UNSW SYDNEY

Neuroscience & Non-Communicable Diseases WEBINAR – All welcome

Friday 19 June, 3pm

"Proteomic analysis of the intermittent fasting response identifies a novel peptide hormone"

Speaker: Mark Larance, Cancer Institute NSW Future Research Leader Fellow at the Charles Perkins Centre, University of Sydney.

Abstract:

Low-abundance small proteins in human plasma (e.g. hormones, immune factors, metabolic regulators) play key roles in maintaining metabolic homeostasis and are frequently disrupted in diverse disease states. Using the SPEA protocol we developed previously (Harney *et. al.* 2019. *Mol. Cell. Proteomics,* 18(9):1899-1915), we can identify and quantify peptides derived from active low abundance small-protein hormones in plasma. This has allowed us to explore all components in plasma, including potential novel protein factors, using unbiased mass spectrometry-based analysis. Using the SPEA protocol to analyse human plasma, allowed detection of three peptides from the uncharacterised 8 kDa protein (erusiolin) in human plasma samples, from a clinical trial examining the response to intermittent fasting. One of these was a highly conserved peptide that was significantly increased in abundance after 8-weeks of intermittent fasting. We have tested human plasma from mixed meal tests and observed 10-fold increased abundance of erusiolin approximately 2-3 hours after a breakfast meal. The mRNA encoding erusiolin is largely duodenum-specific and immunohistochemistry analysis of human small intestine using the erusiolin-specific antibody, has demonstrated a staining pattern consistent with expression in enteroendocrine cells of the proximal small intestine. We have used the Quantitative Endocrine Network Interaction Estimation (QENIE) method in mice to identify potential target tissues for erusiolin, which showed the hypothalamus had many transcripts significantly linked to variation in the locus. Strikingly, a significant number of the transcripts were derived from the Prader-Willi Syndrome locus, which is a disease characterised by extreme hyperphagia (over-eating) and subsequent obesity. This leads us to hypothesise that the conserved peptide from erusiolin is secreted by the duodenum into blood plasma and acts on the hypothalamus to trigger hunger signals for the next meal. We have now generated knock-out mice and are currently characterizing their phenotype compared to wildtype littermates for food-intake and related metabolic effects.

Bio:

Mark Larance performed his PhD in the laboratories of Prof. David James and Prof. Michael Guilhaus at the Garvan Institute and the University of New South Wales, respectively. His PhD work focused on the use of mass spectrometry-based proteomics for the analysis of the insulin signalling cascade. After being awarded his PhD in 2007, he began a post-doctoral position in the laboratory of Prof. Angus Lamond at the University of Dundee in Scotland. During this time, he became interested in the response to fasting given the metabolic benefits it can induce across a range of organisms, including increased life span and decreased cancer risk. After being awarded a Cancer Institute NSW Fellowship to start his own lab in Australia, he moved to the Charles Perkins Centre at the University of Sydney in 2016. His work focuses on the analysis of intermittent fasting responses and the molecular mechanisms underlying the beneficial effects.

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