Dr Maureen A Gannon discusses how her background in developmental biology is leading to new approaches in tackling Type 1 and Type 2 diabetes, potentially offering hope to millions around the world.

Could you briefly outline your research background? What led you to develop an interest in cell biology, particularly in relation to diabetes?

During graduate school I became interested in organogenesis, or how organs form during embryonic development. I wanted to study the development of an organ that had relatively few different cell types, and try to determine which genes and signalling pathways controlled the formation of the different cell types and how they were generated in the appropriate numbers to allow for mature organ function. As I explored what was known about the formation of the different organs in the body during embryonic development, I became intrigued about the pancreas. Delving further into the regulation of pancreas organ formation, it became clear that the genes which regulate pancreas organogenesis are also some of the same ones that control the function and differentiation of the insulin-producing cells and also insulin gene expression. So I was plunged into diabetes.

What are your overarching research goals?

The goals of my lab are to identify and characterise transcription factors and signalling molecules that regulate the number of insulin-producing cells throughout the life of the organism during embryogenesis, after birth, in young animals, in older animals, and in response to physiological stimuli such as weight gain and pregnancy. By understanding how these processes are regulated normally, we may be able to increase the number of functioning insulin-producing cells in people with diabetes, thus curing their disease.

Another aim is to understand the plasticity of pancreatic cell types (their ability to interconvert from one cell type to another). We want to know, for example, whether there are genes that can convert duct cells to insulin-producing cells, if acinar cells convert to duct cells during the progression to pancreatic cancer, and whether there are genes that can inhibit the formation of pancreatic cancer.

In what ways are current therapeutic options for diabetics limited?

People with Type 1 diabetes must inject themselves with insulin to stay alive. There is no other therapeutic option. People with Type 2 diabetes still have insulin-producing cells, they just do not work efficiently enough to generate sufficient insulin to keep the blood sugar normal. Thus, therapies for Type 2 diabetes include drugs that increase insulin secretion from the pancreas, drugs that sensitise the liver and other organs to respond to the patient’s own insulin, and some require insulin injections.

Could you provide an overview of some of the novel therapies for diabetes that researchers are currently investigating?

As well as traditional drug targets for Type 2 diabetes, there are also so-called ‘cell-based therapies’ that one could imagine would be relevant for both Type 1 and Type 2 diabetes. These types of therapies aim at increasing the number of insulin-producing cells in a patient’s pancreas. Strategies for achieving this include stimulating the proliferation of already existing β cells in the pancreas; inducing the formation of new insulin cells from other cell types in the pancreas in a process called transdifferentiation; and inducing the formation of insulin-producing cells in other organs. Cell-based therapies also encompass transplantation of whole islets or insulin-producing cells.

You have given a presentation at a public TEDx event and also work with schoolchildren in a voluntary capacity; why do you think it is important that the public and young people are actively engaged with research?

Sometimes I think that people see science as being far removed from their reality and that scientists are people who work in an ivory tower studying things that have no direct relevance to people’s daily lives. I want everyone to realise that science is all around us and that it is life. If scientists don’t connect with people and explain why our work is important, we have no right to complain that funding of scientific research is declining. Why should tax dollars go to something that does not seem important? Plus, I want people to see scientists as real people who live and work in their community, not as people separate from the general community. I want girls and young women to say ‘if she can do that, so can I’.
Deflecting diabetes

Calorific-laden diets and sedentary lifestyles have caused cases of Type 2 diabetes to escalate worldwide in recent decades. Researchers at Vanderbilt University Medical Center are conducting groundbreaking studies exploring the curative potential of novel targets in cell-based therapies.

UNTIL RECENTLY, TYPE 2 diabetes was a relatively rare condition associated with a decline in diet quality and exercise and an increase in age, but now it accounts for 90 per cent of all diabetes cases and affects children and adolescents in addition to adults. According to the World Health Organization (WHO), around 347 million people worldwide currently have a form of diabetes. In the US alone, figures from 2011 show that 8 per cent of the population were diabetic. With WHO projections estimating the number of diabetes-related deaths to rise by more than half in the next 10 years, more effective methods of tackling this sometimes fatal affliction would impact a significant portion of the world’s population.

As an autoimmune disease, Type 1 diabetes differs greatly from Type 2 diabetes, whereby a total absence of insulin-producing β-cells requires regular supplements to be taken for life. Before insulin was discovered in the 1920s, Type 1 diabetes was considered a death sentence but now millions of sufferers can, with vigilance, lead a fulfilling life. However, even the strictest observers will never be able to monitor their insulin levels as well as their own pancreas, and while life expectancy is substantially better than it once was, it remains compromised. Despite their differences, recent treatment efforts for both Type 1 and Type 2 diabetes have focused on cell-based therapies in which the body’s insulin levels can be increased or restored through the manipulation of transcription factors and signalling molecules to make simple replacement of insulin a treatment of the past.

Currently conducting research into the role of β-cell mass in diabetes and its potential to open up new therapeutic targets is Dr Maureen A Gannon, Associate Editor of the American Journal of Physiology, Endocrinology and Metabolism since 2012 and Associate Professor in the Diabetes, Endocrinology and Metabolism Division of the Department of Medicine at Vanderbilt University in Nashville, Tennessee. Gannon’s lab is immersed in multiple projects concerning β-cell mass to elucidate the complex processes governing embryonic development of the pancreas and its functionality in later life.

The work is being furthered through collaborations with various colleagues from Vanderbilt as well as the universities of Geneva, Illinois, Pennsylvania, Wisconsin and the Montreal Diabetes Research Centre (MDRC).

BOOSTING B-CELLS

Studies have shown that the number of β-cells in Type 1 and Type 2 diabetes is significantly reduced. The β-cells makes up around 60-85 per cent of the hormone-producing cells in the pancreas’ islets and are the only cell type in the body that can make insulin. It is for this very important role that β-cells are the subject of intense study in the search for a diabetes cure. Once believed that humans have their total amount of β-cells at birth, it is now known that these cells are initially formed during embryogenesis through β-cell differentiation (neogenesis); their mass continues to increase with growth into adulthood. β-cells are primarily renewed in the adult through proliferation rather than neogenesis, and activation of the cell-cycle can increase β-cell mass in response to proliferative signals throughout an organism’s life. Though neogenesis has been found in models of pancreatic injury, little is known about whether it occurs beyond the postnatal stage of development. Gannon’s lab is currently focusing on ways to differentiate β-cells from precursor populations in efforts to generate an unlimited supply for transplantation. If successful, it could be possible to expand the β-cell populations for both Type 1 and Type 2 diabetes patients.

The formation of mature islets in the pancreas occurs with the second wave of endocrine differentiation, which has been found to rely on the transcription factors HNF6 and PDX1. Both factors are critical components of normal embryonic development of the pancreas and insulin cells. In mice, inactivating mutations of HNF6, for example, have been shown to cause severe diabetes, whilst exaggeration of the transcription factor delivers promising results. “We showed that increased expression of HNF6 in the embryonic pancreas can increase the number of progenitor cells that give rise to insulin-producing cells,” states Gannon. Her lab is currently studying whether HNF6 and PDX1 can work together to form new insulin cells in the adult pancreas.

PROMOTING PROLIFERATION

In attempts to influence the proliferation and neogenesis of β-cells, the connective tissue growth factor (CTGF) gene has provided many useful insights into pancreatic development and production of insulin cells. Known to modulate several growth factor signalling pathways, CTGF is a secreted protein that is
HNF6 mutant mouse pancreas is smaller. Red is Pdx1 might be arrived at. On the other

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Other targets altogether are being examined in a more recent project exploring the role of prostaglandins (PG) in β-cell proliferation and mass expansion as their impairment have been linked to inflammation. Type 2 diabetes is associated with a rise in inflammatory cytokines, which induce PGE2 - in β-cells. Of the four PGE2 receptors that β-cells express, EP3 was found to be increased along with PGE2 in the islets of mice and humans with Type 2 diabetes. On the other hand, EP4 was upregulated in mice with activated FoxM1 – the transcription factor that is vital for the proliferation and mass expansion of β-cells in postnatal development. Gannon predicts that a novel target for enhancing the functional mass of β-cells in Type 2 diabetes might be arrived at through modulating EP4 and EP3 activity.

THERAPEUTIC REALITIES

Though major steps have been taken toward effective differentiation of precursor cells and transdifferentiation of more abundant mature cells, Gannon believes that however promising these approaches are, the efficiency of their ability to achieve a β-cell phenotype remains low. As they stand, the fidelity and stability of research methods being used have not yet been fully evaluated, giving rise to issues of reproducibility that first need to be addressed in order to advance current findings. Before any therapeutic conclusions are obtained from this field, Gannon is positive that further advances in physiological insulin delivery are yet to come, as well as better methods of blood sugar monitoring, as she concludes: “I think that cell-based therapies are a bit further in the future, but I do think those will also eventually become a reality”.

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