Endothelin signaling, enteric nervous system and Hirschsprung disease in zebrafish

This project is one of a number that are in competition for funding from the South West Biosciences Doctoral Training Partnership (SWBio DTP) which is a BBSRC-funded PhD training programme in the biosciences, delivered by a consortium comprising the Universities of Bath, Bristol, Cardiff and Exeter, along with the Rothamsted Research Institute. The partnership has a strong track record in advancing knowledge through high quality research and teaching, in collaboration with industry and government.

Studentships are available for entry in September/October 2019.

All SWBio DTP projects will be supervised by an interdisciplinary team of academic staff and follow a structured 4-year PhD model, combining traditional project-focussed studies with a taught first year which includes directed rotation projects.

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Project description

Hirschsprung's disease is a relatively common congenital disease, affecting around 1:5000 live births. The genetic and cellular basis for the condition is still poorly understood, although it is clear that the condition can arise due to a failure of migratory progenitors of the enteric nervous system to populate the bowel completely.

Endothelin (Edn) signalling via the Endothelin family of G-protein coupled receptors (Ednr) plays a major role in this migration, likely due to misregulation of the balance between progenitor cell proliferation and differentiation. In both human patients and mice with mutations in endothelin signalling pathway components, Hirschsprung's disease if often coupled to pigmentation anomalies (Waardenburg syndrome). In zebrafish, EdnrBa mutants show adult pigment pattern changes, and we have recently shown a role for EdnrAa signalling in maintaining adult pigment stem cell quiescence (Camargo-Sosa et al., BiorXiv https://doi.org/10.1101/308221) but the enteric nervous system has not been examined. The zebrafish offers numerous advantages for study of developmental defects; consequently, determination of the role of endothelin signalling in enteric nervous system development in zebrafish is an exciting avenue for research.

In this project, we will exploit a new set of endothelin ligand (Edn1, Edn2a, Edn2b, Edn3) and receptor (EdnrAa, EdnrAb, EdnrBa, EdnrBb) mutants to evaluate their individual and combined (redundant) roles in enteric nervous system development. Current data indicates that Edn function in fish enteric nervous system development is functionally redundant. Thus, in this project we will use CRISPR-Cas9 mutagenesis to identify knockout mutants for a fourth ligand, Edn4, allowing comprehensive assessment of the Edn pathway components. In addition, we will use a recently published high efficiency CRISPR-Cas9 approach to assess the combinatorial roles of these genes in injected wild-type embryos ('crispants'; Wu et al., 2018, Dev Cell 46, 112).

Further analysis of progenitor cell biology in these mutants will provide quantitative phenotypic data. These data will be used to derive mathematical models allowing the assessment of the effects of disrupted progenitor behaviour on progenitor numbers and ultimately on mutant phenotypes. By

comparing the results of these quantitative models to experimental findings we will verify or falsify experimentally suggested hypotheses on the effects endothelins. Ultimately this will allow us to develop a quantitative model of Hirschsprung's disease capable of making experimentally testable predictions.

At the end of this PhD the student will have a broad range of highly transferable experimental and modelling skills.

Funding

Studentships provide funding for a stipend at the standard UKRI rate (currently £14,777 per annum, 2018/19 rate), research and training costs and UK/EU tuition fees for 4 years.

UK and EU applicants who have been residing in the UK since September 2016 will be eligible for a full award; a limited number of studentships may be available to EU applicants who do not meet the residency requirement. Applicants who are classed as Overseas for tuition fee purposes are not eligible for funding.

Applications

Applicants must have obtained, or be about to obtain, a First or Upper Second Class UK Honours degree, or the equivalent qualifications gained outside the UK, in an appropriate area of science or technology.

Applications should be submitted on the University of Bath's online application form for a PhD in Biosciences. Please ensure that you quote the supervisor's name and project title in the 'Your research interests' section. You may apply for more than one project if you wish but you should submit a separate personal statement relevant to each one.

The deadline for the receipt of applications is Monday 3 December 2018.