## Endothelin signaling and neural crest development 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). The DTP offers an interdisciplinary research training programme delivered by a consortium comprising the Universities of Bath, Bristol and Exeter, Cardiff University and Rothamsted Research, alongside six regional associate partners: Marine Biological Association, Plymouth Marine Laboratory, Swansea University, UCB Pharma, University of the West of England and SETsquared Bristol. 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 October 2021.

All SWBio DTP projects will follow a structured 4-year PhD model, combining traditional project-focussed studies with a taught first year which includes directed rotation projects.

Lead supervisor: Prof Robert Kelsh, Department of Biology & Biochemistry
University of Bath, email bssrnk@bath.ac.uk

Co-supervisor: Prof Adele Murrell, Department of Biology & Biochemistry, University of Bath

### Project description

Endothelin signalling is best known for its role in physiological regulation of vertebrate blood pressure, but endothelins are also important in development. Endothelin ligands (Edns; 3 in mammals, 5 in zebrafish) bind to the Endothelin Receptor family of G-protein coupled receptors (Ednrs; 2 in mammals; 4 in zebrafish), thereby triggering intracellular signalling cascades. In mammals, mutants in Edn3 and EdnrB show similar phenotypes affecting two aspects of neural crest development. These mutants show large white patches in the coat, and have Hirschsprung's disease (a common congenital disease, caused by decreased numbers of enteric neurons). It is thought that these defects likely result from misregulation of the balance between progenitor cell proliferation and differentiation.

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 APSC) quiescence (Camargo-Sosa et al., 2019, PLoS Genetics, e1007941). However, the molecular mechanisms controlling APSCs, enteric nervous system progenitors, and other neural crest stem cells (NCSCs) have not been examined. The zebrafish offers numerous advantages for study of developmental defects; consequently, determination of the role of endothelin signalling in NCSC 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, Edn4) and receptor (EdnrAa, EdnrAb, EdnrBa, EdnrBb) mutants to evaluate their individual and combined (redundant) roles in NCSC development, focusing on enteric nervous system (see McCallum et al. (2020) eLife 9, e56086) and APSCs. Current data indicates that most of these mutants are adult viable as homozygotes, and thus suggests that Edn function in development is at least partially functionally redundant. Our initial aims will be to define the Endothelin signalling components regulating adult pigment stem cell biology and enteric nervous system development. Subsequently, the student will develop and test models for the molecular basis for one or more of these aspects of NSCS biology.

*Continued on next page…*

Biotechnology and Biological Sciences Research Council

The successful student will benefit from a supportive lab and departmental environment, joining a team of experienced zebrafish researchers. During this project the student can expect to develop their skills in various key zebrafish methodologies, including whole-mount in situ hybridisation, RNAscope, FACS purification of transgenically-labelled neural crest cells, RNA-seq and CRISPR/Cas9 mutagenesis. Nurtured within the DTP, they will combine these specific skills with a wide-range of high level generic skills as they grow into an independent researcher.

## References


1) McCallum, S., Obata, Y., Fourli, E., Boeing, S., Peddie, C.J., Xu, Q., Horswell, S., **Kelsh, R.,** Collinson, L., Wilkinson, D.W., Pin, C., Pachnis, V., Heanue, T.A. (2020) *Enteric glia as a source of neural progenitors in adult zebrafish* **eLife 9**, e56086. (DOI: 10.7554/eLife.56086)

2) **Camargo-Sosa, K., Colanesi, S., Mueller, J.**, Schulte-Mercker, S., Howe, K., Caccamo, M., Stemple, D., Patton, E.E. and **Kelsh, R.N..** (2019) Endothelin receptor Aa regulates proliferation and differentiation of Erb-dependent pigment progenitors in zebrafish. **PLoS Genetics 15**: e1007941.


## 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.

Informal enquiries are welcomed and should be addressed to the lead supervisor.

Enquiries about the application process should be addressed to doctoraladmissions@bath.ac.uk.

Formal 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.

If you are an EU/EEA/Swiss national with settled or pre-settled status in the UK under the EU Settlement Scheme, please upload documentary evidence with your application.

More information about applying for a PhD at Bath may be found on our website.

The deadline for the receipt of applications is **Monday 7 December 2020 (23:59 GMT).**