Association of HLA Molecular Mismatch with Risk and Severity of Rejection in Kidney Transplant Recipients
Alexis Kushner BS, Christabel Rebello MS, Kexin Guo MS, Lihui Zhao PhD, Thomas Whisenant PhD, John Friedewald MD

Background
Subclinical and clinical acute rejection is associated with poor outcomes in kidney transplant recipients. Current immunosuppressive medications to prevent rejection following transplant increase risk of infections and cancers. Assessment of individual patient risk level is paramount to determine personalized treatment post-transplant.

Traditional Human Leukocyte Antigen (HLA) mismatch evaluates recipient and donor molecules on the serologic level which fail to account for differences and immune system recognition at the molecular level. Considering molecular mismatch may improve rejection risk stratification. Recent studies have examined the role of eplet mismatch load as a marker of alloimmune risk and have demonstrated a significant association between HLA-DQ mismatch and transplant rejection mediated by de novo formation of donor specific HLA antibodies (dnDSA).

Research Objectives
This project aims to establish the association between molecular HLA mismatch and incidence of acute rejection in the first two years post kidney transplant to improve immunologic risk stratification effectively creating a personalized approach to immunosuppression and immune monitoring post-transplant.

Methods
All donor and recipients that met inclusion criteria underwent HLA molecular genotyping using Next Generation Sequencing. We used the HLA Matchmaker software (http://www.epitopes.net) to enumerate eplet mismatches and mismatch load. Calculations were made for total eplet mismatch load and antibody verified mismatch load, as separate calculations for each locus and donor molecule. Subjects were grouped according to occurrence of acute rejection. The TX group had no occurrences of acute rejection, the subAR group had one or more episodes of subclinical rejection found on protocol biopsy, and the CAR group had one or more episodes of clinical acute rejection, found on indication biopsy. ANOVA test and linear regression was performed to evaluate differences and strengths of association.

References

Cohort Characteristics

Table 1. Main demographic, clinical characteristics, and eplet mismatch load of Class I, Class II Antibody verified and DQ/DQ loci of study population (n=71).

Results

Limitations
Despite a trend in the association of increasing eplet mismatch load and the risk of rejection, the limited cohort size could be the reason for lack of statistically significant results.

Conclusions
We observed a trend towards higher levels of eplet mismatch associating with greater incidence of both sub clinical and clinical acute rejection (with higher mismatch load associating with more severe, clinical acute rejections). The HLA DQ Loci appeared to have the greatest association with episodes rejection, replicating similar work in the field. Future work will focus on expanding the cohort size to continue to evaluate these relationships. We are also exploring the associations between eplet mismatch load and other immunologic events such as emergence of de novo antibodies and positive screening molecular biomarkers.