ABSTRACT

Heart failure is a costly global epidemic. Although many heart failure patients are burdened with the condition for life, some recover through drug therapy or transplantation. However, even those who recover through therapy continue to be treated for life. Indeed, no guidelines exist for diagnosing recovered heart function and the weaning of patients off unnecessary medications. Transplant recipients must be monitored regularly for rejection of the new heart through invasive biopsies and also are treated with immunosuppressives for life. Improved diagnostic and monitoring tools can lessen drug side-effects and allow tailoring of patient management, thereby decreasing the costs of the heart failure epidemic and improving the wellbeing of patients so affected.

The goal of this thesis was to identify biomarkers to diagnose and predict acute cardiac rejection and to monitor for recovered heart function. Using blood, plasma and endomyocardial biopsy samples collected from patients enrolled in the Biomarkers in Transplantation initiative, signatures were pursued with genomic and proteomic platforms and computational analysis. To develop *acute rejection diagnostic biomarkers*, discovery focused on genes differentially expressed between rejection and non-rejection recipients, in both blood and biopsy tissue. These genes were further analyzed in blood and those with greatest ability to separate rejection and non-rejection patients by elastic net classification were selected for inclusion in the biomarker panel. A 12-probe set, clinically relevant biopsy-guided blood-based acute rejection diagnostic biomarker panel was identified. *For acute rejection predictive biomarkers,* transplant donor tissue genes and pre-transplant recipient plasma proteins and blood genes were investigated alone and in combination. The best biomarker panel included 25 probe sets from the donor tissue and 18 probe sets from the pre-transplant recipient blood. Discovery of *recovered heart function biomarkers* was based on recovery seen in the transplant setting. Proteins were followed from pre-transplantation through one year post-transplant and those whose blood level returned to normal were included in elastic net classification. A panel of 17 proteins was discovered which had great replication performance in patients who recovered by means of drug therapy. Once further validated, these biomarker panels could serve as new tools for heart failure and transplant patient management.