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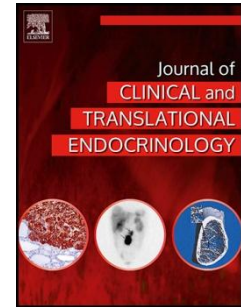
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American Diabetes Association Meeting report – Dr Catriona Hilton¹ and Dr Nicola L Beer^{1,*}

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Since its conception in 1940 the American Diabetes Association (ADA) has been chairing an annual conference, which has become one of the key international forums for sharing knowledge and disseminating new research into diabetes mellitus. June 2016 saw the ADA's 76th Scientific Sessions, this year held in New Orleans, USA. More than 15,000 clinicians, health care professionals and scientists involved in diabetes care and research joined together for a 5 day program. We were fortunate to be sponsored to attend by Elsevier.

The conference consisted of 8 parallel themes, covering acute and chronic complications, behavioural medicine, clinical nutrition, education and exercise, clinical diabetes and therapeutics, epidemiology and genetics, insulin action and molecular metabolism, and integrated physiology and obesity.

Exciting new data emerging from clinical trials

Two of the highlights of this years' scientific sessions were the presentation of the latest results of 2 major clinical trials, the Liraglutide Effect and Action in Diabetes—Evaluation of Cardiovascular Outcome Results (LEADER) Trial and the EMPA-REG Outcome Trial.

The LEADER trial randomised more than 9,000 individuals with type 2 diabetes to GLP-1 agonist Liraglutide or placebo, on top of standard care. Study participants had either had a prior cardiovascular event or were at high risk of future cardiovascular events. In this much anticipated session the investigators reported their findings after between 3.5 and 5 years of follow up. There was a significant 22% reduction in cardiovascular death and a 15% in all-cause mortality, with non-significant reductions in non-fatal myocardial infarction and stroke. The investigators also reported significant reductions on HbA1c, weight and risk of severe hypoglycaemia with Liraglutide. This trial was the first to show a cardiovascular benefit of a GLP-1 inhibitor.

The conference also saw the awaited update on the EMPA-REG outcome trial. To date Empagliflozin is the only other diabetes drug of any class to show a cardiovascular benefit. The EMPA-REG outcome trial recruited more than 7,000 individuals with type 2 diabetes and at high cardiovascular risk and randomised them to either the SGLT2 inhibitor Empagliflozin or placebo. Empagliflozin demonstrated a 38% reduction in cardiovascular death, a 32% reduction in all-cause mortality and a 35% reduction in hospitalisation for heart failure, effects that were consistent across age groups and LDL-cholesterol subgroups. New data reported showed that Empagliflozin also significantly decreased the progression of nephropathy by 39%, with an associated reduction in new onset macroalbuminuria. The mechanisms underlying the observed cardiovascular and renal benefits are uncertain but appear to go beyond its effects on glycaemic control. Together the presentation of these trial results sparked much debate about the possibility of using diabetic therapies for benefits beyond their glycaemic effects.

Advances in diabetes disease modelling: genome-edited human stem cells

Another of the biggest talking points of the meeting was the complimentary use of human stem cells and genome-editing technologies for diabetes disease modelling. Dieter Egli (Columbia University Medical Center, USA) kicked off the 'Update on Cell Sources for Beta-Cell Replacement' session by setting the scene for stem cells as a source of human endocrine pancreas-like tissue, discussing the

pros and cons of obtaining such cells via *in vitro*-directed differentiation and *in vivo*-maturation protocols. After approximately one month of differentiation-in-a-dish, Egli's team were able to produce endocrine pancreas-like cells capable of insulin secretion in response to a variety of secretagogues. However, by far and away the most impressive functional data were that obtained from cells matured under the kidney capsule of SCID mice. Egli showed that near 100% of *in vivo*-derived cells were positive for c-peptide (up from 50% of *in vitro* cells), and demonstrated glucose-responsive insulin secretion when tested *ex vivo*, and in STZ-diabetic mice. Glycaemia was even restored when the transplanted stem cell-derived pancreatic progenitors were obtained from donors with type 1 diabetes (T1D). This, teamed with Egli's successful correction of stem cells from individuals with *HNF1A* and *ABCC8* mutations using the site-specific nuclease CRISPR-Cas9 system, suggests that in addition to disease modelling, the eventual use of such cells for autologous transplantation is theoretically possible.

Rohit Kulkarni (Joslin Diabetes Center, USA) also presented data whereby induced pluripotent stem cells (iPSCs) derived from T1D 'medallists' (individuals with T1D for 50 years or over) were used to understand the mechanisms underlying diabetes-associated complications. Kulkarni and colleagues showed a major role for DNA damage repair genes, as well as inflammatory pathways, highlighting the utility of patient-derived stem cells in modelling all aspects of diabetes dysfunction and comorbidities.

Whilst much of our understanding of endocrine pancreas development has been gleaned from rodent studies, the overlap with human islet generation is not complete. Paul Gadue (University of Pennsylvania, USA) demonstrated the utility of stem cell-derived islet-like cells in modelling human development, by using cells from individuals harbouring pancreatic agenesis-causing *GATA6* mutations to show that this transcription factor transmits pro-survival signals following primitive streak induction. Additionally, and by far and away the biggest achievement of Gadue's team was the generation of 'endodermal progenitor stem cell lines' – sorted definitive endoderm cells cultured in a cocktail of BMP4, bFGF, VEGF, and EGF – which can be bulked up, banked, and revived for use in disease modelling. This not only abolishes the need for per-experiment definitive endoderm induction and the heterogeneity this brings, but also facilitates disease modelling where mutations (like those in *GATA6*) reducing viability of endodermal- and early islet-developmental cell types, can be studied.

This work was complemented by that of Danwei Huangfu (Memorial Sloan Kettering Center, USA) who presented data on her innovative inducible CRISPR-Cas9 system. Upregulation of this site-specific nuclease from the safe-harbour *AAVS1* locus in human stem cells was used to generate both hetero- and homozygous *GATA4* and *GATA6* knockout lines, as well as introduce the novel R546C-*GATA6* mutation. Huangfu's team showed that dysfunctional *GATA6* leads to: i) reduced overall *PDX1* levels in pancreatic progenitor cells, ii) fewer cells co-expressing *PDX1* and *NKX6.1* (a transcription factor needed for *INS* induction), and iii) lower *PTF1A*, *NEUROD1*, and *NKX2.2* expression. Reduction in these five transcription factors correlated with reduced islet-like function, confirming their importance in endocrine pancreas cell maturation.

Moving on from disease modelling: 'naked stem cells' could be transplanted into any individual with diabetes

Looking to the future and moving on from the 'simple' use of stem cell-derived islet-like cells in disease modelling, as an alternative source of endocrine pancreas tissue, it is theoretically very possible that these cells could be transplanted into individuals with diabetes. However, for any stem cell-derived cells to be of use in diabetes treatment, their tolerance by and/or protection from an

individual's immune system must be addressed. Whilst several in the field continue to investigate the use of artificial encapsulation devices in the clinic, Chad Cowan (Harvard Stem Cell Institute, USA) presented an innovative take on this issue; using CRISPR-Cas9 to generate universal donor stem cells. Such 'naked stem cells' would be analogous to O Rhd negative blood, which with the absence of antigens, could be given to any donor. By targeting the major histocompatibility complex genes alongside those encoding master regulators of antigen presentation (*CIITA* and *NLRC5*), it was hoped that these cells would not be rejected upon transplantation into mice with humanised immune systems. However, their quick rejection and destruction suggests that they are still recognisable to a subset of memory T-cells within these rodents. Accordingly, Cowan's team continue with a two-pronged attack on transplantation of islet-like cells, working to 'induce immune tolerance' in the cell recipient alongside reducing the immunogenicity of transplanted cells.

The future of diabetes research and clinical care looks bright

This year's scientific sessions saw a high standard of both clinical and basic science research, and provided a forum for lively discussion from clinicians and scientists from across the globe. We are in an exciting era for diabetes; with the presented advances in biological understanding gleaned from clinical trials alongside state-of-the-art human physiologically-relevant disease models, the sense from this year's scientific sessions was that diabetes research and care is moving forward at a timely pace.