Project Details	
Project Code	CMD27Br Carroll
Title	Understanding the link between lipid droplet biology and bone health
Research Theme	Cardiometabolic Disease
Project Type	Wet lab
Summary	Cells require a tightly regulated supply of lipids to sustain metabolism and growth. When lipids are abundant, fatty acids are packaged into lipid droplets, which act as an energy reserve. We recently identified a new regulator of lipid droplets and interestingly, analysis of large genetic datasets and in vivo models implicates this gene in bone growth and health. Using a combination of molecular genetics, mechanistic cell biology and in vivo models, the aim of this PhD is to reveal new understanding of how lipid droplets regulate bone health and disease.
Description	Cells require a constant, and tightly regulated supply of nutrients to sustain metabolism and growth. Lipids are particularly important: they provide a high-energy fuel source and supply essential building blocks to produce new membranes required for growth. Too few and too many lipids are both associated with negative health outcomes, from impaired growth and tissue regeneration to obesity, metabolic disease, and age-related decline. When lipids are abundant, surplus fatty acids are packaged into lipid droplets (LDs)- specialised organelles that act as an energy reserve and protect against lipotoxicity. LDs are highly dynamic organelles- they grow and shrink rapidly in response to metabolic challenge, they support signalling pathways, and form functional contact sites with multiple organelles, most notably the endoplasmic reticulum (ER) and mitochondria. Thus, LDs are key regulators of cellular metabolism. However, many questions remain about the spatiotemporal mechanisms that control LD dynamics and very little is known about how LD behaviour is adapted to meet the specific demands of different tissues, for example bone, which undergoes extensive growth, followed long-term homeostasis, and remodelling following injury. We recently identified and characterised a new regulator of LDs, an ER-resident protein called TMEM263/C12orf23 (10.1101/2025.07.04.663055). We discovered that TMEM263 localises to newly forming LDs, and loss of TMEM263 in cells and in zebrafish significantly impairs lipid droplet accumulation. Mechanistically, TMEM263 is a transmembrane protein which can interact with and support the condensation of neutral lipids to promote lipid droplet formation and growth. Mutations or knock-out (KO) of TMEM263, are associated with whole-body growth deficiency (dwarfism) and skeletal defects in mice (PMID: 38241182), chickens (PMID: 29930570) and humans (PMID: 34238371). Consistently, human GWAS analysis associate Tmem263 variants with bone mineral density, osteoblast function and osteoarthritis (PMID: 28869591). Across these models, there are no consistent changes in common drivers of dwarfism (e.g. low circulating IGF-1 and reduced growth hormone receptor expression) indicating the mechanism is distinct. Based on our data in cells and in zebrafish, we hypothesise that TMEM263 has a tissue intrinsic role in controlling bone health.

	To test our hypothesis, this PhD programme will integrate in silico, in cells, and in vivo models across two main objectives: Objective 1 will establish the molecular and cellular regulation of TMEM263 in vitro. We will use a combination of molecular dynamics simulations, biochemical assays and cell biology to identify how and why TMEM263 localises to the ER and to LDs. One of the key experiments will be to explore the protein interactions of TMEM263 during the lifecycle of a LD using proximity proteomics. Objective 2 will test the hypothesis that TMEM263-dependent regulation of LDs controls bone health. Using Tmem263 knockout zebrafish, we will characterise bone formation and repair by integrating transcriptomic and transgenic reporter approaches. We will interrogate genetic databases to understand the relationship between TMEM263 and bone health at the population level.
Can be completed part time?	Yes
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