Project Details	
Project Code	MRC22NMHCa Waller-Evans
Title	Developing zebrafish models of drug-induced seizures and childhood neurodegenerative epilepsies for use in drug development.
Research Theme	Neuroscience & Mental Health
Summary	Epileptic seizures can be caused by medications or genetic changes. This project will characterise seizure activity in zebrafish to identify seizure-causing drugs, and to specific seizure phenotypes in childhood epilepsy models to create a platform for drug discovery. The developmental basis for seizures in these epilepsies, and effects of drugs on neural connectivity, will be investigated to understand disease mechanisms and identify novel therapeutic targets.
Description	Seizures are the most common neurological adverse event encountered during drug development. Seizure liability testing is not carried out routinely as the tests are invasive, harmful, technically challenging and difficult to interpret. A simple, robust, seizure liability assay would detect compounds that cause seizures at an earlier stage during drug development, which could then be removed from the drug discovery pipeline, facilitating the development of more suitable compounds. Significant effort has been invested in developing high throughput seizure assays in zebrafish larvae using automated analysis of swimming behaviour. These assays use 7 day old larvae, which are protected under the Animals (Scientific Procedures) Act. This PhD will determine to what extent younger, unprotected, larvae can be used, which will benefit animal welfare (younger larvae are not aware enough to suffer as a result of these tests). In addition will use the cln3 and kif1a genetic models (see below) with an increased predisposition for seizures to identify convulsant/proconvulsant compounds. Our initial experiments found identical responses in 4 day old larvae, where all brain components, including neurotransmitter receptor expression and a mature blood-brain barrier are present. This project will determine the extent to which these younger larvae can predict which drugs cause seizures, using behavioural analysis, gene expression and neuronal activity, and examine reasons for any failures to detect seizure-inducing compounds using knock-down/overexpression of neurotransmitter receptor genes and assessment of neuronal connectivity. The seizure-like activities defined in developing a drug-induced seizure model will be used to identify behavioural abnormalities in zebrafish models of two genetic neurological childhood disorders characterised by visual loss and epilepsy - CLN3 disease and KIF1a-associated neurological disorder. Robust behavioural or gene expression abnormalities will be used to conduct drug screens to identify potential disease-modifying therapies for these disorders, neither of which has any available treatment. To better understand the mechanisms leading to seizures in these disorders, we will investigate whether differences in neuronal connectivity underlie differences in seizure induction, through imaging brain-wide spontaneous neuronal activity and elucidating the neurotransmitter phenotypes of affected neuronal networks. To elucidate the mechanisms behind visual loss, we will investigate how neuronal differentiation, axonal growth, guidance and synapse formation are affected in the retina, particularly focusing on retinal

	ganglion cells. We will also investigate how functional connectivity is affected by imaging the activity of their post-synaptic target cells. Finally, using cell and tissue grafting techniques, we will be able to demonstrate whether the function of the cln3/kif1a protein lies within these long axon-bearing neurons or their post-synaptic targets. This project will develop the first humane whole-organism seizure assay, uncover novel neurodevelopmental defects underlying childhood epilepsy and visual loss, and identify new potential therapies for devastating childhood neurodegenerative epilepsies. The student will gain experience in drug discovery, developmental biology, and functional neuroscience. Techniques will include whole-organism gene knockdown, behavioural analysis, EEG recordings, neuronal activity recordings, whole-organism neuronal imaging, tissue grafting, gene expression analysis by in situ hybridisation and qPCR, and whole-mount immunohistochemistry. The project will utilise state-of-the-art facilities including automated zebrafish behavioural analysis, high-content fluorescence microscopy, lightsheet microscopy and super-resolution confocal microscopy. Applicants for this PhD post with experience and/or a degree in biology or neuroscience are encouraged.
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