

Congratulations to IMCB's latest PhD graduate – Blaise Su Jun LOW

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Blaise Su Jun LOW

Thesis Title: Investigating The Effects of A Novel HNF1A Mutation In Maturity Onset Diabetes of The Young 3 (Mody3)

Maturity onset diabetes of the young (MODY) is an autosomal dominant inherited form of monogenic diabetes. MODY3, one of the most common MODY subtype, is caused by heterozygous mutations in the *HNF1A* gene, which encodes a transcription factor. MODY3 is typically characterized by progressive β cell failure and insulin secretion defects. In this study, I leveraged upon MODY3 patient-derived human induced pluripotent stem cells (hiPSCs) to study the effects of a novel *HNF1A*^{+/*H126D*} mutation on β cell function. Using *in vitro* pancreatic differentiation, I generated MODY3 hiPSC-derived β -like cells which exhibited defective glucose-stimulated insulin secretion function. Genome-wide RNA-Seq and CHIP-Seq analyses on MODY3 hiPSC-derived endocrine progenitors revealed numerous downregulated gene targets, some of which were directly bound by HNF1A protein. The MODY3 β -like cells displayed impaired glucose uptake capacity and reduced ATP production, which was associated with decreased transcript and protein expression of GLUT2, a β cell glucose transporter. CHIP analyses revealed reduced HNF1A binding to the *GLUT2* promoter in the *HNF1A*^{+/*H126D*} endocrine progenitors. My findings suggest that *HNF1A* mutations dysregulate GLUT2 expression, which reduces the glucose uptake capacity of human β cells, hence resulting in decreased ATP production, and contributing to impaired glucose-stimulated insulin secretion. Overall, my MODY3-hiPSC model reveals the importance of HNF1A in regulating several target genes, including *GLUT2*, that are involved in insulin secretion function, which may account for the insulin secretory defect observed in MODY3 patients.

Supervisors: Dr Adrian Kee Keong TEO and Prof E Shyong TAI

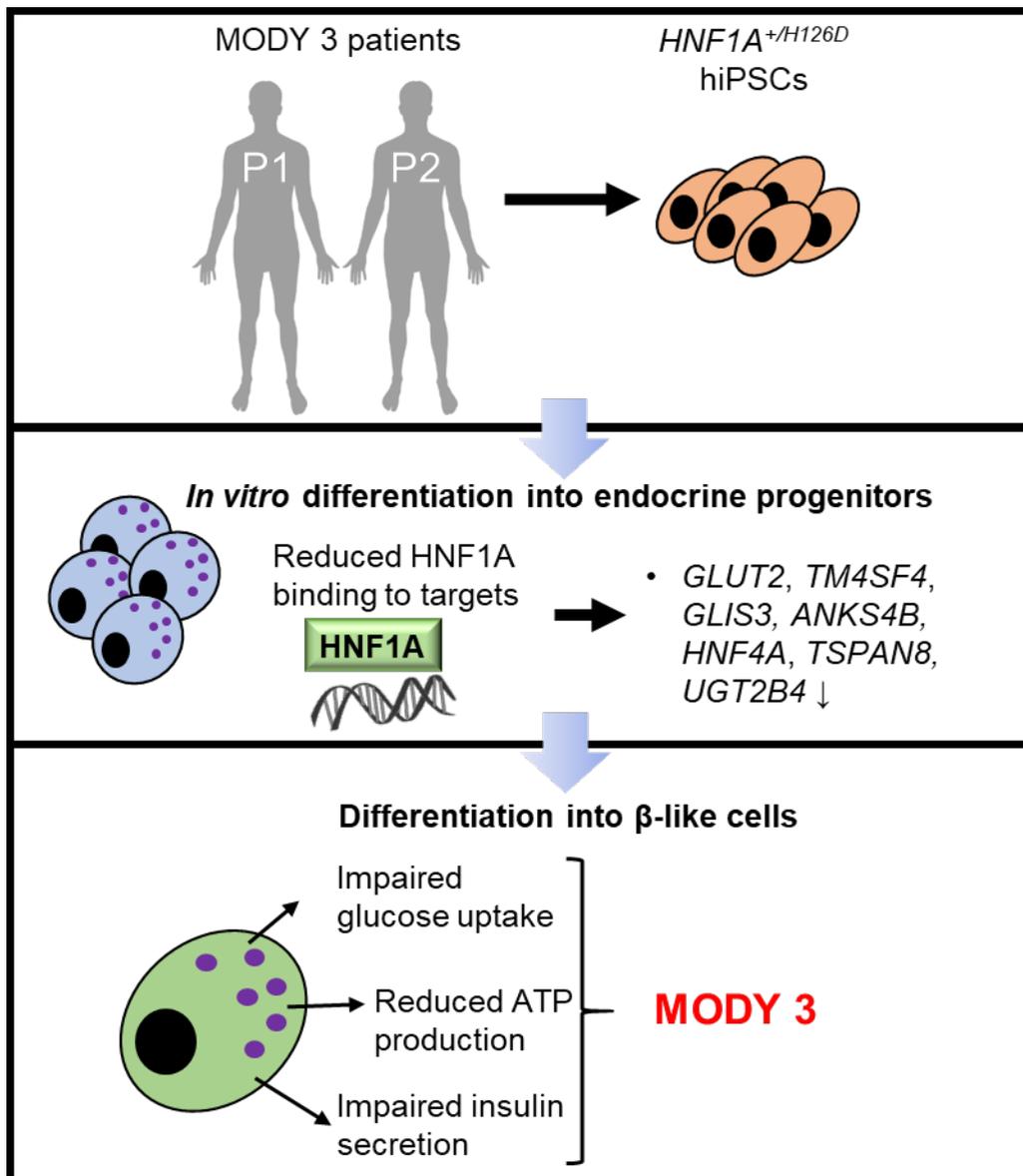


Figure Legend: I have established an *in vitro* platform for MODY3 disease modeling via patient-derived hiPSCs, generated from two MODY3 patients (P1 and P2) harbouring the heterozygous $HNF1A^{+/H126D}$ mutation. The $HNF1A^{+/H126D}$ mutation reduced the binding of the mutant HNF1A transcription factor to its target genes, many of which are involved in β cell function. The decreased expression of these essential β cell genes, resulted in impaired glucose uptake and reduced ATP production in the MODY3 β -like cells. These functional defects have contributed to the lack of insulin secretory capacity in the diseased β cells, to result in the pathology of MODY3.

List of publications

Low, B.S.J., Lim, C.S., Ding, S.S.L., Tan, Y.S., Ng, N.H.J., Krishnan, V.G., Ang, S.F., Neo, C.W.Y., Verma, C.S., Hoon, S., Lim, S.C., Tai, E.S., Teo, A.K.K. (2021). Decreased GLUT2 and Glucose Uptake Contribute to Insulin Secretion Defects in MODY3/HNF1A hiPSC-derived Mutant β Cells. (*Re-submitted for minor revision*)

Amirruddin, N.S.* , **Low, B.S.J.*** , Lee, K.O., Tai, E.S., and Teo, A.K.K. (2019). New Insights Into Human Beta Cell Biology Using Human Pluripotent Stem Cells. *Semin. Cell Dev. Biol.*

Santosa, M.M., **Low, B.S.J.**, Pek, N.M.Q., and Teo, A.K.K. Knowledge Gaps in Rodent Pancreas Biology: Taking Human Pluripotent Stem Cell-Derived Pancreatic Beta Cells into Our Own Hands. (2016). *Frontiers in Nutrition and Frontiers in Endocrinology.*