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Regulatory T cells for promotion of durable mixed hematopoietic chimerism and immune tolerance in a nonhuman primate model.

Mixed hematopoietic chimerism is a promising approach to the achievement of transplantation tolerance. The recent success in achieving graft survival without chronic immunosuppresson in patients receiving non-myeloablative conditioning followed by combined kidney and bone marrow transplantation (BMT) highlights the potential of this approach. However, using this approach, only transient chimerism was achieved and it is likely that the kidney itself contributed to tolerance induction, as systemic donor-specific unresponsiveness was not achieved in recipients of BMT alone with the same regimen. An additional limitation of the preparative regimen used in these studies is the requirement for conditioning beginning 6 days prior to organ transplantation, making it applicable only for recipients of living donor allografts. We aim to improve this regimen to achieve durable multilineage chimerism and thereby tolerance to kidneys and any other organs from the same living or deceased donor. In nonhuman primates, nonmyeloablative recipient conditioning with BMT induces transient mixed hematopoietic chimerism and donor specific renal allograft tolerance. In mice, regulatory T cells (Tregs) promote the achievement of durable mixed chimerism and tolerance using conventional, clinically achievable doses of bone marrow cells, without any cytoreductive or myelosuppressive recipient conditioning. We propose to use this approach to achieve durable mixed chimerism and allograft tolerance in a nonhuman primate model. We will therefore use the established conditioning regimen with bone marrow transplantation and add ex vivo expanded Tregs. We have developed an approach for the rapid generation of large numbers of recipient monkey CD4+CD25+Foxp3+ Tregs via culture with rapamycin, mouse L-cells transfected with human CD80, CD58 and CD32 and allogeneic PBMCs. >95% of expanded Tregs express FoxP3 and these cells strongly suppress T-cell activation. We aim to evaluate the ability of *ex vivo* expanded Tregs to promote the induction of durable mixed allogeneic hematopoietic chimerism and tolerance for kidneys and islets, using protocols compatible for both living and deceased donors in a nonhuman primate model.