**Transplant Surgery Scientist Training Program (TSSTP) Projects**

### Immune Mediated Mechanisms of Lung Ischemia Reperfusion Injury
**Ramiro Fernandez, MD (Primary Mentor: Ankit Bharat, MD)**

Ischemia-reperfusion injury, a form of sterile inflammation, is the leading risk factor for both short-term mortality following pulmonary transplantation as well as chronic lung allograft dysfunction. While it is well recognized that neutrophils are critical mediators of acute lung injury, processes that guide their entry into pulmonary tissue are not well understood. Here, we found that CCR2+ classical monocytes are necessary and sufficient for mediating extravasation of neutrophils into pulmonary tissue during ischemia-reperfusion injury following hilar clamping or lung transplantation. The classical monocytes are mobilized from the host spleen and splenectomy attenuates the recruitment of classical monocytes as well as entry of neutrophils into injured lung tissue, which is associated with improved graft function. Neutrophil extravasation is mediated by MyD88-dependent IL-1β production by graft-infiltrating classical monocytes, which downregulates the expression of the tight junction-associated protein ZO-2 in pulmonary vascular endothelial cells. Thus, we have uncovered a crucial role for classical monocytes, mobilized from the spleen, in mediating neutrophil extravasation with potential implications for targeting of recipient classical monocytes to ameliorate pulmonary ischemia-reperfusion injury in the clinics.

### Tolerance for Islet Cell Xenotransplantation in Humanized Mice
**Frances Tangherlini Lee, MD (Primary Mentor: Xunrong Luo, MD, PhD)**

Tolerance for porcine islet cell transplantation could render a feasible and sustainable cure for Type 1 Diabetes. To study the human immune response to xenogeneic islet transplantation, we use a pig-to-humanized mouse model of transplantation which serves as a valuable pre-clinical tool with potential clinical applications. Tolerance induction with the use of ECDI-fixed donor splenocytes has been proven to be effective in allogeneic models, and with the addition of other adjuncts (rituximab and rapamycin) is also effective in concordant xenogeneic models. In applying this specialized therapy known as ‘triple therapy’ to our pig-to-humanized mouse model of islet transplantation, we have shown sustained graft survival and function up to 60 days from transplantation. Due to the differences seen in graft cellular infiltration between untreated and treated subjects, it appears that human B cells may be key mediators in xenogeneic rejection. Moreover, we hypothesize that triple therapy initially depletes B cells in recipients and may modify the B cell phenotype in a manner that prevents their infiltration in the xenograft despite peripheral reconstitution by day 60.

### Demonstrating Pathways to Value-Based Care for Patients with Liver Cirrhosis from Wait Listing to Liver Transplantation
**Nikhilesh Mazumder, MD (Primary Mentor: Josh Leventhal, MD, PhD)**

My project carries forth my interest in using large databases to generate and investigate hypotheses regarding clinical outcomes for patients with cirrhosis. Specifically, we plan to examine predictors of waitlist mortality for low MELD patients who are typically de-prioritized during the organ allocation process. My project builds on our group’s previous work which investigated this question in a large, Chicago-wide database (HealthLNK). My plan is to improve this model, validate it in another dataset, and to create an easy to use calculator for use in the clinic. Our ultimate goal is to help transplant practitioners gain insight into the potential benefit of living donor transplant.

### Personalized Tolerance: Alloantigen Specific T Regulatory Cell therapy Following Organ Transplantation
**Jessica Heinrichs Voss, PhD (Primary Mentor: Joseph Leventhal, MD, PhD)**

Transplant tolerance is a state of immune quiescence where the donor organ is accepted by the recipient with little or no immunosuppression. Current standard of care, following kidney transplantation, rarely results in development of tolerance. Although immunosuppressive drugs have drastically reduced the incidence of acute rejection, the long-term effects of broad immune suppression are numerous: infection, malignancy, nephrotoxicity, and diabetes. In order to extend survival of donor organs alternative tolerance induction therapies are desperately needed. Regulatory T cells (Tregs) are naturally occurring suppressive cells within our immune system. Tregs main function is to maintain immune homeostasis by suppressing aberrant inflammatory responses. For clinical translation, Tregs must be expanded ex vivo to achieve sufficient cell doses, this is usually polyclonal non-specific expansion. However, it is possible that non-specific Tregs could have the same adverse side effects as broad immunosuppressive drugs. The overarching theme arises which is the need for targeted immune suppression. Recently, we and others have expanded donor antigen specific Tregs (Ag-Tregs) and found more potent and specific suppression of the alloresponse compared to polyclonal Tregs (P-Tregs). However, adequate cell doses of Ag-Tregs for in vivo testing could not be reached using our current protocol. Therefore, we will test an optimized protocol, using two rounds of donor antigen followed by polyclonal stimulation, to increase cell yield while maintaining antigen specificity. We will also test the safety and efficacy of Ag-Tregs in an in vivo transplantation model, using human skin grafts on NSG mice. Importantly, we will also address if Ag-Tregs are superior to P-Tregs in the suppression of graft rejection. The long-term objectives of this study will be to obtain a streamlined Ag-Treg expansion protocol with proven pre-clinical safety and efficacy for translation into our cGMP facility with the goal of obtaining an IND for future phase I safety trials.

For more information, please contact Hayden Polancich at hayden.polancich@nm.org