**Gene therapy: unlocking the potential to prevent and cure type 1 diabetes**

Aims:

Type 1 diabetes (T1D) is caused by the autoimmune destruction of the pancreatic insulin producing beta (β)-cells. The aim of this study was to investigate a novel gene therapy approach to prevent disease development by replacing pancreatic β-cell function with that from liver cells that had undergone pancreatic transdifferentiation.

Methods:

A clinically applicable third-generation lentiviral vector (pRRLSIN.cPPT.PGK-GFP.wpre vector (WPT) was used to deliver a cocktail of β-cell transcription factors (*Pdx1, ND1 and MafA)* to the portal vein of 5-6-week-old female non-obese diabetic (NOD) mice. The control group received saline. Weight and blood glucose levels were monitored. Intraperitoneal glucose tolerance tests (IPGTTs) were performed. Immunofluorescence was carried out to monitor transduction efficiency utilising marker genes. RT-PCR was used to identify expression of pancreatic genes.

Results:

At the experimental endpoint (30-weeks), 100% of the NOD mice that received the lentiviral vector expressing the three β-cell transcription factors were normoglycemic (6.6 ± 0.5 mmol/l). By comparison the blood glucose levels (BGLs) of the control group began increasing at approximately 90 days after saline injection, when the mice were 17-18 weeks of age (17.0 ± 3.9 mmol/l). Additionally, IPGTTs revealed that treated NOD mice could normalise blood glucose concentrations as efficiently as non-diabetic control animals. RT-PCR detected a range of pancreatic markers, such as somatostatin, Glut2 and most importantly mouse insulin 1/2, which was also found to be in the liver. The livers of treated animals stored 3.0 ± 0.5mU/insulin/mg, whilst the pancreas of these animals stored 7.5 ± 0.01 X 10-2mU/mg. Liver function tests remained normal.

Conclusion:

Collectively, this data shows expression of these β-cell transcription factors led to partial liver pancreatic transdifferentiation and halted the development of hyperglycemia and abnormal glucose tolerance, which are the hallmarks of T1D. Thus, this approach holds substantial promise as a potential prophylactic strategy.