**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | The evolution of serotonergic neurons |
| **Project Summary**  |
| Serotonin (5-HT) levels play fundamental roles in the correct functioning of the human brain 1–3. 5-HT is produced by specialized serotonergic neurons (SNs), and their dysfunction is associated with many psychotic disorders 2–4. While fundamental for human biology, the evolutionary history of SNs is unclear: when did they evolve and are the SNs found in animals (from fly/worm to humans) homologous or analogous? Recent developments in single-cell biology 5 and analytical tools 6 to investigate the relationship between cell types offers a unique opportunity to clarify the origin and diversification of SNs. This project will address these outstanding questions by integrating comparative genomics with computational and molecular biology.  **Objectives** The overall goal of this proposal is to understand the origin and evolution of SNs.   **Methodology** This multidisciplinary project makes use of state-of-the-art techniques in molecular biology, novel computational methods, and classical genetics. In particular, the candidate will: 1. Perform mass spectrometry on non-bilaterians metazoans, i.e., sponges, ctenophores, cnidarians and placozoa, to evaluate the presence of serotonin. Given our previous work on the distribution of the enzymatic machinery7, we hypothesize that serotonin and SNs are only present in the Bilateria. Alternatively, if serotonin is detected, non-bilaterian metazoans will use different enzymes for its production.
2. Multiomics (routinely used in the laboratory) will be employed to evaluate the mRNA expression and chromatin accessibility at the single-cell level on human pluripotent stem cell (hPSC)8 derived SNs and those obtained from *Drosophila* brains. SCENIC9 will be used to identify the gene regulatory network (GRN) controlling the specification of SNs in both species. These results will identify transcription factors (TFs) expressed in SNs in two distantly related bilaterian species.
3. Finally, we will test the common ancestry of SNs. Using existing single-cell data and computation pipelines, SNs will be identified in other species (e.g., mice, sea urchins and worms) and examined for the homology of TFs. If in different species SNs express a similar combination of homologous TFs,  this will imply common ancestry6.

This project will equip the candidate with a unique combination of cutting-edge expertise in experimental and computational biology, and the data analyses can be transferred to large, diverse sets of biological problems. The PhD student will join a large and successful Neurogenetics research grouping that includes 8 PIs, 14 PhDs students and 9 PDRAs working on different aspects of neurobiology (from electrophysiology and molecular neurogenetics to computational genomics). This position offers ample opportunity for training and collaboration with the U.K. and European laboratories. Finally, this project will also provide the opportunity to publish in international 4-star general journals, which are regularly generated by the Neurogenetics group. Techniques that will be undertaken during the project:* *Drosophila* genetics and husbandry
* Single-cell RNA sequencing
* ATAC-sequencing
* Bioinformatics analyses
* Immunohistochemistry
* Confocal.

These diverse sets of skills ranging from human stem cells to microscopy and bioinformatic analysis, will provide the student with robust training highly valued in academia and industry. BBSRC Strategic Research Priority: Understanding the Rules of Life - Neuroscience and behaviour, Stem Cells, Systems Biology |
| **References** |
| **1** Azmitia, E. C. in *Handbook of Behavioral Neuroscience* (eds. Müller, C. P. & Jacobs, B. L.) 21, 3–22 (Elsevier, 2010) **2** Deneris, E. S. *et al.* *Nat Neurosci* 15, 519–527 (2012) **3** Geyer, M. A. *et al.* *Trends in Pharmacological Sciences* 29, 445–453 (2008) **4** Lucki, I. *J Clin Psychiatry* 57 Suppl 6, 5–10 (1996) **5** Tanay, A. *et al.* *Nature* 541, 331–338 (2017) **6** Arendt, D. *et al.* *Nature Reviews Genetics* 17, 744–757 (2016) **7** Goulty, M. *et al.* 2022.08.01.501419 (2022) **8** Lu, J. *et al.* *Nat Biotechnol* 34, 89–94 (2016) **9** Van de Sande, B. *et al.* *Nat Protoc* 15, 2247–2276 (2020)  |