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Generation of long-term human pancreatic islet cell activity *in vivo* by induction of immune tolerance to human stem cells

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If performed at the appropriate developmental age, in utero transplantation (IUT) in experimental animals will permit human stem cells (SC) to engraft/express differentiated cells/proteins into adulthood. It requires performing the procedure coincident with ontogenic programming of self-tolerance. We believe this developmental period to be a powerful investigative tool. We investigated IUT in sheep to assess the differentiative capacity of human SCs with regard to islet cell activity. Two different SC populations were assessed for the presence of human DNA in sheep pancreas (chimeric index) and secretion of human insulin (functional engraftment). Both projects involved intraperitoneal injection of SCs at the optimal developmental age to establish long-term tolerance permitting unfettered stem cell differentiation/expansion *in vivo*. Two protocols were utilized. The first used human fetal pancreas derived mesenchymal SC (hfpd-MSC) and the second used human embryonic SC derived CD34+ cells (ESCd-CD34+). Using hfpd-MSC, the chimeric incidence was 79% with functional engraftment of 50%. In study 2, a combined functional engraftment of 35% was noted using two different ESCd-CD34+ populations. It must be realized that the chimeric index was based on limited sampling and no methods were used to stimulate graft functionality. In both studies circulating human C-peptide was detected years after transplantation. In situ analysis detected human insulin in both studies. In study 2, identifiable islets stained for human chromogranin A and proinsulin. In summary, these studies re-emphasize IUT's utility as a method to study human stem differentiation and may prove applicable in attempts to produce human islets *in vivo*.

Biography

John S Pixley was trained in Internal Medicine at Westchester County Medical Center and Rheumatology/Immunology at SUNY-at-Stony Brook in New York. He has been on the Faculty of the University of Nevada SOM as Director of the Rheumatology Division and Chief of Rheumatology at the VA Sierra Health Care System since 1987. His publications include experimental observations on *in utero* transplantation and clinical observations on extra-articular manifestations of rheumatoid arthritis. He serves on the editorial board of *World Journal of Stem Cells and reviews manuscripts for World Journal of Stem Cells, Clinical Rheumatology, Cytotherapy* and *World Journal of Immunology*.

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