

Metabolic Research Unit

Research Program Overview.

Type 2 Diabetes has rapidly become one of the greatest health concerns around the globe. At the Metabolic Research Unit we characterise the events leading to the development of Type 2 Diabetes and identify new therapeutics to treat individuals with Type 2 Diabetes. To achieve this we have implemented a new technique called Gene Expression Signature (GES) to the study of Diabetes. Our GESs consist of small sets of genes that can differentiate between a healthy insulin-responsive state and an insulin-insensitive (resistant) state. Some of these genes are well known mediators of insulin action and glucose metabolism, while others are not been previously implicated in the development of Type 2 Diabetes. Part of our research effort is focussed in generating specific GES for different forms of insulin resistance and insulin production deficiency. We also aim to identify new drugs that are able to reverse the GES profile characteristic of an insulin-resistant state, as they constitute good therapeutic candidates. Finally, other research projects will investigate the molecular mechanisms by which genes within the GES may regulate insulin action and glucose metabolism.

Project 1: Using Gene Expression Signatures to dissect Insulin Resistance Heterogeneity in Type 2 Diabetes

Supervisors: Dr Nicky Konstantopoulos, Dr Juan Molero, Dr Victoria Foletta

A key feature of type 2 diabetes is the failure of metabolic tissues such as muscle and fat to respond normally to insulin. This 'insulin resistance' is caused by a number of mechanisms. We will use cutting-edge technology to identify small sets of genes (termed Gene Expression Signatures; GES), that define different subtypes of insulin resistance. These gene sets will be used to diagnose sub-types of insulin resistance and could facilitate the development of personalised therapies to effectively treat individuals with Type 2 Diabetes.

Project 2: Generation of Screening Tools for the Identification of Novel Agents to treat Type 2 Diabetes.

Supervisors: Dr Ken Walder, Dr Kelly Windmill

Type 2 Diabetes has reached epidemic proportions around the world. Unfortunately, a fully effective therapeutic treatment has not been developed yet. This study aims to develop high-throughput cell-based and enzymatic assays based on recent new findings at the Metabolic Research Unit using Gene expression Signature (GES), Signal Sequence Trap (SST) and GLUT4 translocation assay technologies. These assays will be able to identify new compounds within small molecule libraries that will help to fill the requirements for new therapeutics to treat diabetic patients.

Project 3: Using Gene Expression Signatures to characterise pancreatic dysfunction in Type 2 Diabetes.

Supervisors: Dr Victoria Foletta, Dr Nicky Konstantopoulos

One critical issue in the management of type 2 diabetes is control of pancreatic β -cell function. These cells produce insulin, the major hormone responsible for control of glucose

metabolism. This study aims to identify small sets of genes able to characterise dysfunctional states of β -cells. To address this a novel screening tool called a Gene Expression Signature (GES) will be produced, which will allow the identification of pharmacological agents that restore pancreatic β -cells to a healthy state and protect the cells against the long term effects of elevated circulating glucose levels. The implication of generating a successful GES is far-reaching as this technological platform has the potential to be applied to numerous diseases to search for new therapeutics.

Project 4: Functional Analysis of new proteins involved in Insulin Action and Type 2 Diabetes

Supervisors: Dr Nicky Konstantopoulos, Dr Juan Molero

Impairment of insulin action is an early defect that contributes to insulin resistance, obesity and Type 2 Diabetes (T2D). However, there are multiple and redundant metabolic pathways that control the actions of insulin. Our approach was to identify the smallest number of genes that can discriminate between insulin-sensitive cells and cells that cannot effectively respond to insulin (insulin resistant). This project will focus on determining how specific genes impact insulin action by suppressing their endogenous gene expression levels in fat, liver and muscle cells using a powerful tool known as RNA interference. This study will determine if such genes are involved in T2D, and can be developed into a therapeutic strategy.

Project 5: Chemerin: A new adipokine associated with Type 2 Diabetes

Supervisors: Dr Kyimet Bozaoglu, Dr Ken Walder, Dr Kelly Windmill

We have recently identified chemerin as a new cytokine associated to obesity and Diabetes. This study will investigate the role of chemerin in the development of these diseases by examining its effects on the molecular mechanism governing glucose and lipid metabolism in cultured cells and animal models. This study will investigate the effects of chemerin supplementation and suppression of chemerin action by using specific chemerin-blocking antibodies and depletion of chemerin receptors using RNAi technology in cultured cells. The physiological relevance of chemerin will be assessed by treating animals with chemerin and chemerin-blocking antibodies. These studies will establish the foundation for new therapeutic avenues to the treatment of obesity and Diabetes.

Project 6: Regulation of muscle metabolism by ubiquitin ligases

Supervisors: Dr Juan Molero, Dr Victoria Foletta

c-Cbl is a proto-oncogene that regulates the degradation and function of growth factor receptors. We have identified a new role of this protein in whole-body energy metabolism and fat accumulation by controlling muscle function. This project will investigate the molecular mechanisms by which c-Cbl regulates energy balance in muscle, in particular mitochondrial biogenesis and glucose metabolism. This study will improve our basic knowledge of muscle function and our understanding of the molecular mechanisms leading to muscle debilitating diseases or Type 2 Diabetes.

Project 7: Novel regulators of skeletal muscle function

Supervisors: Dr Victoria Foletta, Dr Juan Molero and Dr Nicole Stupka

We have recently identified two novel genes, Abelson integration site-1 gene (AHI-1) and N-myc downstream regulated gene 2 (NDRG2) that are differentially expressed in insulin resistant and exercised skeletal muscle. Preliminary experiments have identified a putative role for AHI-1 in insulin signalling while NDRG2 is a key regulator of myoblast growth and differentiation. This study will dissect the molecular pathways mediating the effects of these genes using a variety of techniques including RNA interference and viral over-expression systems both in vitro and in vivo.