Project Details	
Project Code	MRCNMH25Br Mifsud
Title	Exploring the role of hyaluronan in cognition across the lifespan.
Research Theme	Neuroscience & Mental Health
Summary	Hyaluronan (HA) is a structural component found in the spaces between the cells. HA is involved in a range of physiological functions that depend on the length of HA present. HA plays a significant role in cognition, the ability to acquire and use knowledge productively, but the cellular/molecular mechanisms behind this association remain ill-defined. Understanding these mechanisms is important because cognitive decline is associated with poor health/wellbeing, with age being a major risk factor. This project will deliver training in highly desirable experimental skills, linking fundamental mechanistic studies in vivo with molecular epidemiological studies of human cohorts.
Description	Good cognitive health, the ability to think, learn and remember, is of vital importance across species, contributing to a productive life and sense of wellbeing. Ageing is a major risk factor for poor cognition, which has a negative impact on quality of life. The hippocampus is a critical area of the brain associated with cognitive function and has been identified as a primary location mediating aspects of cognition vulnerable to ageing, such as spatial-dependent learning. Hyaluronan (HA), is a principal component of the extracellular matrix in the brain, with diverse functions dependant on its molecular weight; short HA chains exert stimulatory actions such as inducing proliferation, inflammation, and angiogenesis whereas longer forms are more stabilising, facilitating adaption of networks, cellular maturation and conferring anti-inflammatory actions. Despite growing evidence supporting the importance of HA in hippocampal-dependent cognition, understanding of how HA is regulated in the brain, and how it is affected by cognitive challenges and ageing, remains poor. Pilot work conducted by the Lead Supervisor indicates that spatial learning induces transient remodelling of the hippocampal HA environment, in a transcription-dependent manner, which is likely facilitating the adaptive learning process. Furthermore, an additional, currently underpowered study indicates that HAS2 mRNA expression maybe downregulated in older rats, hinting that the detrimental effects of ageing on cognition may be mediated by changes in the hippocampal HA. This PhD studentship aims to build on these exciting studies to investigate the molecular mechanisms underpinning the observed gene expression changes to HA-related genes following spatial learning. They will determine if these are functionally relevant for adaptive learning, investigate the impact of age, and determine the translatability of these finding in the human population. The specific objectives that the student will be working towards are: 1.To determine the cellular origin of the observed changes in HA-related gene expression following spatial learning in the rodent hippocampus. 2.To investigate the (epi)genetic mechanism(s) responsible for regulating HA-related gene expression following spatial learning.

	3.To determine the impact of age on the hippocampal HA environment and expression of HA-related genes and if this is mediating, in part, age-related cognitive decline. 4.To determine if (epi)genetic mediators of hippocampal HA expression (i.e. preidentified (epi)genetic markers known to affect HA-related gene expression identified in rodents from Obj 2 and/or wider literature) are causally associated with cognition, and mediating the detrimental effect of age on human cognitive function. Research activities undertaken by the student to address these objectives will be confirmed following the prep period and directed by the student. There is a good deal of flexibility in the project depending on the background or interests of the student, and the outline below is just one format the project could take. The student will be required to undertake Home Office training modules in the first year to obtain a personal licence as a legal requirement to perform the experiments in vivo that are required for this project. Feasible options to address the objectives above include: Obj.1: Use of RNAScope technology (advanced in situ hybridisation technique) to compare spatial RNA expression profiles of HA-related genes with immunofluorescent markers (NeuN, GFAP etc.) to identify the cellular origin of changes in HA-related gene transcription in the hippocampi of rodents after spatial learning, compared with non-learning controls. Obj.2: Literature review to identify mechanisms of (epi)genetic (DNA methylation, histone associations, SNP, indels, structural variants) regulation of HA-related genes in other tissues and determine relevance in brain. This is likely to include an intervention study incorporating a manipulation to the epigenetic landscape to understand causality of mechanisms. Quantitative PCR can be used to quantify mRNA and microRNA expression. DNA bisulphite conversion with pyrosequencing and/or long read sequencing using the in-house Oxford Nanopore GridIon can also be considered to address this objective. Obj.3: Young (12 week), middle-aged (9 months) and older (18 months) rats undergoing spatial learning could be used with or without a manipulation to HA environment. Such manipulations could include targeting important epigenetic processes identified in Obj. 2, treatment with 4-MU (HA synthase inhibitor) or stimulation of HA synthesis respectively to determine the relationship between ageing, hippocampal HA and spatial learning. HA concentration will be measured by ELISA and HA molecular weight by SS-nanopore technology. Depending on the student's personal circumstances, availability of external funds, and research interests, this could involve an in-person or remote visit to Wake Forest University, USA where the molecular weight analysis is undertaken. Obj.4: Relevant human cohort datasets can be used to assess the links between (epi)genetic proxies for differential hippocampal HA levels and measures of cognitive function. Inclusion criteria and outcome measures will be determined and relevant epidemiological analyses performed to determine any putative causal relationship between HA by (epi)genetic proxy, cognition and ageing. The student will have the option to travel to

	Bath or complete this objective remotely under the guidance of Co-Supervisor 1.
Supervisory Team	
Lead Supervisor	
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