Project Details	
Project Code	NMH27Ba Mason
Title	Boosting the Brain Cell Recycling System: Peptide Activation of TFEB in Neurodegeneration
Research Theme	Neuroscience & Mental Health
Project Type	Other
Summary	Many neurodegenerative diseases, including Parkinson's disease, involve failure of the cell's waste-clearance system, allowing damaged proteins and organelles to accumulate. TFEB is a master regulator that switches on genes controlling lysosomes and autophagy, the pathways cells use to recycle unwanted material. This project will develop peptide-based molecules that bind directly to TFEB and increase its activity. The student will combine peptide design, biochemical screening, structural and biophysical analysis, and cell biology to test whether TFEB activation improves lysosomal function, autophagy and toxic protein clearance in disease-relevant neuronal models.
Description	Neurodegenerative diseases such as Parkinson's disease are strongly associated with failure of cellular waste-clearance pathways. Long-lived cells, including neurons, depend on lysosomes and autophagy to remove damaged proteins, defective organelles and toxic aggregates. When this system becomes inefficient, harmful material can accumulate and contribute to cellular dysfunction. A major regulator of this process is transcription factor EB (TFEB), a master switch that activates genes controlling lysosome biogenesis, autophagy and cellular recycling. Increasing TFEB activity is therefore an attractive strategy for restoring proteostasis in neurodegeneration, but current approaches often work indirectly through broad upstream pathways such as mTORC1, limiting specificity. This project will develop a direct biochemical strategy to enhance TFEB activity. TFEB functions through a basic helix-loop-helix leucine zipper region that enables dimerisation and DNA binding at CLEAR gene elements. These interactions are difficult to target using conventional small molecules but are well suited to engineered peptide approaches. Importantly, the TFEB bHLHZip/dimerisation region has already been shown to be structurally tractable, providing a realistic basis for biochemical, NMR and, where appropriate, X-ray crystallographic studies of peptide-mediated complex formation and DNA recognition. The central hypothesis is that peptide-based molecules can be designed to bind TFEB directly, stabilise productive TFEB complexes, and increase transcription of genes that restore autophagy-lysosome function. The central research question is: can direct peptide-mediated activation of TFEB enhance lysosomal function, autophagy and toxic protein clearance in neurodegeneration-relevant cellular models? The student will work towards three linked aims. Aim 1: Discover and optimise TFEB-binding peptides. The student will analyse the TFEB dimerisation/DNA-binding region and use existing pilot data from the Mason laboratory as starting points for optimisation. Recombinant TFEB constructs will be produced to support screening and validation. The student will use computational design, including InsiliCoil, together with intracellular peptide screening to identify sequences that bind TFEB and enhance its activity. Linear, cell-

	penetrating and structurally constrained peptides will be compared to determine how sequence, helicity, stability and cell entry influence function. NGS analysis of screening outputs will be used to identify enriched TFEB-binding sequences, assess sequence convergence and prioritise hits for synthesis and testing. Aim 2: Define the biochemical and structural mechanism of TFEB activation. Lead peptides will be characterised to determine how they bind TFEB and how this affects TFEB dimerisation and DNA recognition. The student will use circular dichroism, fluorescence polarisation, electrophoretic mobility shift assays, isothermal titration calorimetry where appropriate, and structural analysis with Professor Crump that can include both NMR-informed and X-ray crystallographic approaches. NMR will be particularly valuable for detecting and mapping peptide–TFEB interactions, especially where complexes are dynamic or initially weak. These experiments will establish whether peptides directly engage TFEB, stabilise productive TFEB complexes and influence binding to CLEAR DNA elements. The resulting mechanistic data will guide further peptide optimisation and help distinguish genuine TFEB activation from non-specific effects on protein stability, aggregation or cellular stress. Aim 3: Test whether peptide-mediated TFEB activation restores autophagy–lysosome function in neurodegeneration-relevant cell models. The most promising peptides will be tested in cellular systems with Dr Bernadette Carroll to determine whether direct TFEB modulation produces the intended biological response. Readouts will include TFEB nuclear localisation, CLEAR reporter activity, expression of TFEB target genes, lysosomal mass, lysosomal pH, cathepsin activity, autophagic flux, p62 turnover and clearance of disease-relevant protein burden such as α-synuclein. qPCR and transcriptomic analysis will be used to confirm that TFEB-regulated mRNAs and broader lysosome/autophagy gene networks are increased. This aim will determine whether biochemical activation of TFEB is realised inside cells and whether it enhances cellular waste-clearance pathways relevant to neurodegeneration. The project is designed to give the student substantial ownership. In the early phase, they will help prioritise which TFEB interfaces, peptide formats and screening outputs to pursue. As the project progresses, they will choose which lead peptides to optimise, which mechanistic assays best resolve their mode of action, and which cellular phenotypes provide the most informative evidence of TFEB activation. Depending on progress and interests, the student could steer the project towards deeper structural mechanism, peptide optimisation, neurodegeneration-relevant cellular phenotyping, or broader application of TFEB activation to lysosomal dysfunction. Overall, this PhD will provide interdisciplinary training across chemical biology, peptide design, protein biochemistry, structural biology and neurodegeneration cell biology. It will generate new tools to probe TFEB regulation and test whether direct activation of the autophagy-lysosome pathway can provide a rational route to restoring cellular waste clearance in neurodegenerative disease.

Can be completed part time?	Yes
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