PhD Project Advertisement

Project title: ***Protein-protein interactions for control of the ruminant parasite the liver fluke***
Project No: FBS25-68-Morphew-aq

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Project description: Parasitic worms are responsible for >55% of livestock diseases threatening global food security. Infection from the parasitic liver fluke, Fasciola hepatica, has a negative impact on livestock production and welfare. In the absence of vaccines, control is reliant on drugs, particularly triclabendazole which is effective against juvenile and adult worms. However, control is failing, and our overreliance has led to triclabendazole resistance demonstrating the need for alternative drugs.

One option to uncover new drug targets is to explore the interactions of proteins at the cellular level and how they interact with other proteins. These interactions are known as protein-protein interactions, or PPIs. We now know that many biological functions are regulated via protein complexes and PPIs. Therefore, modulating or disrupting a PPI network represents a novel target for developing new drugs.

At present, uncovering PPIs in the liver fluke has been neglected despite the recognition that PPIs are likely to perform vital functions both for the liver fluke (regulating its own process) and between the liver fluke and its host (regulating the host processes to promote survival). Interactions with the host are likely to be facilitated by extracellular vesicles (EVs) released by the liver fluke and thus host-liver fluke EV PPIs represent exciting targets for drug control.

New proteomic approaches for the large-scale analysis of PPIs are now available and have been utilised in many systems. However, none have been explored within any parasitic worm to date.

This project will aim to investigate PPIs of the liver fluke using new proteomic approaches. It will characterise PPIs of the liver fluke and PPIs formed between the liver fluke and the host through EV PPIs.

The successful PhD student will initially map PPIs in the liver fluke using novel proteomic approaches. This will be supported by network theory to identify key PPI nodes that are highly connected and represent high value drug targets. These targets will then be knocked down using RNA interference to assess their impact on the survival of the liver fluke. Highly connected node PPIs, that demonstrate a significant detrimental phenotype following RNA interference, will be subjected to computer Aided Drug Discovery (CADD) and in vitro drug screening to identify potential lead compounds for the next generation of liver fluke drugs. Finally, the student will also identify PPIs of liver fluke EVs interacting with host cells.

Training opportunities: The successful student will receive training in a wide range of classical parasitology methods. This will include the collection, excystment and in vitro maintenance of worms, including BSL2 GLP and containment procedures, and the purification and quantitation of worm EVs. In addition, the student will gain training in molecular methods that will include proteomics and biomolecule purification, RNA interference and target validation, CADD and compound screening, and target localization through confocal and electron microscopy. This project will also develop multidisciplinary skills providing the student with training in mathematical network theory analysis to identify key PPI nodes. This project will provide the student with an excellent insight into industry and big-scale veterinary pharmacology with a short term placement at Boehringer Ingelheim Animal Health UK Limited who will be active participants within this PhD programme.

Project supervision style: The student will be supervised through a series of structured and informal meetings. RM operates an open-door policy and thus will meet with the student weekly on a one to one/face to face basis likely several times each week. In addition, the student will benefit from the monthly RM lab meetings to gain insights into the wider research team. In addition, a monthly online supervisory meeting with all academic supervisors (RM, KH, KK & AM) will be conducted. Every quarter, the online monthly meeting will also allow for the industry partner, BI, to join in to feed into the project. The provision of feedback on completed docum6ents (i.e. lit review) will follow the AU standard of 15 working days. All email correspondence will be answered within the AU standard of 3 working days. The RM group operates a Lab group WhatsApp chat providing often instant support during working hours.

Student profile: We are looking for candidates with a background in biological sciences e.g. biochemistry, bioinformatics, parasitology.

Stipend (Salary): FoodBioSystems DTP students receive an annual tax free stipend (salary) that is paid in instalments throughout the year. For 2024/25 this is £19,237 (£21,237 at Brunel University) and it will increase slightly each year at rate set by UKRI.

Equity Diversity and Inclusion: The FoodBioSystems DTP is committed to equity, 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 and include:

- Offering reasonable adjustments at interview for shortlisted candidates who have disclosed a disability or specific learning difference.
- Guaranteed interview and applicant mentoring schemes for applicants, with UK home fees status, from eligible under-represented ethnic groups.

These are opt-in processes**.**

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.

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