Project Details	
Project Code	MRCNMH26Ex Flynn
Title	Architects of the Genome: Using genomic technologies to elucidate the role of CTCF in neurodevelopmental disorders
Research Theme	NMH
Project Type	The project is primarily wet-lab based, with a dry-lab component in Years 2 and 3.
Summary	Genetic variants in the CTCF gene, which encodes a protein that organizes DNA, cause neurodevelopmental disorders including intellectual disability and autism. However, the mechanisms responsible are not well understood. This project will use human stem cell models to investigate how CTCF variants disrupt DNA organization controls brain development. You will examine whether (i) binding of CTCF to DNA, (ii) chromatin structure and function and (iii) neural differentiation and brain organoid development are affected. You will also explore approaches to rescue the developmental defects. The student will gain valuable training in stem cell culture, genomics, and bioinformatic analyses of large datasets.
Description	CTCF (CCCTC-binding factor) is a master regulator of 3D genome structure, orchestrating chromatin loops and topologically associating domains (TADs) that are essential for proper gene expression. Pathogenic genetic variants in CTCF have been causally linked to intellectual disability, autism spectrum disorders, and other neurodevelopmental conditions. Despite this established clinical association, the molecular mechanisms by which CTCF variants disrupt brain development remain poorly understood, limiting our ability to develop targeted therapeutic interventions. During brain development, precise enhancer–promoter communication is required to regulate long neural genes and transcriptional programs critical for cell fate determination. CTCF plays a central role in organising regulatory domains that control these interactions. However, important questions remain regarding how CTCF dosage affects chromatin in neurodevelopmental disorders, and how to therapeutically reverse the effects. Recent evidence suggests that CTCF binding is influenced by non-canonical DNA structures such as R-loops and G-quadruplex (G4) DNA, which are abundant at gene regulatory elements. These structures interact with CTCF at key genomic domains, yet their role in human neurons and relevance to disease remains poorly understood. Project Aims Year 1 The student will be trained in iPSC culture, neural differentiation, and genome editing techniques. We will generate isogenic human induced pluripotent stem cells (iPSC) lines carrying heterozygous loss-of-function variants in CTCF using CRISPR-Cas9 genome editing. We will derive brain cell types including neural progenitor cells, neurons, and brain organoid from CRISPR-edited and control iPSCs, and begin profiling chromatin changes (e.g. using CUT&Tag for CTCF, histone modifications such as H3K27ac, and chromatin accessibility). Year 2

	The student will assess the downstream effects of CTCF haploinsufficiency using 3D genome mapping (Hi-C or Viewpoint Hi-C on Accessible Regulatory DNA) and RNA-seq to measure changes in genome topology and gene expression. Integrative bioinformatics analysis will be used to identify altered chromatin interactions, enhancer–promoter miscommunication, and gene regulatory disruptions that result from CTCF variants. Year 3 An objective of Year 3 is to identify chromatin features that could be targeted to reverse the molecular effects of CTCF haploinsufficiency. One focus may be on R-loop and G4 DNA structures, which may influence CTCF binding and chromatin looping at regulatory domains in neurons. The student may decide to map G4s and R-loop structures across the genome to assess their distribution and function in wild-type and mutant neurons. These experiments will test the hypothesis that DNA secondary structures contribute to CTCF-mediated genome organization and are perturbed in disease. The student will be encouraged to develop a specific research question that interests them and devise and execute the experiments to address it independently. To support this, the supervisors will provide complementary expertise in functional genomics, stem cell and neuroscience approaches providing the student with an optimal environment to develop as an independent researcher. Depending on their interests, this may include: - targeted epigenome editing, -small molecule modulators of chromatin architecture, -profiling human brain tissue. The student will receive valuable training across stem cell biology, epigenomics, genome editing, and data science, preparing them for a future career in functional genomics and neuroscience. They will also have opportunities to present and discuss their work with leaders in the field at international conferences. Overall, this project will reveal important insights into neurodevelopment and provide the student with the freedom to develop into an independent scientist.
Supervisory Team	
Lead Supervisor	
Name	Dr Sean Flynn
Affiliation	Exeter
College/Faculty	Faculty of Health & Life Sciences
Department/School	Clinical and Biomedical Sciences
Email Address	S.M.Flynn@exeter.ac.uk
Co-Supervisor 1	
Name	Dr Greg Ngo
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	School of Medicine
Co-Supervisor 2	
Name	Professor Albert Basson
Affiliation	
College/Faculty	Faculty of Health & Life Sciences
Department/School	Clinical and Biomedical Sciences