Dr. Megan Sykes

This U19 proposal aims to achieve islet and kidney allograft tolerance through mixed chimerism in two complementary projects that are supported by three cores. Both projects have relevance for end-stage renal disease (ESRD) and curative therapy for Type 1 diabetes (T1D). They employ related approaches to achieve tolerance for deceased and living donor grafts, respectively. Project 1 aims to use expanded polyclonal recipient Tregs to develop a compressed conditioning regimen that induces tolerance of simultaneous bone marrow, kidney and islet allografts from deceased donors. We have previously used a 6- day conditioning protocol that is relevant only for living donors, to achieve transient chimerism and kidney allograft tolerance. We now aim to develop a conditioning protocol that could be initiated after identification of a deceased donor, allowing transplantation (Tx) within 24 hours. Our approach builds on our demonstration that expanded polyclonal recipient Tregs can achieve far more prolonged chimerism and more robust tolerance than has previously been possible. Tolerance obviates the need for long-term immunosuppressive therapy with its destructive effects on islet grafts. Moreover, our studies have shown that non-myeloablative induction of durable mixed chimerism reverses advanced anti-islet autoimmunity, simultaneously avoiding the alloimmunity, autoimmunity and drug toxicity that currently limit the efficacy of islet Tx in T1D. Project 2 aims to develop a tolerance induction strategy for curative treatment of end-stage diabetic nephropathy using living related donor (LRD) composite Islet-Kidney (IK) Tx. The project builds on our observation that transplanting pre-vascularized islets as part of composite IKs requires far fewer islets to achieve insulin independence than Tx of free, non-vascularized islets. We recently achieved tolerance of IKs using a novel, low intensity, hematopoietic cell transplant protocol in a “parent-to-offspring” combination. Project 2 aims to adjust components of the conditioning regimen and/or donor cell source that may have an early negative impact on islet function. Taking advantage of the ability to generate potent donor-specific Tregs prior to LRD Tx, we will test the ability of these cells to promote durable mixed allogeneic chimerism, with its potential to reverse T1D. Both projects will include extensive mechanistic analyses that build on a high-throughput TCR sequencing-based approach for tracking the alloreactive T cell repertoire that we have developed in humans and will apply to the model in Core B. Thus, we aim to achieve durable mixed chimerism in both projects to cure autoimmunity while simultaneously preventing alloimmune attack by inducing tolerance. Core A will provide islets for both projects and Core B will develop a high throughput T cell receptor (TCR) sequencing platform that will be used to identify and track the fate of donor-specific alloreactive T cell clones, providing a unique mechanistic tool to be applied in both projects. Core C will provide administrative, biorepository and data management support for all of the projects and cores.