**University of Leicester**

**BBSRC MIBTP Studentship Project 2024-5 entry.**

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| **Project Reference** |  |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | Understanding the role of pigmentation in retinal and vision development  |
| **Project Summary**  |
| Establishing structure-function correlations in vision development  The aim of this project is to develop methods to study the relationship between pigmentation and vision development in humans and zebrafish.  Recently, in a multicentre collaboration (12 centres across 9 countries), we have shown the global burden of arrested retinal development and its impact on visual acuity.1 Many genes implicated are those involved in the melanin biosynthesis pathway. Thus understanding how melanin and pigmentation influences normal retinal development is important and has implications across the fields of neuroscience, genetics, developmental biology and clinical medicine.  Retinal development is a dynamic process that begins *in utero* and continues postnatally up to the age of 13 years. Within the retina, a highly specialised structure called the fovea is responsible for our fine visual acuity (VA). The development of the fovea is characterised by three developmental events namely centrifugal displacement of the inner retinal layers, centripetal migration of cone photoreceptors and cone photoreceptor specialisation.2 This ensures that there is tight cone packing and the cone mosaic responsible for 6/6 or 20/20 vision. Zebrafish are the best choice of model organism to study vision development due to multiple factors. Zebrafish retinal anatomy, development and physiological characteristics are similar to humans. By 72 hours post-fertilisation (hpf) retinal morphology and function is robust like adults and testable using visual behaviour assays. Moreover, the retinal structure has an area of specialisation (area temporalis),3 which is cone rich and with cone density close to human fovea. Using an optokinetic assay and altering the spatial frequency of sinusoidal gratings (stimuli) we can derive visual acuity. Similarly using electrophysiological techniques we can establish functional characteristics of the retinal cells and their role in vision. A team of interdisciplinary researchers based at the Ulverscroft Eye Unit (UEU) and Department of Genetics will support the student. The UEU currently has 15 researchers, which includes senior research fellows, post-docs, PhD and masters’ students in addition to tenured academic staff members.  In this project, we will use CRISPR-Cas9 based techniques to modify genes involved in the melanin biosynthesis pathway and correlate this to retinal structure, and function in zebrafish. In Leicester, we have access to a large cohort of healthy individuals with genotype and linked health data (n=10,000) that can be interrogated to identify subpopulations with specific genotypes of interest. By recruiting and performing high-resolution retinal scans, we will correlate genotype to structure and function. This targeted approach will provide a fundamental understanding on the mechanisms of normal vision development and normal variations to structure and function.  This project will provide methodology development and training in the following areas: 1) visual behaviour assays in zebrafish, 2) CRISPR-Cas9 techniques, 3) single-cell electrophysiology assays, 4) interrogation of large datasets and 5) retinal phenotyping in humans. Based on the student’s interest we can tailor the project and techniques to be lab or human phenotyping focussed.  Techniques that will be undertaken during the projectThe student will gain a deep understanding and experience in a range of lab based and human phenotyping techniques. Dependent on student preference the project can be tailored to be more lab or human phenotyping focussed. Molecular biology techniques such as CRISPR-Cas9 approaches to genetic engineering and gene expression studies (qPCR, in situ). As part of the CRISPR-Cas tools used they will get comprehensive training in analysing databases and identifying targets and appropriate guides. Performing microinjection and zebrafish husbandry. They will also acquire skills in carrying out visual behavioural assays and histological characterisation. The student will utilise the electron microscopy facility (including TEM and SEM) to characterise retinal structure and its relationship to function (behaviour and electrophysiology). The McDearmid lab will provide electrophysiology training with access to latest equipment for single cell recordings.  For the human studies, they will have training in analysing large datasets to identify genes and populations of interest. The student will also get training in retinal phenotyping techniques such as optical coherence tomography. We will provide extensive training in analytical techniques for both image and video-based techniques to derive meaningful data for subsequent statistical analysis. |
| **References** |
| 1. Kuht HJ et al. Genotypic and Phenotypic Spectrum of Foveal Hypoplasia: A Multicenter Study. Ophthalmology. 2022 Jun;129(6):708-718.
2. Thomas MG et al. Normal and abnormal foveal development. Br J Ophthalmol. 2020 Nov 4:bjophthalmol-2020-316348.
3. Yoshimatsu T, et al. Fovea-like Photoreceptor Specializations Underlie Single
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**To apply please refer to**

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