Project Details	
Project Code	NMH27Ex Dempster
Title	Developing Blood Tests for the Early Detection of Neurodegeneration Following Traumatic Brain Injury
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	Traumatic brain injury (TBI), including repetitive head impacts during contact sports, increases the risk of developing later-life neurodegenerative diseases such as chronic traumatic encephalopathy (CTE) and Alzheimer's disease. However, the earliest molecular changes linking brain injury to neurodegeneration remain poorly understood. This interdisciplinary PhD will develop a next-generation, minimally invasive blood test (liquid biopsy) to investigate these processes. The student will combine cutting-edge genomics, long-read sequencing and extracellular vesicle biology to analyse cell-free DNA and neuron-derived extracellular vesicles from the same blood sample, uncovering early biomarkers and molecular mechanisms that could transform the diagnosis, monitoring and treatment of neurodegenerative disease.
Description	Background Traumatic brain injury (TBI) is increasingly recognised as a major risk factor for later-life neurodegenerative disease. Even mild repetitive head impacts are associated with chronic neuroinflammation, tau pathology and progressive neuronal dysfunction that can ultimately culminate in disorders such as chronic traumatic encephalopathy (CTE) and Alzheimer's disease. However, the earliest molecular events linking brain injury to neurodegeneration remain poorly understood, limiting opportunities for early diagnosis and therapeutic intervention. Blood-based liquid biopsy technologies offer an unprecedented opportunity to study these early pathological processes through minimally invasive blood sampling. Two particularly promising biomarker classes have emerged. Cell-free DNA (cfDNA), released during neuronal injury, retains cell-type-specific DNA methylation signatures that allow its tissue of origin to be determined, while neuron-derived extracellular vesicles (NDEVs) transport proteins, RNA and other molecular cargo that reflect neuronal physiology and pathological signalling. Combining these complementary analytes has the potential to improve early risk stratification, provide mechanistic insight into the biological processes underlying neurodegeneration, and identify individuals who may benefit from early intervention. Building on internationally recognised expertise at Exeter in cell-type-specific epigenomics and Oxford Nanopore sequencing (ED), combined with expertise in extracellular vesicle biology (PWP) and computational genomics at Bristol (MS), this project will develop an Integrated Neural Liquid Biopsy platform capable of simultaneously interrogating both biomarker classes. Central hypothesis Traumatic brain injury initiates a coordinated molecular response involving neuronal cell death, extracellular signalling and neuroinflammation. These complementary biological processes are reflected by the release of brain-derived cell-free DNA and neuron-derived extracellular vesicles into the circulation. Simultaneous analysis

	of these complementary sources of molecular information will provide unprecedented insight into the earliest mechanisms of neurodegeneration and identify biomarker signatures that outperform either modality alone. Aim 1: Development of an Integrated Neural Liquid Biopsy platform The student will optimise a novel laboratory workflow enabling simultaneous extraction of high-quality cfDNA and neuron-derived extracellular vesicles using plasma samples available within collaborating cohorts. Different extraction methodologies, plasma processing protocols and quality-control metrics will be systematically evaluated to establish a robust, reproducible platform suitable for downstream multi-omic analyses. Aim 2: Oxford Nanopore sequencing of cfDNA in TBI Using the optimised workflow, plasma cell-free DNA (cfDNA) from individuals with traumatic brain injury (TBI), those with mild repetitive head impacts from contact sport participation (PWP), and matched non-contact-sport athletes will undergo Oxford Nanopore Technology (ONT) sequencing to characterise DNA methylation, hydroxymethylation, and fragment-based analysis (fragmentomics). Computational deconvolution approaches developed in the EDs laboratory will be used to estimate neuronal and glial contributions to plasma cfDNA by comparison with existing cell-type-specific methylome reference datasets. These analyses will quantify neuronal injury, identify epigenetic alterations associated with traumatic brain injury and concussion, and enable comparison with existing cfDNA ONT datasets generated within the Dempster laboratory from motor neuron disease, Alzheimer's disease and Huntington's disease Aim 3: Multi-omic profiling of neuron-derived extracellular vesicles Neuron-derived extracellular vesicles will be enriched and characterised using complementary molecular approaches, including nanoparticle tracking analysis, RNA sequencing and targeted analysis of neurodegeneration-associated proteins (oligomeric tau, phosphorylated tau, misfolded tau and IL-6). (PWP) The student will determine how EV cargo reflects neuronal injury and whether these molecular changes correspond with other measures of neuronal damage. Aim 4: Integrated biomarker discovery The final analysis will combine cfDNA epigenetic signatures, extracellular vesicle cargo, clinical measures, plasma protein biomarkers (Nf-L, UCH-L1, and GFAP) and head impact exposure using multivariable regression, Bayesian modelling and machine learning approaches (MS). This integrated analysis will identify molecular signatures associated with early neurodegenerative processes and establish a framework for future longitudinal studies across multiple neurodegenerative diseases. Expected outcomes of the PhD project 1) A validated integrated neural liquid biopsy platform. 2)Novel cfDNA and extracellular vesicle biomarkers of neuronal injury. 3) Mechanistic insight into the earliest molecular events linking traumatic brain injury with neurodegeneration 4) A multi-marker framework for predicting long-term neurological outcomes following TBI

Can be completed part time?	Yes
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