Diabetes: Following the science in the search for a cure

AstraZeneca

Diabetes is one of the priority cardiovascular, renal and metabolic diseases for which AstraZeneca is developing novel therapies. The global number of people living with diabetes is expected to rise to 700 million by 2045 (ref. 1). AstraZeneca's ambition is not just to reduce the raised blood glucose typical of the disease, it is to tackle the underlying pathophysiological drivers in order to instigate diabetes remission, prevent diabetic complications and deaths and, ultimately, to deliver a cure.

"AstraZeneca recognises that diabetes is more than a disease of the pancreas, and our research is focused on the underlying mechanisms that link diabetes to comorbidities, especially the main causes of death from the disease, including myocardial infarction and stroke, as well as heart and kidney failure," says David Baker, Head of Metabolism Bioscience, Biopharmaceuticals R&D.

INDUCE REMISSION

New approaches for the treatment of type 2 diabetes aim to induce remission as soon as possible after diagnosis by achieving durable responses to novel medicines designed to target the causes of type 2 diabetes and its related complications.

Obesity and insulin resistance are two key drivers in the development of type 2 diabetes, and are also connected to the development of diseases of the heart and circulation, liver and kidneys.

In people with obesity, bariatric surgery can cause remission of type 2 diabetes, and therapeutic alternatives are being sought to achieve levels of weight loss comparable to surgery[2]. Insulin resistance (reduced cell response to the glucose-lowering pancreatic hormone, insulin) has been a target for anti-diabetic medicines for many years. However, growing understanding of its central role in the development of blood vessel, kidney and liver diseases, has made it a research priority for addressing a key gap in the therapeutic armoury available to doctors and patients.

PRECISION MEDICINE

There is no single gene for type 2 diabetes but identification of the genomic drivers of the multiple biological mechanisms that lead to diabetes holds considerable promise. It is expected that new genomic understanding, linked to clinical phenotypes, will help to differentiate sub-groups of patients according to their risk of developing diabetes and progressing to diabetic complications. This segmentation of type 2 diabetes could also indicate opportunities for targeted therapies to intervene early in the disease.

NOVEL THERAPEUTICS

Advancing our understanding of disease biology enables us to uncover potential novel approaches for future diabetes treatments. At AstraZeneca, our toolbox of drug modalities enables us to address almost any drug target in diabetes using a range of therapeutics from classical small drug molecules to novel agents such as oligonucleotide and mRNA therapies. Approaches are being developed that can repair or modify a cell's blueprint for making key proteins that can be applied to type 2 diabetes and its complications.

Antisense oligonucleotides are short, synthetic, chemically modified pieces of RNA that can be used to 'silence' genes and prevent detrimental proteins from being made. Antisense oligonucleotides have been designed for delivery specifically into the insulin-producing beta-cells of the pancreas whose dysfunction can lead to diabetes[2]. This has opened the door to antisense oligonucleotide therapy aimed at restoring beta-cell function in diabetes and potentially 'knocking out' other genes in a way that could support long-term remission or even cure (**Fig. 1**).

Figure 1. Pancreactic beta cells at different stages of regeneration.

Messenger RNA (mRNA) has also been investigated for its potential in treating the small blood vessel damage, which commonly occurs with diabetes and can lead to organ failure. Encouraging results were obtained with injections of modified mRNA encoding for vascular endothelial growth factor A (VEGF-A), a protein involved in blood vessel formation. Local expression of VEGF-A was accompanied by improved blood flow in the skin of men with type 2 diabetes[3].

Making insulin-resistant cells more sensitive to insulin is another goal of novel therapeutics for diabetes. In preclinical research, insulin sensitivity has been improved with gene therapy, antisense oligonucleotides and novel biologic approaches to decrease ectopic fat, particularly in the liver, which in turn alleviates insulin resistance and rejuvenates beta-cell function, leading to diabetes remission.

FROM REMISSION TO CURE

If we want to change the trajectory of rising diabetes cases, we need to use novel approaches that target the drivers of diseases.

At AstraZeneca, we are using our genomics expertise and state-of-the-art drug discovery technologies to build on strong science to develop potential medicines aimed at treating – and ultimately curing – diabetes.

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