

School of Life and Environmental Sciences:

Academic Researcher:	Professor David James
Project Title:	Insulin-mediated regulation of adipocyte lipolysis
Project Summary:	Insulin, a hormone that is released after a meal, regulates many aspects of metabolism including a process called lipolysis that involves the release of fatty acids into the circulation. Insulin suppresses the release of fatty acids from the fat tissue and while dysregulation of this process can markedly impact whole body metabolism, it is not well understood how insulin regulates this process. Here we will shed light on the mechanism by which insulin regulates lipolysis.
Project Synopsis:	Non-alcoholic hepatosteatosis is a major problem worldwide inspiring much interest in the molecular control of lipid homeostasis particularly in liver. However, there is an emerging interest in the role of fat cell lipolysis. In insulin resistance, fat cell lipolysis is hyper-activated and this not only provides excess fatty acids for ectopic accumulation in the liver but this also plays a major role in regulating hepatic glucose output, another major defect in pre-diabetes. Despite this, the mechanism by which insulin regulates lipolysis is poorly understood. It was thought that insulin stimulated Akt activity in adipocytes leads to phosphorylation and inhibition of the phosphodiesterase PDE3B thus suppressing lipolysis. However, this mechanism has been challenged. We have recently identified a novel regulator of lipolysis, the abhydrolase domain containing protein ABHD15 that forms a complex with PDE3B. In the absence of ABHD15 insulin is unable to suppress lipolysis in vitro and in vivo. We hypothesise that the ABHD15/PDE3B complex is crucial for insulin regulation of lipolysis and we will define the mechanism in Aim 1 using our established adipocyte cell lines expressing functional and non-functional ABHD15 mutants. In Aim 2 we will solve the structure of the ABHD15/PDE3B complex using a cryo-electron microscopy approach. This project will not only unravel the mechanism of this important insulin regulated process but possibly also provide putative drug targets for combatting obesity and metabolic disease.