

Project Title

From genes to movement: the role of microRNA regulation during the development of motor circuitry in flies and fish

Collaborating Laboratories

Alonso Lab, University of Sussex (<http://www.sussex.ac.uk/lifesci/alonsolab/>)

Miller Lab, HKUST (<http://calcium-aequorin.ust.hk/index.html>)

One-sentence summary: We investigate the molecular mechanisms that underlie the origins of movement in two modern genetically-tractable systems, *Drosophila* and zebrafish.

Introduction: Observations in invertebrates and vertebrates (including humans) demonstrate that the nervous system becomes active before the formation of the organism is complete. In *Drosophila*, for instance, embryonic motor output is first very poorly organised but coordinated “crawling-like” behaviour in the form of peristaltic waves gradually emerges over subsequent phases of embryonic development. Recent work shows that such early activity in the embryo is indeed required for normal development of motor circuitry but the molecular cellular mechanisms underlying the emergence of coordinated movement remain unknown. This project investigates this open question in invertebrates and vertebrates. The richness of behavioural patterns, imaging accessibility, genetic and cell labelling tools, combined with the simplicity of the larval brain and motor neuron networks make *Drosophila* and zebrafish ideal systems for this project.

Work that led to this application: The cellular components underlying behaviour are in one way or another affected by the activity of genes [Benzer (1967) *PNAS*]. Through meticulous analysis of individual gene mutations and their effects on behaviour, it became possible to identify several genes linked to specific behaviours. Indeed, a recent high-throughput behavioural genetic screen conducted in the Alonso lab at the University of Sussex led to the identification of several genes with pervasive effects on early *Drosophila* larval movement [Picao-Osorio, et al. 2015 *Science*; Picao-Osorio et al. 2017 *Genetics*]. These genes encode small non-coding RNAs termed *microRNAs* (miRNAs) that when mutated lead to the acceleration, deceleration or asymmetric generation of peristaltic waves in young first instar *Drosophila* larvae [O’Garro-Priddie, et al. (Alonso Lab) – in preparation]. Interestingly, several of these ‘motor-miRNAs’ are evolutionarily conserved between *Drosophila* and zebrafish and are expressed during zebrafish embryogenesis/larval stages suggesting the hypothesis that they may play similar roles in the development of movement in the fish.

The complementary nature of this collaborative work: This is a new and exciting collaboration between two laboratories at Sussex (Alonso) and HKUST (Miller). The project is based on: (i) recent findings in the Alonso Lab showing that specific microRNAs can affect early larval movement in *Drosophila* [Picao-Osorio et al 2015, *Science*; Picao-Osorio, et al. 2017 *Genetics*; O’Garro-Priddie, et al. (Alonso Lab) – in preparation]; (ii) the fact that several of these “motor-miRNAs” are evolutionarily conserved between flies and fish, and they are actively expressed during the embryonic and larval development of zebrafish; (iii) the strong track record of the Miller lab in the investigation of the generation of neural activity and early motility during zebrafish development [Webb et al., 2005; Cheung et al., 2011; Kellu et al., 2015, 2017a, 2017b]; and (iv) recent discoveries in the Miller lab regarding the use of molecular beacons in zebrafish with the dual purpose of mapping miRNA expression (in fixed samples) and blocking miRNA function (in live specimens) [Li et al., 2017]. We are therefore in an excellent position to develop the work very successfully within the remit of a PhD studentship and train the student in advanced genetic and microscopy techniques to study the molecular basis of behaviour in two flagship genetically-tractable systems within the invertebrates (*Drosophila*) and vertebrates (zebrafish). The latter were introduced as a research model at HKUST in the mid-1990s and are now firmly established as the premier model system used by a number of research groups. A number of gene-editing techniques along with state-of-the-art imaging platforms that take advantage of the genetic tractability and optical clarity of zebrafish embryos and larvae, respectively, have been established at HKUST. When added to the *Drosophila* expertise at Sussex, this will enable a potential joint student the opportunity to acquire in-depth training in the use and potential of these two model systems.

Student’s timeline at Sussex and HKUST

The student will start their work in the Alonso Lab at Sussex and then go to Hong Kong. Sussex Neuroscience conforms a world-leading multidisciplinary community for research in neurobiology ranked among the top-10 Neuroscience research units in the UK in the latest national evaluation (REF). The Miller lab at HKUST is part of a State Key Laboratory (SKL) of Molecular Neuroscience, established by the Ministry of Science and Technology of China. The HKUST SKL is directed by Prof. Nancy Ip, and is associated with a partner SKL in Shanghai. While at HKUST the student will participate in SKL events and interact with other members of the SKL in Hong Kong and Shanghai. The setting should therefore provide an excellent and highly stimulating research environment to develop a PhD project of the highest international standards.

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