Dr. Barry Fine

Heart transplant allocation is especially sensitive to the combined pressure of a very limited supply coupled with an expanding demand of candidates with end stage heart failure. As such, it requires vigorous pre-transplant risk stratification to limit post-operative complications and optimize outcomes. The leading cause of death within the first 30 days of heart transplant is primary graft dysfunction (PGD), defined as allograft dysfunction without a clinically discernible etiology such as rejection, bleeding, or infection. Its mortality rate is 30% and its incidence varies across institutions ranging up to 25% of recipients. The cause of PGF remains unknown and we are currently unable to predict which individual will develop PGF.

Retrospective clinical studies have shown weak correlations between donor clinical variables and PGD. However, in preliminary serum studies, we identified significant differences *prior to transplant* in recipients who developed PGD versus those that did not. First, luminex assays showed upregulated inflammatory cytokines in serum of patients who developed PGF. Second, pre-transplant serum exosome analysis by mass spectrometry generated a significantly different proteomic profile associated with PGD. Pathway and network analysis of the PGD exosome signature suggests activation of the complement cascade and innate immune response driven by multiple inflammatory regulators. Lastly, we treated beating cardiomyocytes generated from human inducible pluripotent stem cells (iPSC's) with pre-transplant serum and observed significant decreases in measurements of strain, beating frequency and calcium handling in the PGD cohort. Taken together, these experiments support our hypothesis that an inflammatory milieu in the recipient can be detected before transplant and may be contributing to ventricular dysfunction.

The proposed studies will validate the PGD exosome signature in an external set of sera and apply machine learning to explore and refine the expression model of PGD. In order to explore its potential as a biomarker, complement activity and levels will be measured from freshly collected serum prior to transplant. Finally, we will attempt to model PGD *in vitro* by treating engineered heart tissue (EHT) with PGD and non-PGD serum samples. These experiments will lay a multidisciplinary foundation for mechanistic studies, modeling and biomarker analysis through competitive funding sources.