

## A potential new treatment for Type 2 diabetes

**MEDIA RELEASE 6 May 2010**

Australian scientists propose that a drug, already being used to treat rare inherited disorders, may also help people with Type 2 diabetes.

Type 2 diabetes occurs when the body no longer controls blood sugar levels properly. We need insulin, a hormone made in the pancreas, to channel sugar from our blood into our cells. The insulin-producing cells of the pancreas, known as 'islets' or 'beta cells', become progressively less efficient in people with Type 2 diabetes. At the same time, their muscles become less responsive to insulin, a condition known as 'insulin resistance'. The combined result is high blood sugar levels, which can be very damaging to blood vessels and organs.

Kim Cheng and Drs Kenneth Ho and Jenny Gunton from Sydney's Garvan Institute of Medical Research, show that the reduced expression of the HIF-1 alpha gene in beta cells – with the resulting reduction of HIF-1 alpha protein – helps explain the impaired ability of the pancreas to produce insulin in people with Type 2 diabetes. More importantly though, they were able to show that administering a drug (already approved for another rare disorder) increased levels of HIF-1 alpha protein and may restore insulin production. The findings are now online in the *Journal of Clinical Investigation*.

"We believe that HIF-1 alpha is a key player, effectively orchestrating many events in the cell that eventually start to shut down insulin secretion," said Dr Gunton.

"HIF-1 alpha is a transcription factor, which means that it controls the way genes are expressed, or transcribed. This particular transcription factor happens to impact many genes that affect glucose uptake and metabolism in the pancreas. So when it is low, the beta cells have less energy."

"Beta cells secrete insulin when they detect an increase in their own energy. When they can't 'see' glucose, as rising energy, they don't secrete insulin."

The group tested and confirmed the importance of HIF-1 alpha in several ways.

First, they genetically engineered mice without the HIF-1 alpha gene in beta cells. These mice were mildly glucose intolerant, meaning that their blood sugar levels were higher than normal.

Next, they replicated the animal findings in cultured islets, in which the levels of HIF-1 alpha protein had been reduced.

After that, they fed genetically engineered and normal mice a high fat diet to make them fat and induce insulin resistance. Under these conditions, glucose levels deteriorate rapidly because beta cells are forced to work much harder to maintain normal sugar levels.

When all the mice were given the drug to stimulate the production of HIF-1 alpha protein, glucose levels improved in the 'normal' mice, despite the fact they continued on a high fat diet. The drug had absolutely no effect on the mice without the HIF-1 alpha gene in their beta cells.

"These tests left no doubt that it's beta cell HIF-1 alpha that is needed for this drug to affect glucose tolerance," said Gunton.

"Once we'd established that, we did a new study treating the 'normal' mice for six months to establish the drug's safety over the longer-term. We did not detect side effects and the mice developed better glucose tolerance."

"Then to be really thorough, we showed the same results in a completely different genetic line of mice."

"Finally, we treated the islets of people with Type 2 diabetes with the drug, which resulted in normalised gene expression, or restored function."

"This is a completely different mechanism of action from any of the drugs currently available for treating Type 2 diabetes, and so offers the potential of combined therapy."

"Of course, you'd need to do a proper randomised placebo-controlled trial to see whether the drug works in people. The fact that it works on human islets gives me hope."

"The fact that the drug is already approved by the Therapeutic Goods Administration in Australia and the US Food and Drug Administration is an excellent first step."

"We've designed a potential trial and now we're looking for funding."

## **ABOUT GARVAN**

The Garvan Institute of Medical Research was founded in 1963. Initially a research department of St Vincent's Hospital in Sydney, it is now one of Australia's largest medical research institutions with nearly 500 scientists, students and support staff. Garvan's main research programs are: Cancer, Diabetes & Obesity, Immunology and Inflammation and Neuroscience. Garvan's mission is to make significant contributions to medical science that will change the directions of science and medicine and have major impacts on human health. The outcome of Garvan's discoveries is the development of better methods of diagnosis, treatment, and ultimately, prevention of disease.

## **MEDIA ENQUIRIES**

Alison Heather  
Science Communications Manager  
Garvan Institute of Medical Research  
+61 2 9295 8128  
+61 434 071 326  
a.heather "at" garvan.org.au