NCRIS
National Research Infrastructure for Australia
An Australian Government Initiative

CASE STUDY

BEATING DIABETES – CONTRIBUTIONS FROM NCRIS CHARACTERISATION FACILITIES

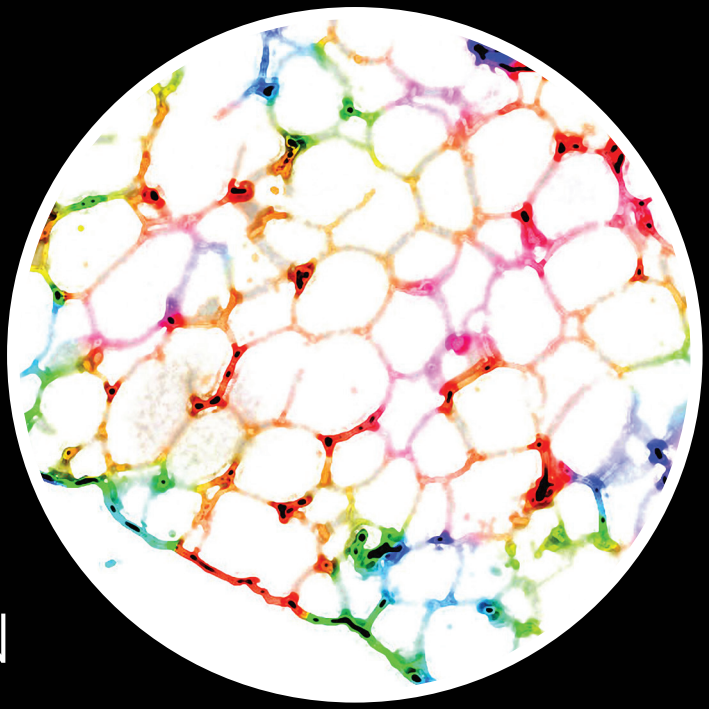


Image: Fat cells: Dr James Burchfield

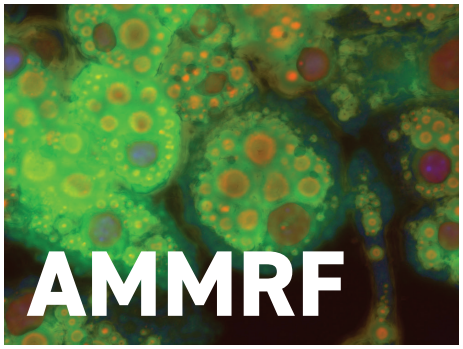
Diabetes is a group of diseases of major global significance. Researchers around Australia are making significant contributions towards understanding the complexity of diabetes – its causes and how to develop better treatments and management strategies.

The study of diabetes must reflect the fact that it operates at the molecular and cellular level right through to exerting effects on the whole body. Tackling these wide-ranging effects requires a diverse range of characterisation tools – tools provided by the integrated characterisation environment of NCRIS-funded research infrastructure.

Researchers tackling diabetes have been specifically attracted to, or retained in, Australia by this environment, one that enables them to access the advanced facilities they need to make world-leading discoveries in diabetes research. NCRIS characterisation infrastructure (AMMRF, ANSTO/Synchrotron and NIF) is enabling studies that address the basic biology, development and delivery of new drugs, modulation of the immune system and whole body effects of glucose control including:

- identification of critical molecules that could be targets for new drugs
- more effective drug delivery mechanisms
- how current drugs are metabolised
- how broader metabolic processes are disrupted in diabetes
- how insulin production is regulated
- how protein structures affect cellular processes in diabetes
- behaviour of tissues and organ systems in diabetic patients
- ways to stop immune destruction of insulin-producing cells in type 1 diabetes
- stem cell treatments

Together this work contributes to new, integrated knowledge of this complex and multi-scale disease.

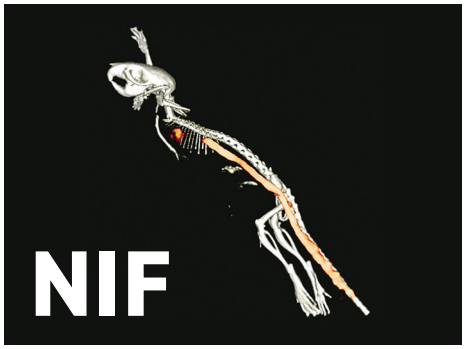


The Charles Perkins Centre at the University of Sydney is an important centre of diabetes research in Australia and its researchers make extensive use of the AMMRF. The Centre's diverse and multidisciplinary scientists are using super-resolution microscopy to enable their research into the effectiveness of reprogrammed stem cells in treating the loss of insulin-producing cells in type 1 diabetes. Physicists and tissue engineers on the project also rely on AMMRF microscopy as they develop specialised capsules to protect these stem cells from immune attack inside the body.

Microscopy is also critical for other Charles Perkins Centre researchers as they understand how insulin resistance initially develops. Insulin resistance is a precursor to type 2 diabetes, which accounts for more than 80% of all diabetes cases. TIRF microscopy has allowed the researchers to interrogate insulin signaling and glucose uptake in insulin responsive tissues, particularly observing the process in living cells. This team has contributed to the characterisation of the steps, rates and machinery involved in this process. They have also demonstrated that cells appear to have an innate pre-programmed sensitivity to insulin. This knowledge is helping the understanding of how normal cells progress towards a metabolic disease state.

This team has also begun to identify a number of proteins important for insulin signalling and exercise physiology. With the use of confocal microscopy they have been able to elucidate the roles of the proteins AKAP1, an important metabolic target in exercise and energy use, and TUSC5, which is involved in glucose transport and the sensitisation of cells to insulin stimuli. The researchers are currently using microscopic techniques to investigate the precise function of these and other proteins and their roles in diabetes and its precursors. By using the sensitivity of both TIRF and spinning disk confocal microscopy, the team has been able to detect features of a master regulator of insulin signaling called Akt and how it moves to the cell membrane – something that had previously gone undetected and unreported. This challenged the perceived understanding of Akt activation in insulin signalling and therefore of type 2 diabetes.

Image: Combined light, TIRF, fluorescent image of fat cells showing proteins at the cell surfaces: Dr James Burchfield



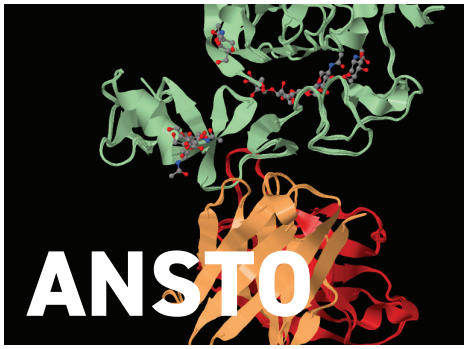
Type 2 diabetes is characterised by decreased levels of high density lipoprotein (HDL) cholesterol, and of apolipoprotein A-I (apoA-I). Therapies that increase HDL levels in the blood improve glucose control in patients with type 2 diabetes.

Treatment with HDL or apoA-I has been shown to increase glucose uptake into skeletal muscle and fat tissue. It also increases insulin secretion and production in isolated pancreatic islets. ANSTO human health researchers investigated how these improvements in glucose uptake occur by using Positron Emission Tomography (PET) imaging at NIF, incorporating radio-labelled glucose into whole mice with type 2 diabetes.

The study demonstrated that treatment with apoA-I significantly increased the rate of glucose uptake by skeletal muscle in the mice and also improved insulin sensitivity. The flexibility of PET imaging at NIF allows the study to be extended to investigate multiple organs and even changes as they occur over time.

NIF has also been used by other Australian researchers to develop magnetic resonance imaging techniques to non-invasively track encapsulated insulin-producing cells by labelling then with magnetic microspheres. They successfully demonstrated that the labelled cells could be followed by MRI and that the microspheres did not interfere with how the cells function.

Image: PET and CT image of a mouse 10 s after administering radiolabelled glucose: Dr. Blake Cochran



By using the Australian Synchrotron an research team from the Walter and Eliza Hall Institute of Medical Research obtained the world's first 3D pictures of insulin in the process of binding to its receptor on the surface of cells.

This interaction is a process essential for cells to take up sugar from the blood. This work was published in the journal, Nature. An understanding of the precise mechanism of this interaction will enable development of improved forms of insulin for treating type 1 and type 2 diabetes.

Another large Australian-led team of researchers has used the Synchrotron to understand the prevalence of autoimmune reactions to the protein glutamate decarboxylase (GAD65) in patients with autoimmune type 1 diabetes. They demonstrated that this protein has a very flexible structure that is needed for its correct regulation. However, the consequence of this flexibility is the tendency for it to induce autoantibodies that then attack the protein. These findings can now inform therapeutic antibody and vaccine design.

Image: Molecular model of insulin binding to its receptor. Data from A/Prof. Mike Lawrence

These research contributions represent bricks in the wall of understanding diabetes and would not be possible in Australia without the environment of infrastructure supplied by the characterisation NCRIS facilities.

OVER 5,000 RESEARCHERS ANNUALLY

Government supported characterisation infrastructure:

AMMRF, ANSTO and NIF supply instruments with diverse capabilities, along with associated technical expertise, to over 5,000 researchers annually.

NCRIS National Research Infrastructure for Australia
An Australian Government Initiative

ammrf Australian Microscopy & Microanalysis Research Facility

National Imaging Facility

Australian Synchrotron

ansto