Project Details	
Project Code	MRCNMH26Ex Bhinge
Title	Communication Breakdown: Using human assembloid models to understand disruption of neuron-glia interactions in ALS.
Research Theme	NMH
Project Type	Primarily wet-lab with a strong computational component.
Summary	ALS is a devastating neurological disease with no cure, and we urgently need new ways to understand and treat it. This exciting PhD project combines cutting-edge stem cell technology, 3D brain cell models, and advanced genomic analysis to explore how nerve cells and support cells interact in health and disease. You'll model a key ALS feature seen in most patients and use high-resolution single-cell techniques and drug screening to uncover new disease mechanisms and drug candidates. This highly interdisciplinary and collaborative project offers exceptional training in neuroscience, genomics, bioinformatics and translational research.
Description	Amyotrophic lateral sclerosis (ALS) is a devastating, progressive neurodegenerative disorder marked by the selective loss of motor neurons (MNs). Patients typically experience increasing immobility, paralysis, and ultimately succumb to respiratory failure within 3–5 years of diagnosis. Despite decades of research, effective treatments remain limited. A deeper understanding of the molecular and cellular events leading to MN degeneration is urgently needed to develop effective therapeutic strategies. Approximately 85% of ALS cases are sporadic (sALS), while 15% are familial (fALS) and linked to known genetic mutations. A consistent molecular hallmark across nearly all ALS cases is the mislocalization of TDP-43, a nuclear RNA-binding protein involved in splicing and other aspects of RNA metabolism. In ALS, TDP-43 abnormally accumulates in the cytoplasm, resulting in a loss of its nuclear function and widespread splicing defects. These aberrant splicing events often produce truncated, dysfunctional proteins, particularly in genes essential for neuronal health. While MNs are the primary cells affected, there is growing recognition that ALS is a non-cell-autonomous disease. Glial cells, including oligodendrocytes and microglia, play essential roles in maintaining neuronal homeostasis and have been implicated in disease progression through mechanisms such as neuroinflammation and metabolic dysregulation. However, the dynamic interplay between these cell types—especially how glia contribute to MN degeneration—remains poorly understood. This project aims to investigate neuron-glia interactions in the context of ALS, using cutting-edge human stem cell-derived models and genomics. Specifically, it will examine how TDP-43 mislocalization impacts intercellular communication and contributes to neurodegeneration. The findings will provide novel insights into non-cell-autonomous mechanisms and may identify new targets for therapeutic intervention. We will utilize induced pluripotent stem cells (iPSCs) to generate MNs, microglia, and oligodendrocytes. To model TDP-43 pathology without introducing mutations or external stressors, we will employ a novel system developed in-house that induces cytoplasmic mislocalization of

	endogenous TDP-43, closely mimicking the molecular phenotype of sporadic ALS. Specific Objectives 1. Develop a human iPSC-derived assembloid model of ALS The student will generate spinal MNs, oligodendrocytes, and microglia from iPSCs using established differentiation protocols optimized in the Bhinge and Syed labs. These cells will be assembled into 3D co-cultures ("assembloids") by combining them in varying ratios to determine optimal conditions for cellular organization and function. Assembly will be performed using low-attachment plates and centrifugation to promote aggregation. Different assembloid configurations—with and without specific glial populations—will be compared to assess the contribution of each cell type to MN health. Over a four-week period, the student will perform detailed phenotypic characterization, including assessments of neuronal survival, neurite outgrowth, synapse formation, oligodendrocyte maturation, and microglial activation via immunostaining. Student ownership: The student will take a leading role in optimizing co-culture conditions, selecting relevant functional assays, and interpreting phenotypic outcomes. 2. Characterize the assembloid model using single-cell transcriptomics To dissect molecular changes at the cellular level, single-cell RNA sequencing (scRNA-seq) will be performed on assembloids and simpler co-cultures (e.g., neuron-glia pairs). This will allow precise mapping of transcriptomic alterations in each cell type and the identification of cell-type-specific responses to TDP-43 pathology. The student will conduct ligand-receptor interaction analyses to explore how intercellular communication is disrupted. Network analysis will identify key regulatory genes and pathways affected by TDP-43 mislocalisation. Long-read Oxford Nanopore sequencing will be used to detect splicing abnormalities, including CE inclusion, associated with TDP-43 dysfunction. Dr. Strauss will provide expert guidance on the bioinformatic analysis of single-cell transcriptomic data, including clustering, differential gene expression, pathway analysis, and cell-cell communication modelling. Their support will ensure robust interpretation and integration of the transcriptomic datasets. 3. Identify and test candidate therapeutics to reverse ALS phenotypes Transcriptomic signatures from TDP-43 assembloids will be compared against the Broad Institute's Connectivity Map (CMap), which profiles the transcriptional effects of over 1,300 bioactive compounds. Compounds whose expression signatures are inversely correlated with disease profiles will be shortlisted as potential therapeutic candidates. Top candidates will be tested in vitro using the iPSC-derived assembloids. The student will evaluate the efficacy of these compounds in rescuing ALS-associated phenotypes using both immunocytochemistry and scRNA-seq. Expression and activity of drug targets will be further validated at the protein level in post-mortem spinal cord tissue from ALS patients, to confirm relevance to human disease.

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