Project Details	
Project Code	NMH27Ex Bhinge
Title	Communication Breakdown: Using human 3D bioprinted models to understand disruption of neuron-muscle interactions in ALS.
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
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 bioprinting, 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 identify novel drug candidates. This highly interdisciplinary and collaborative project offers exceptional training in neuroscience, genomics, bioinformatics, bioengineering and translational research.
Description	Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease defined by progressive loss of upper and lower motor neurons, leading to paralysis and death from respiratory failure within three to five years of diagnosis. Effective treatments remain limited. A molecular hallmark shared by almost all cases, sporadic and familial, is mislocalisation of TDP-43, a nuclear RNA-binding protein central to RNA metabolism. In ALS, TDP-43 is depleted from the nucleus and accumulates in the cytoplasm, causing loss of its splicing function and widespread cryptic exon inclusion in transcripts essential for neuronal and muscle health, including STMN2 and UNC13A. The motor system is a connected multicellular circuit: cortical motor neurons drive spinal motor neurons, which innervate skeletal muscle at the neuromuscular junction (NMJ). There is growing evidence that ALS is non-cell-autonomous and that the earliest pathology occurs distally, at the NMJ and within muscle, before motor neurons are lost. Whether TDP-43 mislocalisation acts primarily in neurons, in muscle, or through disrupted communication between them remains unresolved. Progress is limited by the absence of models that reconstruct the connected neuron-muscle unit; two-dimensional cultures and animal models do not recapitulate human NMJ biology or allow the contribution of each compartment to be isolated. This project will use 3D bioprinting to build spatially defined, compartmentalised human neuromuscular models. Bioprinting gives reproducible control over tissue geometry and precise and reproducible cell patterning that self-organising organoids cannot, allowing neuron and muscle compartments to be built and manipulated independently. Research question How does mislocalisation of endogenous TDP-43, in neurons versus in muscle, disrupt neuron-muscle communication and drive breakdown of the motor unit in ALS? Objectives 1. Engineer a 3D bioprinted human neuromuscular model. The student will differentiate cortical projection neurons, spinal motor neurons, and skeletal muscle from iPSCs using protocols established in the Bhinge lab, and bioprint them into a compartmentalised construct that permits

	axonal projection and NMJ formation between compartments. Two hydrogel formulations will be developed: compartment dividers that restrict cell bodies while permitting axonal crossing, and encapsulation matrices tuned to each cell type. Working with Dr Armstrong (Bristol) on biofabrication and Dr Gielen (Exeter) on microfluidic integration for controlled perfusion and delivery of bioactive compounds, the student will optimise bioink composition, compartment geometry, and culture conditions, and confirm connectivity by immunostaining, and calcium imaging. Student ownership: leading the design of construct geometry, selection of bioinks, and the assembly and maturation strategy. 2. Model TDP-43 mislocalisation and characterise phenotypes by imaging and transcriptomics. Using an in-house system that induces cytoplasmic mislocalisation of endogenous TDP-43 without mutations or exogenous stress, the student will trigger pathology selectively in neurons, in muscle, or in both. High-content imaging will quantify NMJ number and morphology, neurite integrity, muscle fibre structure, and contractile function, comparing configurations to attribute phenotypes to each compartment. Phenotypes will be tracked longitudinally, with phosphorylated TDP-43 and neurofilament light quantified as translatable markers. In parallel, because each compartment can be sampled separately, bulk RNA sequencing will be performed on neuron and muscle compartments to map compartment-specific responses to TDP-43 mislocalisation. Comparing ligand expression in one compartment with receptor expression in the other will identify disrupted neuron-muscle signalling, and long-read Oxford Nanopore sequencing will resolve cryptic exon inclusion and other splicing defects. Integrating imaging and transcriptomic data, the student will nominate candidate mediators of neuron-muscle breakdown. Student ownership: selecting functional and imaging assays, prioritising signalling candidates, and interpreting compartment-specific phenotypes. 3. Identify and test candidate compounds to reverse ALS phenotypes. Transcriptomic signatures from TDP-43 mislocalised models will be compared against the Broad Institute's Connectivity Map (CMap), which profiles the transcriptional effects of over 1,300 bioactive compounds. Compounds whose signatures are inversely correlated with the disease profile will be shortlisted. Top candidates will be tested in the bioprinted models, with rescue of neuromuscular phenotypes assessed by high-content imaging and bulk RNA sequencing. Drug-target expression will be validated at the protein level in post-mortem ALS spinal cord to confirm human relevance. Student ownership: prioritising candidate compounds and designing the rescue-testing strategy. Across the studentship the student will progress from tissue engineering to disease modelling to functional genomics and therapeutic screening, gaining unusual breadth, with scope to steer the project toward the compartments and mechanisms they find most compelling.
Can be completed part time?	No

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