms of action of bioactive molecules within EVs.
4) Assess changes in immune parameters in bovine macrophages stimulated with EVs from adult RF over time, to better understand immediate and longer-term immune responses.

Training opportunities:

The student will be trained in relevant experimental methods for the project, including:

1) Collection and *in vitro* maintenance of helminth parasites, including BSL2 GLP and containment procedures.
2) EV purification/quantitation.
3) Tissue and cell culture.
4) Proteomics.
5) Transcriptomics.
6) Protein synthesis.
7) Confocal and electron microscopy.
8) ELISA

General research training will also be provided, including:

1) Research development/CPD: Generic research training modules will be taken by the student at Aberystwyth alongside the subject specific research development training provided as a part of the project at AU and QUB. Training in bioinformatics, data handling and statistical analysis is also available at both institutes.
2) Science communication: The student will receive supervisory training in academic scientific communication, e.g., publication writing, conference presentation styles. Attendance and presentation at departmental seminars will also be encouraged. Furthermore, they will be encouraged to also engage with stakeholders and wider general public communication through communications with farmers unions and ruminant farmers at University attendance at Agricultural shows.

Supervisors will provide opportunities for industry communication; e.g. Dr Robinson is an advisor on parasite control for Animal Health Ireland and the student may avail of resulting networking opportunities.

Student profile:

Applicants should hold, or expect to obtain, an upper-second class honors degree or higher in biological or animal sciences or related subjects. Applicants with practical experience in cell biology and parasitology are particularly welcome. An interest in animal health and an understanding of the challenges facing livestock health as a part of a sustainable Agri-Food sector are desirable.

AU is a Bilingual Institution which complies with the Welsh Language Standards and is committed to Equal Opportunities. Students are welcome to apply in Welsh or English and any application submitted will be treated equally.

Stipend (Salary):

FoodBioSystems DTP students receive an annual tax free stipend (salary) that is paid in instalments throughout the year. For 2022/23 this will be £17,668 and this will increase slightly each year at rate set by UKRI.

Equality Diversity and Inclusion:

The FoodBioSystems DTP is committed to equality, diversity and inclusion (EDI), to building a doctoral researcher(DR) and staff body that reflects the diversity of society, and to encourage applications from under-represented and disadvantaged groups. Our actions to promote diversity and inclusion are detailed on the FoodBioSystems DTP website.

In accordance with UKRI guidelines, our studentships are offered on a part time basis in addition to full time registration. The minimum registration is 50% FT and the studentship end date will be extended to reflect the part-time registration.

References:

- Allen, N. R., Taylor-Mew, A. R., Wilkinson, T. J., Huws, S., Phillips, H., Morphew, R. M., Brophy, P. M. (2021). Modulation of Rumen Microbes Through Extracellular Vesicle Released by the Rumen Fluke Calicophoron daubneyi. Frontiers in Cellular and Infection Microbiology 11.
- Huson, K. M., Morphew, R. M., Allen, N. R., Hegarty, M. J., Worgan, H. J., Girdwood, S. E., et al. (2018). Polyomic tools for an emerging livestock parasite, the rumen fluke Calicophoron daubneyi; identifying shifts in rumen functionality. Parasites Vectors 11 (1), 617.
- Ji, X., Tong,H., Settlage, R., Yao, W. and Jiang, H. (2021). Establishment of a bovine rumen epithelial cell line. Journal of Animal Science 99(10), 1-9.

For up to date information on funding eligibility, studentship rates and part time registration, please visit the FoodBioSystems website.