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Transplantation across major genetic barriers

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Studies in mice and humans demonstrate that transplantation of hematopoietic progenitors in numbers larger than commonly used ('megadose' transplants) overcomes major genetic barriers. In vitro studies suggest that veto cells, contained in the population of hematopoietic progenitors, facilitate this favorable outcome. In sublethally irradiated mice we showed recently that megadose grafts surmount resistance to engraftment posed by numerous lymphocytes that survive sublethal conditioning. Consequently, an allogeneic chimera, generated by transplantation of large numbers of $Sca1^{+}Lin^{-}$ cells, permanently accepts allogeneic skin grafts derived from the donor of the hematopoietic progenitors. However, the numbers of hematopoietic progenitors required for induction of tolerance may be difficult to collect from humans prompting a study of alternative sources of veto cells. In one approach, we demonstrated that it is possible to harvest about 28-80 fold more veto cells upon culturing of purified $CD34^{+}$ cells for 7-12 days with an early acting cytokine cocktail including FL, SCF and TPO. Alternatively, we found that non-alloreactive $CD8^{+}$ T cells synergize with $Sca1^{+}Lin^{-}$ cells in the veto effect. Experiments with mice deficient in FasL and Fas, with transfer of FasL gene and with anti-CD8 antibody suggest that the veto activity requires simultaneous expression of FasL and CD8 (Fig. 1). It is hoped that by combining megadose $CD34^{+}$ stem cells with other types of veto cells we shall be able to achieve engraftment in human recipients conditioned by minimal cytoreductive protocols without any GVHD. Once this goal is achieved in man, the road will be open to novel cell therapy in autoimmunity, solid tumors or as a prelude for organ transplantation all of which do not justify any form of transplant related mortality.

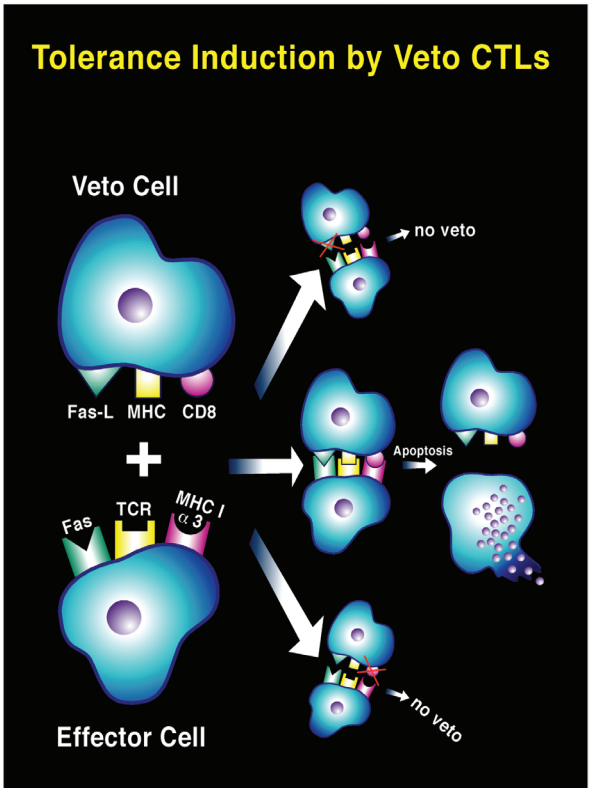

Fig. 1 *The veto activity of CTLs was blocked by anti-CD8 antibodies (Bottom right) or Fas-Fc fusion protein (Top right).*

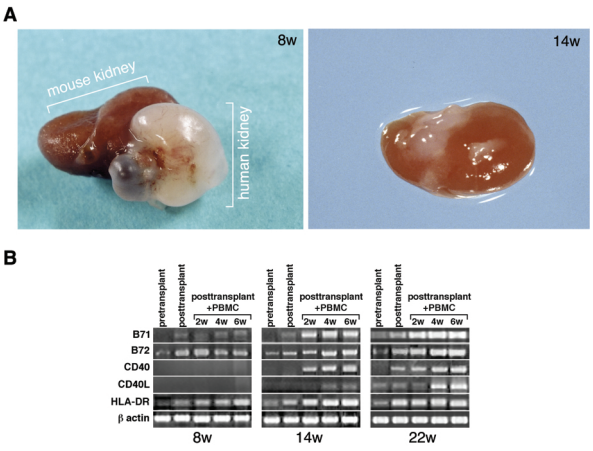

Fig. 2 *A. Differential engraftment and growth of human kidney progenitors derived from 8 and 14 -week embryos transplanted with alloreactive human PBMC. B. Tolerance to kidney precursors derived from 8 week embryos is associated with the absence of CD40:CD40L.*

A completely different approach for achieving, safely, immune tolerance for organ transplantation, is offered by the potential use of embryonic tissues. A key issue in this field of investigation

is to define the time of gestation affording minimal allogenicity, without losing the potential for growth and differentiation (Fig. 2). Very recently we were able to define these parameters for human and pig kidney precursors. To that end we have used the 'trimera mouse' which accepts the engraftment of functioning human haematopoietic cells or solid tissues. These studies suggest that undifferentiated human or pig kidney progenitors may not only afford a new source for renal transplantation but may also ameliorate the need for life long chronic immunosuppression.

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