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seminar

Wednesday, 1st December, 9.30am, Online

Host: Dr. Jesús Ruiz-Cabello

Heteroplasmy of wild type mitochondrial DNA variants in mice causes metabolic heart disease with pulmonary hypertension and frailty

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In most eukaryotic cells, mitochondrial DNA (mtDNA) is uniparentally transmitted and present in multiple copies derived from the clonal expansion of maternally inherited mtDNA; all copies are therefore near-identical, or homoplasmic. Heteroplasmy, the presence of more than one mtDNA variant in the same cytoplasm, can arise naturally or result from new medical technologies aimed at preventing mitochondrial genetic diseases or improving fertility that can generate heteroplasmy between divergent non-pathological mtDNAs (DNPH).

We performed the characterization of engineered heteroplasmic mice throughout their lifespan through transcriptomic, metabolomic, biochemical, physiological and phenotyping studies. Using in vivo imaging techniques for non-invasive assessment of cardiac and pulmonary energy metabolism we demostrate that DNPH impairs mitochondrial function, with profound consequences in critical tissues that cannot resolve heteroplasmy, particularly cardiac and skeletal muscle. Progressive metabolic stress in these tissues leads to severe pathology in adulthood, including pulmonary hypertension and heart failure, skeletal muscle wasting, frailty, and premature death.