

## PhD Project Advertisement

**Project title:** Close encounters of the protein kind: Exploiting protein-protein interactions for liver fluke control.

**Project No:** FBS2024-032-Morphew-aq

**Lead supervisor:** Russ Morphew, Department of Life Sciences, Aberystwyth University

**Email:** rom@aber.ac.uk

**Co-supervisors:**

Aaron Maule, Queen's University Belfast

Karl Hoffmann, Aberystwyth University

Peter Brophy, Aberystwyth

### Project description:

#### Justification

Helminth parasites are responsible for >55% of livestock diseases threatening global food security. Zoonotic fascioliasis, caused by the liver fluke (LF), *Fasciola hepatica*, has a negative impact on livestock production and welfare with extensive losses worldwide. In the absence of vaccines, control of LF is reliant on drugs, particularly triclabendazole which is uniquely effective against juvenile and adult flukes. However, control is failing. Coupled to this is an overreliance which has led to triclabendazole resistance demonstrating a real need to identify novel drugs and alternative control options.

Biological function is regulated via protein complexes which are themselves controlled by protein-protein interactions (PPIs). Modulating the pathways of PPIs, its PPI interactome, represents a highly novel and exciting target for drug intervention. This new drug discovery route has been neglected in *F. hepatica* control despite PPIs being recognised to perform vital functions both within *F. hepatica* and between *F. hepatica* and its, often ruminant, host. Indeed, the successful establishment of infection by *F. hepatica* is partly due to its ability to interact with the host, through PPIs, including through proteins presented to the host as components of extracellular vesicles (EVs) (Morphew and Brophy Group: Davis et al. 2019; Davis et al. 2021). We now have new proteomic approaches for the analysis of global PPI networks. Of note are Cross Linking proteomic (XLMS) approaches and Co-Fractionation Mass Spectrometry (CoFMS). Despite having early success, neither have been explored within *F. hepatica* control with the exception of some preliminary work from within the Morphew group using XLMS.

#### Hypothesis:

Can PPIs of *F. hepatica* (both intra-fluke PPIs and inter-fluke/host PPIs) be mapped using proteomic technologies? If they can, can any highly interacting nodes then be utilised for screening PPI chemical modulators for novel control?

The student will broadly be working in the following areas and objectives.

**Objective 1:** PPI mapping in *F. hepatica*. The student will assess PPIs in *F. hepatica* using two methods. XLMS will be used with the methodology of Wang et al. (2019). The student will also assess Co-Fractionation Mass Spectrometry (CoFMS) according to McWhite et al. (2020) utilising size exclusion chromatography (SEC). Both approaches will generate extensive data on *F. hepatica* PPIs. The student will then utilise network analysis to highlight key interacting partners and identify key PPI nodes.

**Objective 2:** PPIs of EV-Host Interaction. Based on the data generated by the student in Objective 1 the student will then map PPIs of *F. hepatica* EVs with host cells. PPI analysis will utilise XLMS or CoFMS depending on Objective 1 and nodes identified through network analysis.

**Objective 3:** Targeting key nodes with RNAi. The student will then exploiting an *in vitro* culture and gene silencing platform developed by the Maule lab (QUB) to validate PPI nodes as key target.

**Objective 4:** Targeted drug design for PPI node. Finally, the student will employ Computer Aided Drug Discovery (CADD) and *in silico* docking to identify potential compounds to target identified nodes as previously performed by the Hoffmann lab (Padalino et al., 2020).

#### Training opportunities:

The student will gain experience and training in a wide range of molecular and parasitological methods including biochemistry, molecular biology and *in vitro* parasite maintenance. This will also include purification and analysis of extracellular vesicles. In addition, training will be provided in functional genomics (Proteomic technologies, gene silencing and bioinformatics for the analysis of large-scale omic datasets). Furthermore, the student will gain experience in analytical mass spectrometry and biomolecule purification. The student will also spend time with Boehringer Ingelheim to gain valuable insights into Veterinary Health Pharama. The student will also play a central role in communicating project goals and progress with stakeholders (local farmers and farmers unions etc).

#### Student profile:

We are seeking a student who has obtained (or predicted to obtain) an honours degree in a course relevant to the proposal (biochemistry, zoology, microbiology, molecular sciences, animal sciences, veterinary sciences, etc.) with evidence of considerable laboratory or computational experience. Advanced technical/practical training in parasitology, analytical mass spectrometry or omic data analysis would be desirable.

#### Stipend (Salary):

FoodBioSystems DTP students receive an annual tax free stipend (salary) that is paid in instalments throughout the year. For 2023/24 this is £18,622 and it 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:

- Davis CN, Phillips H, Tomes JJ, Swain MT, Wilkinson TJ, Brophy PM, Morphey RM. The importance of extracellular vesicle purification for downstream analysis: A comparison of differential centrifugation and size exclusion chromatography for helminth pathogens. *PLoS Negl Trop Dis*. 2019 Feb 27;13(2):e0007191. doi: 10.1371/journal.pntd.0007191.
- Davis CN, Winters A, Milic I, Devitt A, Cookson A, Brophy PM, Morphey RM. Evidence of sequestration of triclabendazole and associated metabolites by extracellular vesicles of *Fasciola hepatica*. *Sci Rep*. 2020 Aug 10;10(1):13445. doi: 10.1038/s41598-020-69970-4.
- Padalino G, Chalmers IW, Brancale A, Hoffmann KF. Identification of 6-(piperazin-1-yl)-1,3,5-triazine as a chemical scaffold with broad anti-schistosomal activities. *Wellcome Open Res*. 2020 Nov 13;5:169. doi: 10.12688/wellcomeopenres.16069.2.
- Wang H, He M, Willard B, Wu Q. Cross-linking, Immunoprecipitation and Proteomic Analysis to Identify Interacting Proteins in Cultured Cells. *Bio Protoc*. 2019 Jun 5;9(11):e3258. doi: 10.21769/BioProtoc.3258.
- McWhite CD, Papoulas O, Drew K, Cox RM, June V, Dong OX, Kwon T, Wan C, Salmi ML, Roux SJ, Browning KS, Chen ZJ, Ronald PC, Marcotte EM. A Pan-plant Protein Complex Map Reveals Deep Conservation and Novel Assemblies. *Cell*. 2020 Apr 16;181(2):460-474.e14. doi: 10.1016/j.cell.2020.02.049. Epub 2020 Mar 18.

**For up to date information on funding eligibility, studentship rates and part time registration, please visit the [FoodBioSystems website](#).**