Cell and molecular approaches aiming at human β-cell replacement: the Brazilian experience.

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NUCEL (Cell and Molecular Therapy Center www.usp.br/nucel) is a translational research center comprising the Cell and Molecular Biology team, dedicated to the molecular basis of cell proliferation control and neoplasia and the Human Pancreatic Islet Unit, which focuses on innovative approaches to improve the Islet Transplantation success rate. By taking a genomic and proteomic approach, we revealed a number of differentially expressed genes and proteins upon comparing human islets in the absence and in the presence of β-cell mitogens and anti-apoptotic agents, and with human insulinoma tumor samples. Functional genomics was used to probe into the role of some of these gene targets in β-cell proliferation, differentiation and insulin production and secretion. We also designed a new method to scale-up β-cell cultures using bioreactors and a practical and rapid assay to assess the β-cell response to glucose by microcalorimetry. In addition, we isolated and characterized three human β-cell lines and dedicated a large amount of effort to islet encapsulation, using a previously described biomaterial (Biodritin^{TM}). This prompted a number of studies both *in vitro* and *in vivo* and the generation of NUCEL´s first spin-off company, CellProtect Biotechnology (www.cellprotect.com.br). Modifications of Biodritin^{TM} led us to a new biomaterial/composite (under patenting), which allowed a significant improvement in pre-clinical tests of Diabetes reversal in immunocompetent diabetic mice, opening new avenues for clinical transplantation of encapsulated islets. However, the scarcity of cadaveric pancreas donors and the cumbersome and costly islet isolation and purification procedure, led us to search for alternative sources of insulin-producing cells. Both murine and human embryonic stem cells and adult progenitor cells from different sources were isolated and fully characterized, aiming at their differentiation into β-cells. The results obtained so far with some of these stem cells are very promising, however, still require optimization to generate large amounts of fully differentiated β-cells. Genetic Engineering was also employed to generate induced pluripotent cells (iPSC) without interfering with the cell genome. This work involves a multidisciplinary group of about 60 people, dedicated to face the great challenges posed by Regenerative Medicine and to continuous training of qualified researchers to impact the Cell and Molecular Therapy field.

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