PhD PROGRAM IN EXPERIMENTAL AND CLINICAL MEDICINE

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PROJECT TITLE: Exploiting targeted genome editing to avoid immune rejection and to increase safety of insulin-producing cells derived from human iPSC

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The recent demonstration that human induced Pluripotent Stem Cells (iPSC) can differentiate into insulin-producing cells [1–3] and reverse diabetes, upon transplantation into diabetic mice, raises the possibility of using a similar cell replacement strategy to treat patients with type 1 diabetes (T1D). However, two main hurdles limit the clinical translation of this approach: first, differentiated iPSC would encounter a T cell-mediated allo and autoimmune rejection upon transplantation; and second, the risk of tumorigenesis intrinsic to reprogrammed cells and of the possible infusion of contaminating pluripotent cells together with insulin-producing cells.
The objective of this project is to develop a treatment for T1D centred on transplantation of "universally compatible" insulin-producing cells derived from iPSC, engineered through targeted genome editing. These modified iPSC would allow for the enrichment of terminally differentiated insulin-producing cells that are hidden from the immune system of the host but pose no major safety concern. The project will be carried out in collaboration with the Unit of Epigenetic regulation and targeted genome editing at Telethon Institute for Gene Therapy (SR-TIGET).
The project specifically aims at generating through genetic engineering iPSC that are:
1. devoid of endogenous HLA class I and ectopically express a tolerogenic chimeric HLA-E[4], to evade both T and NK cells attack
2. endowed with the suicide gene TK[5], acting as a safety kill-switch in the case of adverse events, allowing the graft to be purged *in vivo* upon treatment with ganciclovir.
3. endowed with a ΔLNGFR gene under the control of an insulin promoter, acting as a positive selection surface marker allowing the enrichment of insulin producing cells.
In addition, our project includes steps aiming at:
4. characterizing the glucose responsiveness, the immune evasive capacity, and the safety of the insulin-producing cells derived from the genetically engineered iPSC.

References:

1. Rezania A, Nat Biotechnol. 2014.
2. Pagliuca FW, Cell. 2014
3. Pellegrini S, Acta Diabetol. 2015
4. Lilienfeld BG, Xenotransplantation. 2007
5. Greco R, Front Pharmacol. 2015