

PROJECT TITLE:

Immune Mechanisms of Graft Dysfunction after Heart Transplantation – Identification of Potential Biomarkers

PROJECT SUMMARY:

Early detection of allograft rejection is the key approach in the management of heart transplant (HTx) patients. ^{Kirklin 2004, Mehra 2004} Despite the increased understanding of transplant immunobiology and allograft rejection in HTx patients, certain fraction of patients experience unexplained graft dysfunction (GD-U) i.e. graft dysfunction (GD) without histological evidence of acute cellular rejection (ACR), antibody mediated rejection (AMR), and cardiac allograft vasculopathy (CAV) where GD with the positive evidence of above criteria is together referred as GD-E (GD-ACR, GD-AMR, and GD-CAV). For GD-U there are currently no accurate diagnostic tools available. GD-U is associated with significantly higher mortality than GD-E. ^{Shahzad 2010} Our **hypothesis** is that, in patients hospitalized with GD-U, peripheral blood mononuclear cells (PBMCs) display characteristic gene expression profiles (GEP) distinct from patients presenting with GD-E. To delineate Leukocyte Gene Expression Profiles associated with GD-U following HTx (**In Aim 1**), we propose, in Aim 1.1, to create a clinical database of all patients identified with GD in the multicenter clinical trial of "Invasive Monitoring Attenuation Through Gene Expression" (IMAGE) www.clinicaltrials.gov comparing conventional biopsy-based and novel GEP-based non-invasive monitoring of allograft rejection (>54 end-points). ^{Pham 2007, Pham 2010} In Aim 1.2, we will identify the patients with GD-E and GD-U from IMAGE-study participants. To identify leukocyte GEP associated with GD-U (**In Aim 2**), we propose, in Aim 2.1, to perform in-vivo studies of microarray analysis on total RNA obtained from PBMCs and stored as a part of IMAGE-study protocol (GD-U and GD-E), and compare patients with GD-U against patients with GD-E to accurately assess gene expression profiles. In Aim 2.2, we will use standard bioinformatics analysis tools to identify important candidate genes related to GD-U and will validate priority genes identified by array strategy (Aim 2.1) using real-time PCR analysis. Positive study results will lead to the development of "genomic biomarkers" for the accurate diagnosis of unexplained graft dysfunction in heart transplant patients.