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## Long-Term Survival of Donor-Specific Pancreatic Islet Xenografts in Fully Xenogeneic Chimeras

Y. Zeng, S.T. Ildstad, S.M. Wren, H.L.R. Rilo, D.R. Bereiter, P.B. Carroll, A.G. Tzakis, T.E. Starzl, and C. Ricordi

Transplant Institute, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

The development of procedures to isolate large numbers of purified human pancreatic islet cells has made it possible to initiate a new phase of clinical trials in pancreatic islet transplantation for treatment of type I diabetes.<sup>1-4</sup> Although nonspecific immunosuppressive agents have been instrumental in controlling alloreactivity to transplanted islet cells, rejection still occurs and is a major limitation to islet transplantation.<sup>5,6</sup> The induction of donor-specific transplantation across a species barrier, using bone marrow stem cells to produce chimerism and induce donor-specific transplantation tolerance, has been suggested as a potential approach to prevent rejection of transplanted cells.<sup>7-9</sup> The purpose of this study was to determine whether long-term acceptance and function of xenogeneic pancreatic islet grafts could be achieved in fully xenogeneic chimeras.

### MATERIALS AND METHODS

Fully xenogeneic chimeras were prepared by transplantation of  $40 \times 10^6$  non-TCD Wistar Furth bone marrow cells into C57BL/10 Sn mouse recipients conditioned with 950 R rads total body irradiation before transplantation. Animals were typed for chimerism at 4 weeks and made diabetic by intravenous injection of streptozotocin (165 mg/kg). Only mice with a plasma glucose concentration exceeding 300 mg/dL for 1 week were used as islet recipients. Rat pancreatic islets were obtained by the modification of an automated method for isolation of human pancreatic islet cells and purified by the COBE cell separator with Euro-Collins-Ficoll gradients.<sup>4</sup> Eight hundred donor-specific Wistar Furth or third-party F344 rat pancreatic islets were implanted beneath renal capsule of diabetic chimeras. Nonfasting blood glucose levels were determined daily to check function.

### RESULTS AND DISCUSSION

The survival of the donor-specific Wistar Furth rat pancreatic islet xenografts was significantly prolonged (mean survival time > 120 days), while major histocompatibility complex disparate third-party F344 islets were rapidly rejected (mean survival time = 8 days). The donor-specific grafts were functional and maintained the normoglycemic state in chimeras. This study demonstrated that long-term survival and function of donor-specific pancreatic islet xenografts can be obtained in fully xenogeneic chimeras.

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