Project Details	
Project Code	MRCNMH26Br Dick
Title	Targeting lysosomal dysfunction to treat age-related macular degeneration
Research Theme	NMH
Project Type	Wet lab
Summary	Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world. Projected to affect 288M by 2040, there are no therapeutic options for the common form of AMD (dry AMD) approved in the UK. Emerging research highlights common disease pathways between AMD and a group of inherited metabolic diseases, lysosomal storage disorders (LSD), with vision loss a common early symptom in many LSDs. This project will draw on knowledge gained from the study of LSDs to investigate key aspects of lysosomal health in AMD models, and explore the potential for repurposing LSD approved therapeutics to treat AMD.
Description	BACKGROUND: Accumulation of undegraded storage material within lysosomes, known as lipofuscin, is a common hallmark of age-associated disease including age-related macular degeneration (AMD; 1). Lysosomes – acidic multifunctional organelles – are key to cellular recycling and waste clearance. The importance of lysosomal health is highlighted by a group of devastating diseases termed lysosomal storage disorders (LSDs). Furthermore, lysosomal impairment is increasingly considered a key factor in the progression of more prevalent conditions (e.g. Parkinson's, Alzheimer's and AMD). Lessons learned from LSDs are providing new therapeutic approaches to target these complex age-related disorders. Sight complications are a common early symptom in many LSDs, identifying a central role for lysosomal impairment in retinal degeneration (2). Common to both LSDs and AMD, lysosomal accumulation of undigested storage and dysfunction of retinal pigmented epithelium (RPE) are key contributors to retinal degeneration. In RPE, lysosomal function is essential for the RPE to clear waste and recycle essential nutrients from the light-converting cells (photoreceptors) in the eye. This process is required for photoreceptor survival and its disruption is a key contributor to vision loss in both LSDs and AMD. Mounting evidence demonstrates that a loss of lysosomal integrity is central to the pathogenic pathways leading to RPE stress and cell death in both LSDs and AMD. For example, in juvenile Neuronal ceroid lipofuscinosis (NCL) – a fatal neurogenerative LSDs – there is progressive retinal degeneration. This is driven by pathological accumulation of a lipid species, glycosphingolipid, Gb3, specifically in the lysosomes of RPE cells (3). Based off work from the Cardiff team, a small molecule drug (miglustat) to prevent glycosphingolipid production, is stabilising visual acuity in juvenile NCL patients. In the context of AMD, we (4) and others (5) have revealed a role for dysregulated lipid metabolism and lysosomal function in RPE. Modelling AMD disease pathways in RPE cells leads to cholesterol accumulation within lysosomes. Enlarged lysosomes containing electron dense lipid whorls are also observed, which is a common feature in LSD patients

	too. This accumulation is associated with negative outcomes for lysosomal health. It can prevent the lysosomes from protecting RPE cells from inflammation-induced stress and results in a loss of lysosome integrity, leading to cell death. Notably, another LSD approved drug, arimoclomol, can protect against retinal degeneration in a mouse model (6), through clearance of cholesterol and stabilisation of the lysosomal membrane. These findings support a common role for reduced lysosomal storage burden and improved lysosomal integrity in protecting RPE. Targeting therapeutic approaches to RPE lysosomal health could improve several of the dysfunctional pathways that together lead to AMD. AIM: In this project, we will apply mechanistic knowledge from LSDs, to increase the understanding of lysosomal dysfunction during RPE stress AND test the potential for small molecule drugs targeted at lysosomal function and integrity to treat AMD. OBJECTIVES: MILESTONE 1: Characterise lysosomal dysfunction in RPE stress models for AMD. RPE cell lines, iPSC-RPE and animal models of retinal degeneration will be used to characterise lysosomal dysfunction in RPE. The student will have input on approaches used for characterisation, which could include analysis of: • Storage accumulation in lysosomes using markers or antibodies to label different lipid species and the lysosomes • RPE stress, determined by secretion of inflammatory markers, metabolic function, lysosomal calcium signalling and pH. • Lysosomal enzyme acitivty (e.g. lipid associated enzymes) • Lysosomal storage accumulation by Transmission Electron Microscopy • Gene expression analysis of RPE stress markers and lipid processing pathways • Electrophysiological characteristics of ion channels during RPE stress EXPECTED OUTCOME: A comprehensive characterisation of lysosomal storage and dysfunction in RPE stress. Whilst lysosomal-lipid accumulation in RPE is implicated in disease, there has been little prior characterisation of AMD-lysosome-specific changes. MILESTONE 2: Establish whether drugs to reduce lipid accumulation can improve lysosomal function in RPE. The student will select in-development drugs for LSDs to test for efficacy in treating RPE stress. These may include drugs that target lipid pathway enzymes (e.g. miglustat), promote lysosomal integrity (e.g. arimoclomol) or restore lysosomal pH (e.g. C381). The student will determine the best assays to assess treatment efficacy, informed by milestone 1. EXPECTED OUTCOME: Identification of lysosomal modifiers that provide functional improvement in RPE models. MILESTONE 3 – Can lysosomal targeted drugs treat cells isolated from AMD patients?

	The student will select the top drug candidate to test for rescuing disease in patient-derived (dry AMD) iPSC-RPE. The student will triage the most suitable assays, to determine this, informed by milestone 1/2. EXPECTED OUTCOME: Proof-of-concept that improving lysosomal health is a therapeutic avenue for the treatment of AMD. REFERENCES: (1) Moreno-García et al. Frontiers in neuroscience. 2018:12:464 (2) Intartaglia D et al. FEBS J. 2022:289(22):7199-7212 (3) Soldati et al. EMBO Molecular Medicine. 2021:13(10):e13742 (4) Cox et al. Aging Cell. 2025:e70081 (5) Álvarez-Barrios et al. BMC Biol 2025:23(96) (6) Pan et al. PNAS. 2021:118(47):e2100122118
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