AST Basic Science Fellowship Grant

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**Development of specific tolerance in pig-to-human thymic transplantation model using humanized mice**

**Abstract of the proposed research plan:**

**Specific Aim**

There is a critical shortage of allogeneic organs. A more elegant, long-term solution is to use transplantation from other species. However, unresolved questions exsist concerning the susceptibility of xenografts to severe rejection and its mechanism. We have developed a humanized mouse model that allows the reconstitution of immunodeficient mice with human T and B cells and APCs in order to elucidate the immunological mechanisms of xenoresponse and achieve xenograft tolerance. These human cells demonstrate robust immune function, including xenograft rejection, proliferative T cell responses and class-switched antibody responses to protein antigens. We have also shown that normal, polyclonal human T cells can develop in porcine thymic xenografts that replace the human thymus graft in this humanized mouse model. These human T cells are specifically tolerant to the porcine thymus donor, suggesting an approach to achieving xenograft tolerance in humans. The xenogeneic thymus transplant approach has allowed porcine kidney xenograft survival in non-human primates. However, data obtained in the humanized mouse model suggest that there may be defects in human T cell function in pig thymus xenografted mice resulting from a failure of the T cells that are positively selected on porcine thymic epithelium to interact optimally with HLA molecules on human APCs in the periphery. We aim to develop strategies to bypass the effects of MHC incompatibility between porcine positively selecting thymic epithelium and peripheral human APCs (**Aim 1**) and evaluate the mechanism of tolerance to pig and human donor antigens of T cells generated in porcine thymus grafts (**Aim 2**). In **Aim 1** the effect of co-implantating human thymic epithelial cells (huTEC) in the porcine thymic grafts will be explored. A second approach will be to provide porcine APCs in the periphery by inducing mixed xenogeneic chimerism in xenogeneic thymus-grafted humanized mice. We will examine the effects of these manipulations on peripheral T cell responses, phenotypic conversion, survival, and Treg function and phenotype. Additionally, in **Aim 2** the role of deletion of T cells with TCR recognizing pig donor antigens will be explored using human TCR transgenesis into human hematopoietic stem cells. The role of regulatory T cells and the effect of huTEC implantation on regulatory cell function will be explored. The results of these studies will advance this promising approach to xenograft tolerance induction toward clinical application.