Congratulations to IMCB's latest PhD graduate – Shabrina AMIRRUDDIN

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Thesis Title: The impact of INS and STARD10 gene mutations on insulin processing, secretion, and pancreatic beta-cell function in diabetes

Diabetes can be caused by genetic mutations that result in defective insulin processing and secretion by pancreatic β-cells. Here, I will study two genes involved in β-cell function: insulin (*INS*) and *STARD10*. Heterozygous *INS* gene mutations are reported to cause neonatal diabetes in humans, while polymorphisms in the *STARD10* gene, which encodes a lipid-transfer protein, are associated with increased T2D risk. Through various experimental models, we showed that the dominant negative effects of mutant human INS expression are evident

after nine weeks of expression, as shown by the decline in insulin secretory capacity. We also showed that *STARD10* gene knockout downregulated cell cycle gene expression and perturbed several lipid species in *STARD10*$^{-/-}$ stem cell-derived β-like cells. Our results provided deeper insight into the mechanisms of β-cell dysfunction caused by *INS* and *STARD10* gene perturbations. Modulation of mutant INS or its consequences on ER stress can potentially restore the function of WT *INS* allele for patients with heterozygous *INS* mutations. Addressing lipid alterations or indirect effects on β-cell identity caused by *STARD10* gene polymorphisms could also potentially improve β-cell function in these T2D patients.

Supervisors: Dr Adrian Teo and Prof Lee Kok Onn

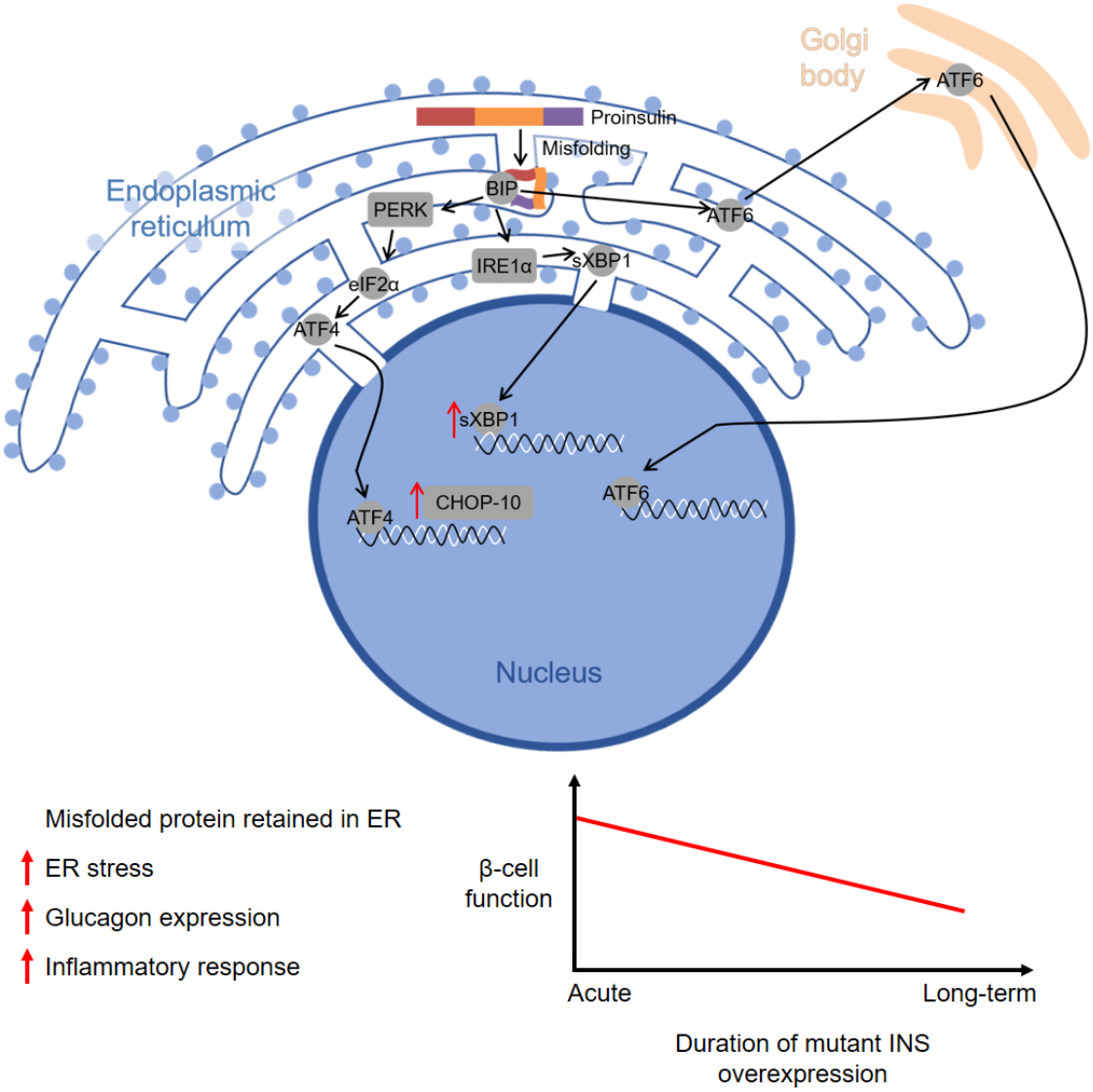

Figure Legend: <u>Schematic of the proposed mechanism underlying heterozygous INS gene mutations and STARD10 KO in β-cells.</u>

Heterozygous *INS* gene mutations such as the C109Y and G32V mutations result in misfolded proinsulin, which upregulates ER stress via XBP1 and CHOP-10, upregulates inflammatory response, and remodels islet cell composition. These three mechanisms will likely exacerbate over time, resulting in decreasing β-cell function, possibly resulting in β-cell apoptosis.

<u>List of publications</u>

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