COVID-19 and diabetes: do shared pathways have therapeutic implications?

This session was dedicated to COVID-19 and diabetes, made even more poignant by the virtual format of the meeting. Juliana Chan (The Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong), provided an overview of the current evidence linking the overlapping characteristics of COVID-19 and diabetes. For example, both diseases disproportionately affect vulnerable populations such as specific ethnicities, individuals of low socioeconomic status, and those with poor access to healthcare. Indeed, the term syndemic would be a more appropriate description of the current crisis; a clustering of biological and environmental factors that worsen the outcomes of coexisting diseases. Chan presented findings from a pair of papers recently published in The Lancet Diabetes & Endocrinology. The first, by Holman et al., comprised a UK COVID-19 population study reporting a marked increase in deaths of people with Type 1 diabetes (T1D) and Type 2 diabetes (T2D) in 2020 compared to mean deaths in 2017–19, with a large proportion being attributable to COVID-19. This was echoed in the second paper by Barren et al., reporting that out of 23698 in-hospital COVID-19-related deaths in the UK, 1.5% had T1D and 31.4% had T2D. Alarming, when adjusted for age, race, sex and other comorbidities, individuals with T1D actually had a higher risk of in-hospital death related to COVID-19 (odds ratio (OR) of 3.51), compared to individuals with T2D (OR of 2.03). Therefore, glucose control is an immediate modifiable risk factor for people with diabetes who are trying to optimize their health during the current pandemic.

Daniel Drucker (Mt. Sinai Hospital, Toronto, Canada) then presented a fascinating talk that summarized the latest evidence indicating that COVID-19 and T2D have shared molecular pathways, which might help or hinder therapeutic strategies. As previously discussed by Chan, the level of glycaemic control in people with diabetes is related to the severity of the outcome following SARS-CoV-2 infection. Angiotensin-converting enzyme 2 (ACE2) is a molecule with key roles in both COVID-19 and diabetes. It is a membrane-bound enzyme that has cardiometabolic action by catalysing the cleavage of angiotensin II into angiotensin (1-7) – a vasodilator. Although levels of ACE2 tends to be reduced in individuals with T2D, its expression may be increased in T2D patients on commonly prescribed ACE inhibitors and/or angiotensin receptor blockers. This might have implications in COVID-19 as ACE2 has also been identified as the major SARS-CoV-2 receptor responsible for binding and internalizing SARS-CoV-2. A further layer of complexity is that internalization of SARS-CoV-2 requires the host serine protease TMPRSS2. TMPRSS2 has a critical role in endocrine-sensitive malignancies, such as prostate cancer, and current efforts are underway to reduce or block the activity of the TMPRSS2 molecule as a therapeutic option to treat COVID-19. Mouse studies that delete TMPRSS2 exhibit reduced infectivity by coronaviruses. This concept is now being applied to humans in randomized control trials, using enzyme inhibitors of TMPRSS2, and modulators of oestrogen and androgen therapy to reduce the levels of TMPRSS2 in people with COVID-19. These trials are ongoing so it is not clear if these strategies will provide a clinically meaningful benefit. However, as SARS-CoV-2 biology and its complex interplay with other diseases becomes better understood, it is hoped that a greater number of therapeutic strategies will prove successful in its management.

Developing better insulins

In a session dedicated to the development of better insulins for the treatment of T2D, two talks focused on promising results from phase 2 clinical trials. Julio Rosenstock (Dallas Diabetes Research Centre at Medical City, Dallas, TX, USA) presented results on the once-weekly basal insulin Icodec. This trial was motivated by individuals with T2D preferring fewer injections than current once-daily basal insulin options. Engineered to improve its molecular stability, insulin Icodec is less prone to enzyme-mediated degradation and receptor-mediated clearance, enabling a half-life of ~1 week (compared to ~1 day shown by longer-acting basal insulin analogues). In this phase 2 randomized, double-blind, double-dummy, parallel group,
treat to target trial, weekly insulin Icodec injections were compared to daily insulin Glargine U100 injections, both in combination with Metformin ±DPP4i in insulin naïve patients with T2D. The primary objective was to investigate the effect of once-weekly insulin Icodec on glycaemic control after 26 weeks, with the secondary objective to assess the safety and tolerability of this treatment. Once-weekly insulin Icodec displayed a similar glucose-lowering effect and safety profile to once-daily insulin Glargine U100, and crucially, no new safety issues were identified in this trial. These encouraging results were published in the *New England Journal of Medicine* to coincide with this talk and insulin Icodec will be further investigated in a phase 3 clinical development program. It is the hope that reducing the number of insulin injections will result in increased adherence and compliance, in turn leading to better management of T2D.

Roy Eldor (Institute of Endocrinology, Metabolism & Hypertension, Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel) presented results from a phase 2b trial using the orally-delivered insulin, ORMD-0801. Typically, basal insulin analogues are susceptible to protein degradation as they pass through the gastrointestinal tract (due to harsh pH, mechanical challenges, proteases and absorption barriers), resulting in low bioavailability. Oramed Pharmaceuticals Inc. (New York, NY, USA) have developed an oral peptide delivery technology that comprises a protective coating that remains intact in acidic conditions, protease inhibitors to counter enzymatic degradation, and absorption enhancers to facilitate passage through the small intestine. The efficacy of ORMD-0801 was tested in a randomized, placebo-controlled, multicentre, phase 2b, dose-finding study administered orally, once, twice or three times daily at 8, 16 or 32 mg in 419 T2D subjects inadequately controlled on standard therapies. Evening treatment of ORMD-0801 at 8 and 32 mg elicited clinically relevant reductions of blood glucose levels. Furthermore, administration was not associated with increased risk of hypoglycaemia or with serious or severe adverse events. These results indicate that an alternative to daily injections of basal insulin is feasible, and this strategy to “make needles needless” is likely to enhance subject compliance and reduce treatment costs, offering renewed hope for the management of this debilitating disease.

**Metabolic and functional specialization of the pancreatic β cell**

The 14th Albert Renold Lecture was delivered by Guy Rutter (Imperial College London, UK) who presented compelling evidence that metabolic and functional heterogeneity are fundamental to pancreatic β cells. Indeed, stable cellular variation is required to establish coordinated functional networks that form an interconnected network (displaying so-called “small worlds” behaviour) in which subpopulations can develop specialized roles. This network is observed across animal species, and connectivity analysis has defined the presence of superconnected cells that appear to be important for overall islet dynamics. Experimental attempts to explore the role of these highly connected “hub” cells, for example by specifically inactivating them using optogenetic approaches, have indicated that they have a possible pacemaker function that determine certain characteristics of the whole islet. When pacemaker cells are inactivated, cellular connections are lost, calcium waves across the islet are inhibited, and pan-islet dysregulation ensues. Careful imaging analysis has revealed that hub cells tend to be located on the periphery of the islet and are enriched for enzymes involved in glucose metabolism and glucose sensing, unlike their less connected counterparts that secrete more insulin. However, documenting the physiological role of β cells in vivo and understanding how their function is altered in disease, and in response to therapy, has so far been hampered by a paucity of suitable imaging modalities and preclinical models.

To overcome these challenges, Rutter presented recent work using intraval imaging of reporter islets in which Ca<sup>2+</sup> dynamics could be recorded at near single cell resolution repeatedly from the same islet. This technique was applied to a vertical sleeve gastrectomy (VSG) mouse model to assess pancreatic β cell function following bariatric surgery. Islets expressing a genetically-encoded calcium reporter were transplanted into the anterior chamber of a recipient eye and Ca<sup>2+</sup> dynamics were recorded pre- and post-VSG surgery. VSG was shown to increase β cell Ca<sup>2+</sup> dynamics within eight weeks post-surgery compared to pre-operative levels and the sham operated group. Furthermore, VSG increased the number and strength of β-to-β cell connections at ten weeks after surgery and islets exhibited greater sensitivity to glucose when compared with sham mice, suggesting changes in glucose metabolism in the islets following VSG. Published as a preprint in Bioxiv in May, 2020, this study demonstrates that bariatric surgery relieves the symptoms of T2D, at least partially by maintaining functional β cell identity and coordinating activity across the islet. While these are exciting results, further studies are needed to fully understand the mechanisms underlying glycaemic normalization following VSG, and importantly, to what extent this preclinical model recapitulates events in patients subjected to bariatric surgery.

**Using stem cells to model diabetes**

In a session dedicated to utilizing human stem cells to model diabetes, Maria Cristina Nostro from McEwen Stem Cell Institute (University Health Network, Toronto, Canada) gave a fascinating talk on the use of human embryonic stem cells (hESCs) to model pancreatic development. The goal is to generate functional cell types from hESCs for regenerative purposes, for example, surrogate pancreatic islet cells to replace those lost in individuals with diabetes. However, efficient stem cell to β cell differentiation has proven difficult. Depending on the differentiation protocol, progenitor cells can be specifically driven into different lineages, to generate a variety of cell types including insulin-producing β cells or glucagon-producing α cells. Nostro presented in vivo mouse data showing that inhibition of Wnt signalling is regulated by modulation of Hedgehog (Hh) signalling from the pancreatic mesenchyme via Sfu and Sppn. When Hh signalling is activated via loss of these regulators, pancreatic growth and β cell genesis are impaired. When these findings were tested in mouse organoid and human stem cell culture, suppression of WNT signalling was also required for endocrine commitment and pancreatic precursor generation, highlighting the translational relevance of these preclinical findings, and the potential to optimize differentiation protocols to enrich β cell generation.

Diego Balboa from The Centre of Genomic Regulation (Barcelona, Spain) then gave a talk on how human pluripotent stem cells (hPSCs) could be used to model monogenic diabetes. Differentiation protocols now exist that enable reliable conversion of hPSCs into maturing β cells. These cells can then be used to model genetic defects causing diabetes. Monogenic diabetes makes up 1-2% of all diabetes cases that are caused by mutations in pancreatic and β cell genes, commonly affecting neonates (permanent neonatal diabetes mellitus) or young individuals (maturity onset diabetes of the young). The approach is to take patient-derived somatic cells and de-differentiate them into induced hPSCs (hiPSCs). Genome editing can then be applied to correct the monogenic mutation, and both patient-derived and corrected hiPSCs can be differentiated into β cells, with the corrected β cells acting as an autologous isogenic control with identical genetic backgrounds except for the disease-causing mutation. These controls also display reduced variation in differentiation efficiency and therefore enables more effective dissection of disease mechanisms. Balboa presented how this approach could be used to define how specific mutations were responsible for particular disease phenotypes. For example, genes responsible for pancreatic developmental defects (*STAT3, INS, RFX6*), insulin secretion defects (*ABCC8, KCNJ11*), and T1D susceptibility genes (*TH2*) have all been explored using CRISPR-Cas9 editing on hiPSCs. Importantly, limitations of this approach were also discussed.
including issues with the specific differentiation protocols currently used. For example, the inability of induced pancreatic progenitor cells to recapitulate the proliferative dynamics exhibited by the human foetal pancreas. A further limitation is that differentiation protocols might bypass important genetic defects unless optimized differentiation protocols are used. In addition, stem cell-derived β cells might display suboptimal functionality compared to their mature adult β cell counterparts, and the reasons underlying these differences need to be understood and factored in to any conclusions that are drawn. It is hoped that as differentiation protocols are refined it will also be possible to use hiPSC technology to start characterizing regulatory mutations in non-coding regions of the genome and their role in diabetes.