FoodBioSystems DTP - PhD Project Advertisement Text

Project Title: FOODBIOSYSTEMS - Repositioning histone modifying enzyme (HME) inhibitors as next-generation flukicides

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Research Group: FOODBIOSYSTEMS BBSRC DTP
Project ID: FBS2020-02

Application Deadline: 6 March 2020

Project Description:
Justification and motivation - Liver fluke (*Fasciola hepatica*) infection costs the UK livestock industry >£300m/year. The global impact of liver fluke infection across the livestock sector is estimated at over US$3.2b/year. Triclabendazole (TCBZ) remains the main flukicide used to control disease because of its unique activity on all fluke stages within mammals, including early and late stage juveniles. The over reliance on TCBZ for liver fluke control has led to drug resistance locally and globally, undermining the sustainability of livestock production in some regions. In UK, losses at farm level are estimated at £25-30/infected animal; the Animal and Plant Health Agency list liver fluke as the most commonly diagnosed helminth parasite of sheep and cattle in England and Wales. Fasciolosis seriously undermines livestock production and the problem is growing. The threat of further development of TCBZ resistant fluke populations has highlighted the need for the identification of new drugs.

Hypothesis - Informed by studies in *Schistosoma mansoni*, a relative of *F. hepatica*, and our preliminary data from an *F. hepatica* RNA interference (RNAi) study, we hypothesise that histone modifying enzymes (HMEs) regulate liver fluke development. As such, we contend that repositioned HME inhibitors (obtained from the Structural Genomics Consortium, SGC) represent promising new, urgently-needed chemotherapies for a key disease (Fasciolosis) of animal production systems.

Objectives - To investigate how HMEs affect liver fluke development, we outline a series of objectives that are well-supported by capabilities across the co-supervisors' laboratories (AU - Hoffmann, Chalmers; QUB -Maule). Supported by Informatics Unlimited's (IU) involvement in developing liver fluke phenotype/motility models, we propose to:

1. **Characterise all *F. hepatica* HMEs.** Collaborating with bioinformaticians and medicinal chemists, we recently described the full complement of *S. mansoni* HMEs (PMID:30455056). We will employ a similar strategy for *F. hepatica*. This will involve a thorough analysis of the two genome assemblies, a comparative assessment of HME transcript abundance across *F. hepatica* lifecycle stages (RNA-Seq data available at QUB) and reconstructing phylogenetic relationships between fluke species (blood and liver

flukes) and (when possible) their intermediate (snail)/definitive (mammalian) hosts. This analysis will result in the study's first manuscript and prioritisation of drug targets for whole-organism validation.

2. **Improve an existing image analysis model for quantifying liver fluke phenotype and motility metrics.** Working with IU, we have recently implemented a high-content image analysis tool for quantifying NEJ phenotype and motility (presented at the 2018 British Society of Parasitology's Spring meeting). As part of a three-month placement at IU, the student will improve upon this tool and build a more accurate method of scoring juvenile phenotype and motility. These approaches will result in the study's second publication and significantly improve quantification of juvenile phenotype and motility (critical to liver fluke drug discovery).
3. **Validate liver fluke HMEs as next-generation drug targets.** Utilising a collection of 37 HME-targeting epigenetic inhibitors obtained from the SGC, we have recently profiled their anthelmintic activity against *S. mansoni* (PMID:31730617). Continuing to collaborate with the SGC, we will obtain and screen all available epigenetic inhibitors against *F. hepatica* utilising existing methodologies in the AU lab (PMID:25768432), or those developed in Objective 2. Validation of the *F. hepatica* HME targets will be facilitated by RNAi, pioneered in the QUB lab (PMID:25254508). *In vitro* growth, stem cell proliferation (PMID:27622752), transcription (PMID:29649665) and histone modifications (PMID:29782530) will be assessed in drug- and/or RNAi- treated parasites. Findings will underpin a third manuscript and facilitate engagement with the Animal Health Industry as the studentship nears completion.

Significance - New flukicidal drugs will improve animal condition/welfare standards as well as increase milk production and meat quality of higher nutritional value. Critically, in the face of growing TCBZ resistance, this PhD studentship will help develop new flukicides that ensure the sustainability and resilience of global livestock production systems.

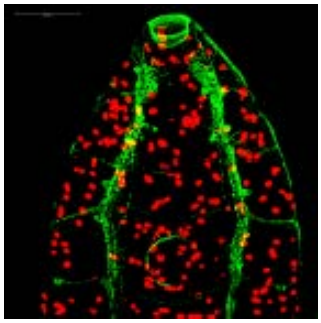

Figure 1. Liver flukes, histone modifying enzymes, stem cells and development. Liver fluke wholemount in situ hybridization (WISH) reveals the broad distribution of replicating neoblasts (red) compared to the restricted localization of fully-differentiated neurons (green). How histone modifying enzymes (HMEs) and their specific inhibitors affect neoblast biology represent a central theme of the proposed PhD project. Image courtesy of Duncan Wells, QUB.

Funding Notes: This project is part of the FoodBioSystems BBSRC Doctoral Training Partnership (DTP), it will be funded subject to a competition to identify the strongest applicants. Due to restrictions on the funding, this studentship is only open to UK students and EU students who have lived in the UK for the past three years.

This project is a CASE studentship with Informatics Unlimited Ltd. Placement at the industrial partner's facilities (Cambridge, UK), for at least three months, will be funded by Informatics Unlimited Ltd.

The FoodBioSystems DTP is a collaboration between the University of Reading, Cranfield University, Queen's University Belfast, Aberystwyth University, Surrey University and Brunel University London. Our vision is to develop the next generation of highly skilled UK Agri-Food bioscientists with expertise spanning the entire food value chain. We have over 60 Associate and Affiliate partners. To find out more about us and the training programme we offer all our postgraduate researchers please visit https://research.reading.ac.uk/foodbiosystems/.

Training opportunities: A significant outcome of this project will be the development of a new image analysis model for quantifying liver fluke motility and phenotype. As such, the student will spend at least three months of the research project embedded within the Industrial Supervisor's facilities (Informatics Unlimited, Ltd., Cambridge) to learn the most cutting-edge techniques/methods in image analysis. In addition to this opportunity, the student will gain invaluable training in molecular, cellular and whole organism biology as well as bioinformatics, bioassay development and working with BSL2 pathogens. Finally, by directly liaising with the Structural Genomics Consortium (SGC) and tangentially interacting with Animal Health companies currently collaborating with the co-supervisors' laboratories, the student will gain experience at the academia/industrial interface.

Student profile: We are seeking a student who has obtained (or predicted to obtain) a 1st class or upper 2nd class degree in a course relevant to the proposal (biochemistry, zoology, molecular sciences, animal sciences, veterinary sciences, etc.) with evidence of considerable laboratory or computational experience. Advanced technical/practical training in parasitology, big data analysis or programming/coding will also be desirable.

References:

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WHATLEY, K. C. L., PADALINO, G., WHITELAND, H., GEYER, K. K., HULME, B. J., CHALMERS, I. W., FORDE-THOMAS, J., FERLA, S., BRANCALE, A. & HOFFMANN, K. F. 2019. The repositioning of epigenetic probes/inhibitors identifies new anti-schistosomal lead compounds and chemotherapeutic targets. PLoS Negl Trop Dis, 13, e0007693.