Research

Stem Cells and Cell Therapy for Diabetes

Diabetes is a debilitating chronic disease spiralling out of control, affecting more than 463 million people in the world. People with diabetes commonly develop severe complications such as blindness, cardiovascular diseases, kidney failures and lower limb amputations, leading to an astronomical healthcare burden. Despite intensive research, mechanisms underlying human pancreatic β cell failure during the development of diabetes and its eventual dysfunction remain to be elucidated. Species-specific differences in pancreas development, islet architecture and distribution pattern of islet cells necessitate a human model for diabetes research.

The Teo Lab seeks to leverage on human cell models such human pluripotent stem cell (hPSC)-derived cells, human islets and human β cells to study diabetes disease mechanisms, develop therapeutics for diabetes and use them as a cell source for cell therapy in diabetes. The three main thrusts of the lab are:

1) Modelling and studying human diabetes disease mechanisms

hPSCs that comprise of human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) derived from patients with monogenic, gestational, type 1 or type 2 diabetes patients will be differentiated into human pancreatic cells or cell types affected in diabetic complications to dissect the pathology of diabetes and its complications (Figure 1). This effort will also contribute directly to the understanding of human potential and development.

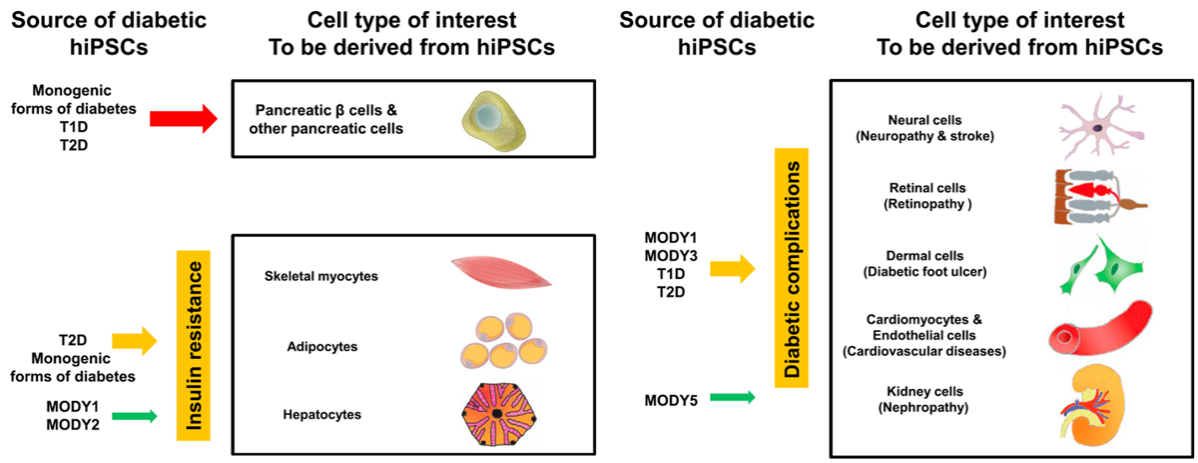

Figure 1. Differentiation of hiPSCs derived from diabetic patients into various cell types for *in vitro* disease modelling of diabetes and its complications (Teo et al., Cell Metab, 2013).

The process of differentiating hPSCs into pancreatic β-like cells will be used to study human β cell development, maturation and function. This will identify critical steps, key pathways and mechanisms which guide human β cell development and maturation (Figure 2).

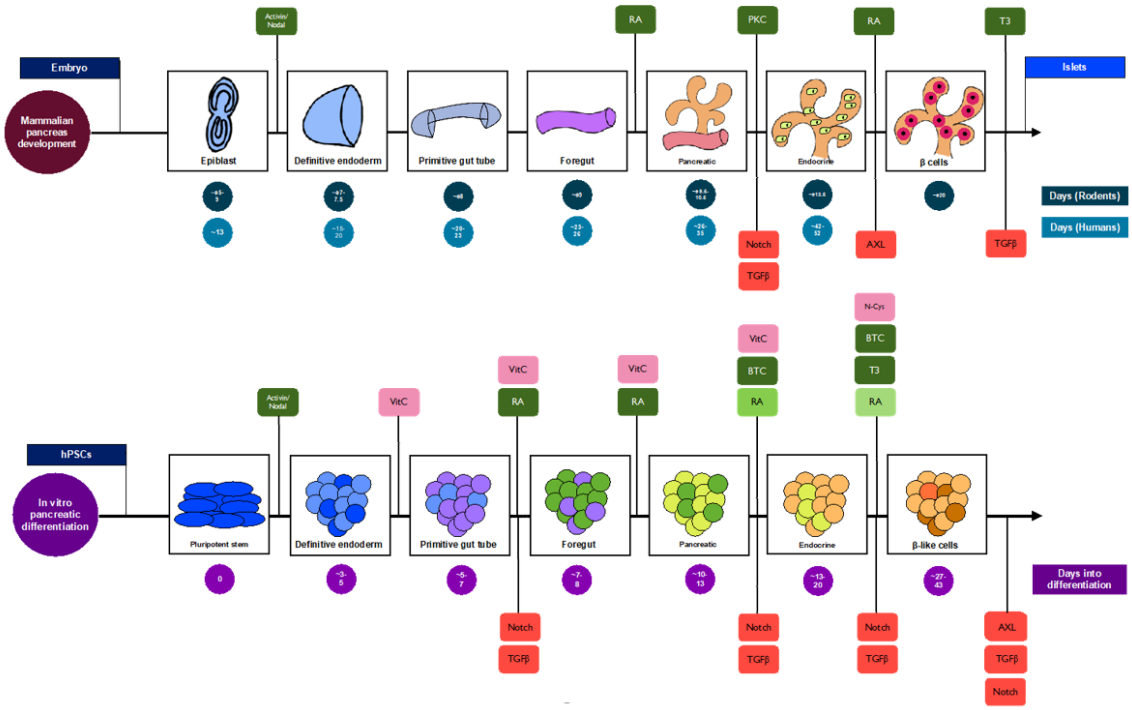

Figure 2. Differentiation of hPSCs into pancreatic β-like cells based on knowledge from mammalian pancreas development (Santosa et al., Front Endo, 2016).

Differentiating hiPSCs that harbour diabetes risk alleles will pinpoint mechanisms of β cell demise at the earliest stage(s) and functionalise the gene variants associated with diabetes (Figure 3). This is otherwise not possible given that clinical manifestation of overt diabetes in humans takes decades to occur and patient material is inaccessible.

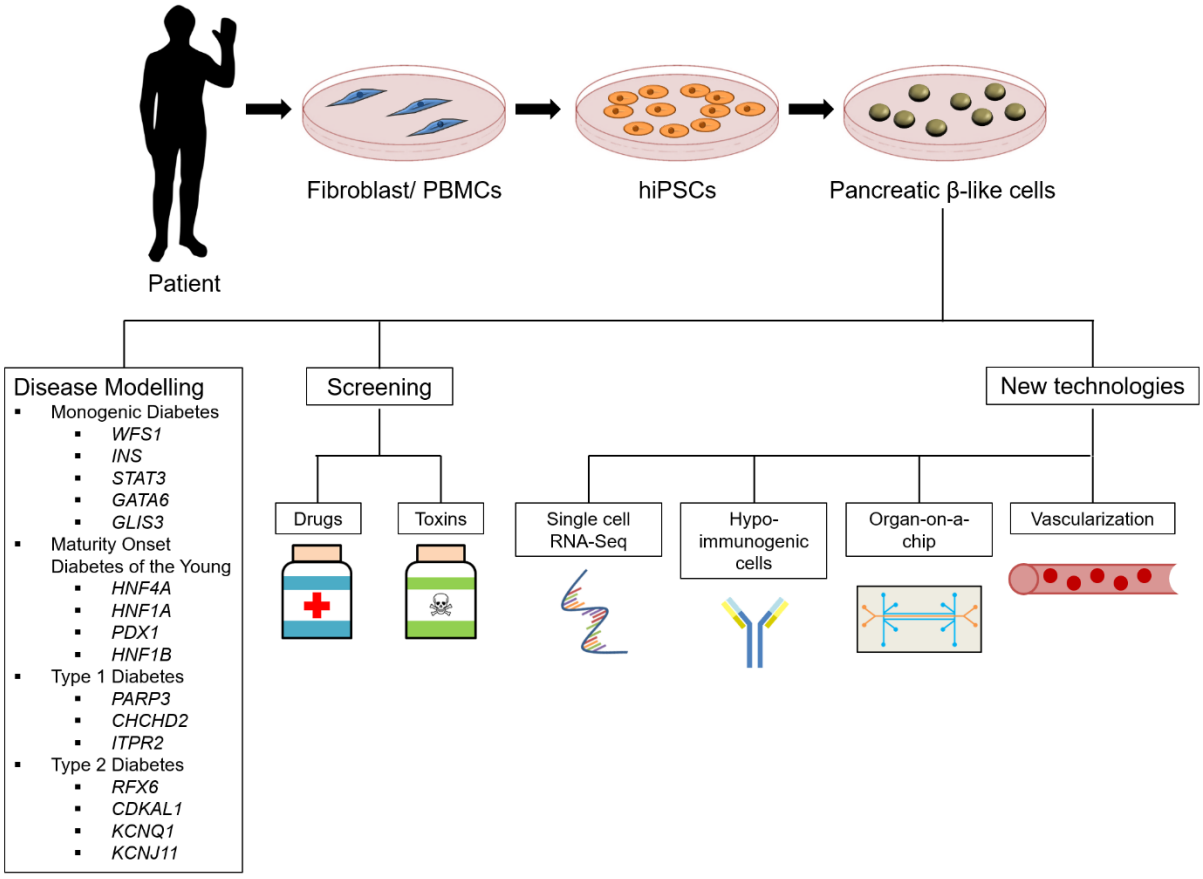

Figure 3. The use of hiPSC-derived pancreatic β-like cells for diabetes disease modelling, drug screening and development of therapeutics using newer technologies (Amirruddin and Low et al., Sem Cell Dev Biol, 2019).

Differentiating hiPSCs from diabetic patients with and without complications, such as diabetic nephropathy, will elucidate genetic and epigenetic perturbations which occur in cells/tissues/organs constantly exposed to hyperglycaemia.

2) Developing new therapeutics to improve pancreatic β cell function

Patient-specific hiPSCs with clinical deficiencies in insulin secretion, such as that of MODY1 and MODY3 (Figure 4), will be used to identify new targets and pathways relating to insulin secretion mechanisms.

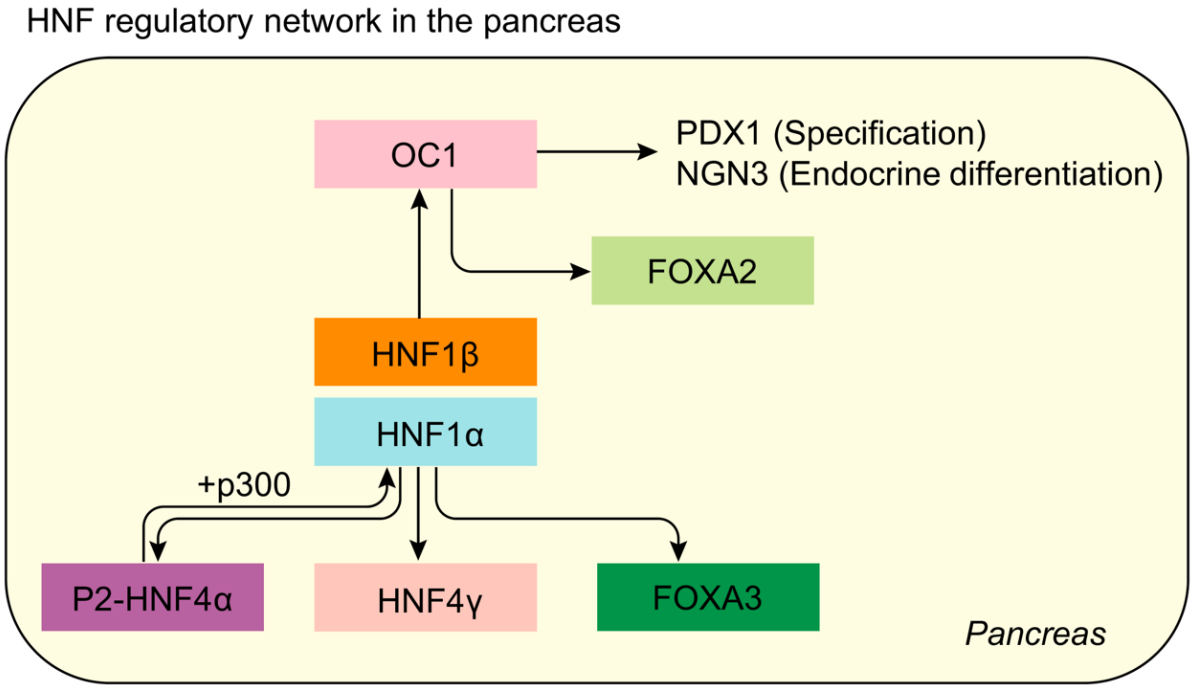

Figure 4. Hepatocyte nuclear factors (HNFs) such as HNF4A/MODY1 and HNF1A/MODY3 are involved in a regulatory network in the pancreas (Lau et al., J Hepatol, 2018). Mutations in these pancreatic transcription factors result in defective insulin secretion in MODY patients.

Novel biological and natural products will also be tested on human islets and human β cells with the goal of identifying new molecules or signalling pathways that can regulate β cell insulin secretion capacity.

3) Developing stem cell-based therapies for the treatment of diabetes

Human stem cells are highly renewable and non-xenogenic. Therefore, they can be appropriately positioned for cell therapy in diabetes patients. Current Good Manufacturing Practice (cGMP) hPSC-derived β cells can potentially be used for islet cell replacement therapy in diabetes patients. Multipotent mesenchymal stromal cells (MSCs) can also be used to confer beneficial immunomodulatory properties upon transplanted human islets or β cells to improve the long-term success of cell replacement therapy. Last but not least, bioengineering efforts including the development of encapsulation devices or the use of scaffolds will complement these stem cell-based development efforts. Together, it is envisioned that the production of sufficient mature and functional human β cells from hPSCs for cell replacement therapy will achieve physiological control of blood glucose levels, to provide a better life for diabetes patients.