Dr. David Sachs

Inbred miniature swine provide a unique preclinical model for the study of transplantation immunity and tolerance. Over the past two decades, we have utilized this model to study a robust form of tolerance of MHC class I-mismatched renal allografts that is routinely achieved following a short course of calcineurin inhibitors. This proposal represents the fifth consecutive renewal of this RO1, the last renewal of which was as a Merit Award (G37). During the last project period, we have made significant progress in understanding the role of regulatory T cells (Treg) in the induction and maintenance of tolerance as well as in the adoptive transfer of tolerance in this model. We have demonstrated a requirement for both the donor kidney graft and the functioning thymus to maintain the balance between alloreactivity and down-regulation of immune reactivity to the graft, needed for persistence of tolerance. We have also demonstrated that the cells required for adoptive transfer of tolerance to a re-transplanted kidney are present within the kidney itself but that transfer of tolerance sufficient for acceptance of a naive, donor-matched kidney requires additional peripheral cells from the tolerant donor. In the next project period, we intend to investigate the nature of the signals that emanate from the kidney and lead to intra-thymic generation of Tregs and the nature of the cells within the kidney and in the periphery that are responsible for the adoptive transfer of tolerance to a naive recipient. Specifically, we will: 1) Examine the nature of the peripheral and intra-thymic processes responsible for the balance between alloagressive and regulatory T cell responses to donor antigens of a renal allograft; and 2) Determine the nature of the intra-graft and peripheral regulatory cells required for adoptive transfer of tolerance to a second donor kidney, following re-transplantation of kidneys from long-term tolerant (LTT) animals. The broader goal of these studies remains to develop an understanding of the mechanisms by which allograft tolerance is induced and maintained in this large-animal model, in order to permit development of appropriate protocols for induction of tolerance to organ allografts in the clinic.