Project Details	
Project Code	NMH27Ca Syed
Title	Mapping Cerebellar Network Dysfunction in Episodic Ataxia Using Human Organoids
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	This project investigates how mutations in the KCNA1 gene cause Episodic Ataxia Type 1 (EA1), a rare neurological disorder characterised by impaired motor coordination. Using patient-derived induced pluripotent stem cells (iPSCs), you will generate three-dimensional human cerebellar organoids to model early brain development and disease mechanisms. The research aims to determine how KCNA1 mutations disrupt neuronal differentiation, synaptic connectivity, and neural network function. Working within a multidisciplinary team specialising in advanced stem cell models of neurological disease, you will receive training in iPSC differentiation, organoid culture, and high-resolution bioimaging while contributing to the development of future therapeutic strategies.
Description	Introduction & Clinical Context: The cerebellum coordinates motor control, balance, and learning. Its dysfunction drives severe early-onset movement disorders, including ataxia, dystonia, and tremors. While genetic profiling has improved diagnosis, treatment remains restricted to symptom management. Progress is halted by an incomplete understanding of how mutations disrupt human brain development and neural network wiring. Because animal models fail to replicate human-specific cerebellar architecture, relevant human experimental systems are urgently needed to uncover underlying disease mechanisms. The Challenge of Episodic Ataxia Type 1 (EA1): This project focuses on Episodic Ataxia Type 1 (EA1), a rare movement disorder caused by mutations in the KCNA1 gene, which encodes the Kv1.1 voltage-gated potassium channel. Kv1.1 channels regulate neuronal excitability and the precise timing of electrical signals. EA1 patients suffer from childhood-onset attacks of incoordination, balance loss, and muscle twitching. Crucially, EA1 exhibits extreme clinical heterogeneity; individuals with identical mutations—even within the same family—display widely differing symptom severities. This divergence suggests that complex, secondary neurodevelopmental and circuit-level factors drive disease progression beyond the initial channel defect. Central Hypothesis & Model System: The central hypothesis is that KCNA1 mutations disrupt the development and maturation of inhibitory cerebellar microcircuits, causing a chronic imbalance between excitation and inhibition, abnormal neuronal synchrony, and loss of motor control.To investigate this without the limitations of animal models, the project utilizes patient-derived induced pluripotent stem cells (iPSCs) to generate 3D human cerebellar organoids. These "mini-brains" self-organize to produce human Purkinje neurons, granule cells, and inhibitory interneurons that form active synapses and generate spontaneous network activity, offering an unprecedented window into human neurodevelopment.

	Research Objectives: Define Developmental & Circuit Pathology: The student will map cell-type composition and growth trajectories in KCNA1-mutant organoids using high-resolution confocal imaging and single-cell profiling. Quantify Network Dysfunction: Using multi-electrode arrays (MEAs) and live-cell calcium imaging, the student will track real-time electrical communication, population synchrony, and synaptic stability. This will be paired with quantitative proteomics to pinpoint dysregulated molecular pathways. Evaluate Targeted Therapies: The project will utilize the organoids as a precision medicine drug-screening platform. The student will test clinically approved drugs (e.g., carbamazepine) alongside novel KCNA1-modulating molecules to identify strategies that rescue network stability. Training & Environment: The student will receive elite, multi-disciplinary training spanning stem cell culture, organoid engineering, advanced electrophysiology, proteomics, and translational drug discovery. Embedded within a highly collaborative network of clinicians and neuroscientists, this project will uncover the fundamental mechanisms of EA1 and pioneer new therapeutic models for complex movement disorders.
Can be completed part time?	No
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