

## Donor Bone Marrow Cell Infusion Without Recipient Cytoablation Induces Acceptance of Rat Islet Allografts

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**L**ETHAL OR sublethal radiation conditioning of bone marrow recipients has been reported to be an effective strategy to induce drug-free acceptance of donor-specific pancreatic islet transplants in rodents.<sup>1-3</sup> Recent experimental evidence indicates that radiation conditioning of the recipient may not be necessary for stem cell engraftment.<sup>4-7</sup> Because irradiation of patients with type 1 diabetes may not represent an acceptable clinical approach to islet transplantation, especially in children and young adults, we tested the effect of donor bone marrow transplantation without irradiation on the survival of rat islet allografts.

### MATERIALS AND METHODS

Male Lewis (LEW, RT1<sup>l</sup>) and Brown-Norway (BN, RT1<sup>n</sup>) rats were used as donors and recipients. Diabetes was induced in the recipient rats by one injection of streptozotocin (185 mg/kg, intravenously, IV). A total of  $2.5 \times 10^8$  donor bone marrow cells (DBMCs) was infused IV immediately prior to transplantation of approximately 1400 islets (average diameter of 150  $\mu$ m) into the renal subcapsular space. Temporary immunosuppression consisted of FK 506 (1 mg/kg, intramuscularly, IM on days 0 to 13, 21, 28). Group 1 received islet transplantation (ITX) alone and no immunosuppression (n = 5), Group 2 received ITX with temporary immunosuppression (n = 5), and Group 3 received DBMC + ITX with temporary immunosuppression (n = 4).

### RESULTS

In Group 1, islet graft survival was  $14.6 \pm 1.3$  days. In Group 2, the addition of temporary immunosuppression resulted in significant prolongation of transplanted islets ( $76.6 \pm 15.0$  days,  $P < .01$  by analysis of variance, ANOVA) as compared to untreated controls. In Group 3, the combination of donor bone marrow cells and temporary immunosuppression resulted in marked prolongation of islet allograft survival to  $>145.8 \pm 8.5$  days ( $P < .01$  and  $P < .05$  compared to both Groups 1 and 2, respectively). Donor bone marrow derived cells were identified in the recipients of donor bone marrow, but not in the recipients of islet transplants alone.

### DISCUSSION

The results both indicate that radiation conditioning of the recipients was not necessary to induce prolonged chimerism

and graft acceptance in this rodent model of islet allotransplantation and confirm the results recently reported by Demetris et al on bone marrow and whole organ allotransplantation.<sup>4</sup>

Conventional wisdom in bone marrow transplantation has supported the requirement for cytoablative treatment of recipients to make space for newly transplanted bone marrow components. This dogma has been recently challenged due to experimental results, which indicate that infusion of a high dose of donor marrow can lead to successful and permanent hematopoietic repopulation without the need for pretransplant irradiation of the recipient.<sup>5,6</sup> Moreover, chimerism without radiation conditioning has been recently obtained in rodents even in the absence of any immunosuppressive treatment of the recipients.<sup>7</sup> Our results may allow for the definition of new strategies for transplantation of donor hematopoietic cells and subsequent enhancement of allograft survival.

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