**Understanding the mechanisms underlying immunomodulatory properties of human islet-derived progenitor cells**

**Background & Aim**

Type 1 diabetes (T1D) is an autoimmune disorder that destroys insulin-producing cells. Targeting immune cells has shown promise in T1D, emphasizing the need to identify new immunomodulatory molecules. Mesenchymal stem cells are being explored for T1D therapy due to their regenerative and immune-regulating properties through paracrine signaling. Our lab studies human (cadaveric) islet-derived progenitor cells (hIPCs), which resemble mesenchymal stem cells, to investigate their immunomodulatory potential and mechanisms.

**Methods**

We co-cultured hIPCs with phytohemagglutinin (PHA) stimulated human peripheral blood mononuclear cells (PBMCs) and assessed immune cell proliferation using flow cytometry. We also tested the effect of hIPCs-derived conditioned media (CM) on the proliferation of PBMCs. Extracellular vesicles (EVs) were isolated from the CM and analysed using Nanosight, and cytokines in supernatants were measured using Olink system. We then performed bulk RNA sequencing of the hIPCs cultured in isolation and in co-culture with PBMCs, followed by analysing differentially expressed genes.

**Results**

We observed hIPCs significantly inhibit *in vitro* proliferation of various immune cell subsets (CD4+ T, CD8+ T, CD19+ B) in a direct co-culture with stimulated PBMCs. This effect also persisted in transwell systems, and with CM from IFN-γ-primed hIPCs, but not with CM from unprimed hIPCs. Size profiles of EVs showed that most were exosomes, ranging from 50-150 nM. When exosomal inhibitors were used in co-culture, hIPCs lost their ability to inhibit proliferation. Co-culture increased gene expression of *IDO1, PD-L1,* and *IL10* in hIPCs, while reducing TGFb1 and IFN-g in the supernatants.

**Discussion/Conclusion**

Human islet-derived cells and their CM exhibit immunomodulatory properties through cytokine signaling and the transfer of bioactive molecules via exosomes. Additionally, priming hIPCs enhances the beneficial effects of hIPC-CM. A detailed characterization of culture supernatants and EVs could lead to the identification of cell-free therapeutics, presenting potential new treatment targets for Type 1 Diabetes.