| Project Details | |
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| Project Code | MRCNMH26Ex Noble |
| Title | Can supporting cells of the brain help to treat Alzheimer's disease? |
| Research Theme | NMH |
| Project Type | Wet lab |
| Summary | Tau tangles accumulate mainly in neurons in Alzheimer's disease brain. We recently found that blocking inflammatory signals in non-neuronal cells caused a reduction in tangles within neurons (doi: 10.1016/j.bbi.2023.09.011). However, it remains unclear which type of cell is responsible for this protective effect, and the precise mechanisms involved. This project will address these questions using newly identified compounds in human iPSC-derived cell models. We will apply innovative methods to uncover the molecular mechanisms through which non-neuronal cell signalling allows the clearance of neuronal tangles and explore how these mechanisms affect wider interactions between neurons and other brain cells. |
| Description | **BACKGROUND:**<br>The glial purinoceptor P2X7R has emerged as a promising therapeutic target in Alzheimer's disease (AD). P2X7R expression is elevated in astrocytes and microglia—but not neurons—in both AD mouse models and affected areas of the human AD brain (DOI: 10.1016/j.bbi.2023.09.011). In AD, aggregates of tau protein accumulate in neurons, driving synaptic dysfunction and neuronal death. In ex vivo tauopathy models, P2X7R antagonism reduces neuronal tau aggregates without affecting soluble tau levels or modifications, suggesting that glial P2X7R inhibition activates mechanisms that promote tau clearance. However, it is not yet clear which glial cell type mediates these effects or what mechanisms are involved. Several possibilities exist based on known P2X7R functions (doi: 10.1042/EBC20220079), such as promoting neuronal autophagy or facilitating glia-to-neuron transfer of clearance-promoting molecules (doi: 10.1126/sciadv.adk9884). These effects may occur via direct glia-neuron contact or through secreted proteins. Further, as P2X7R function differs between rodents and humans, it remains unknown whether its modulation in human glial cells can similarly protect human neurons.<br>To address this, we will use human iPSC-derived neurons, astrocytes, and microglia—including genetically modified cells designed to elucidate glia-neuron interactions. By mimicking disease-relevant inflammatory conditions and applying newly developed, selective P2X7R antagonists (doi: 10.1021/acs.jcim.5c00552), we aim to uncover mechanisms driving neuronal tau clearance. We will also assess the impact of P2X7R antagonism on neuronal function using established assays. Our findings could help clarify how P2X7R modulation supports tau clearance and guide the development of cell-type–specific P2X7R-targeted therapies for AD.<br>**HYPOTHESIS & AIMS:**<br>We hypothesise that P2X7R promotes clearance of pathological tau in human neurons through a non-cell autonomous mechanism involving either astrocytes or microglia. Overall objective: To define the glial cell type(s) and mechanism(s) through which P2X7R activity influences tau pathology in human iPSC-derived neural cultures. |

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| | Specific aims:<br>1. Identify whether P2X7R antagonism reduces neuronal tau aggregates via astrocytes, microglia, or both.<br>2. Determine whether effects are mediated through direct glia-neuron contact or secreted factors.<br>3. Elucidate the underlying molecular mechanisms enabling P2X7R-driven tau clearance.<br>4. Assess the functional consequences of glial P2X7R antagonism for neuronal health.<br>**PROJECT DESIGN:**<br>Aim 1: We will generate iPSC-derived neurons, astrocytes, and microglia using established protocols from the Noble and Piers labs (PMIDs: 40585369, 31907987). Neurons will be seeded with human brain-derived tau aggregates to induce pathology (PMID: 40585369). Selective P2X7R antagonists (PMID: 40566963) will be applied to astrocyte or microglia cultures—both in resting and inflammatory conditions—prior to co-culture with seeded neurons. We will measure changes in tau aggregation using imaging and biochemical assays.<br>Aim2: We will use split-GFP systems to visualise and quantify glia-neuron contacts. Specifically, we will utilise a proximity proteome system using iPSC lines that are edited to express split GFP and a secreted nanobody in a controlled, temporal manner. The iPSC lines will be differentiated into our cell types of interest, and the proteome of the contact site analysed to identify interactions and components at the sites of cellular contact. To test for secreted factor effects, conditioned media from antagonist-treated astrocytes or microglia (after washout) will be applied to seeded neurons. Tau pathology will again be assessed.<br>Aim 3: Based on results from Aims 1 and 2, we will select either astrocytes or microglia for deeper investigation, focusing on whether P2X7R acts via contact-mediated or secreted mechanisms. This aim will be further informed by published P2X7R signalling pathways (doi: 10.1042/EBC20220079). The exact experimental direction will be shaped by the student in consultation with the supervisory team.<br>Aim 4: We will assess the impact of glial P2X7R antagonism on the function of iPSC-derived neurons seeded with human tau. Population activity will be assessed by calcium imaging, while patch clamp will be used to measure synaptic function. These functional readouts will be complemented by analysis of neuronal viability, synapse density, and synaptic protein expression.<br>**STUDENT OWNERSHIP:**<br>The project is designed to support early and active student involvement. Data generated in Aims 1 and 2 will guide the student in shaping Aim 3: they will choose the glial cell type and mechanism to focus on and select methods for further investigation. Supervisors will provide structured mentorship and technical support, but the student will be encouraged to make independent decisions and take intellectual ownership of the research.<br>**OUTCOMES:**<br>This project will shed light on how inflammatory signalling in glial cells influences tau pathology and neuron-glial interactions in AD. It may |

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| | support future efforts to repurpose P2X7R antagonists—already in clinical trials for peripheral immune disorders—for use in dementia. The student will gain interdisciplinary training in iPSC-derived neural models, pharmacology, and functional neuroscience. They will develop transferable skills in experimental design, data analysis, and cross-institution collaboration. By engaging with research teams in both Exeter and Cardiff, they will build a strong professional network and a broad understanding of the dementia research landscape. |
| Supervisory Team | |
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