Mapping the Influence of Autoimmunity Associated, Non-Coding Genetic Diversity on T Cell Function. S DeVoe (Ph.D., Immunology), L Shaw, A Prete, J Scott-Browne. Department of Immunology and Genomic Medicine, National Jewish Health, Denver, CO

Genetic diversity allows for variable immune responses between individuals, which is commonly manipulated to study disease phenotypes. For example, non-obese diabetic (NOD) mice spontaneously develop autoimmune diabetes. Broadly mapped regions of the genome, known as insulin dependent diabetes (Idd) loci, have been linked with susceptibility to disease. However, over 5 million SNPs exist between the NOD and C57BL6J (B6) strains contributing to divergent T cell behavior and regulation even in the absence of disease. We sought to identify polymorphisms influencing diverging behaviors in exhausted CD8 T cells between NOD and B6 mice. Low-input omni ATACseq was used to identify accessible chromatin regions in B6 and NOD mice in naïve, memory, chronic LCMV-specific, and tumor-infiltrating CART CD8 T cells. Reads were processed to strain-specific genomes with the ENCODE pipeline. NOD coordinates were shifted to mm10 coordinates with MMARGE. Differential chromatin accessibility was assessed between strains with limma-voom, and transcription factor motif sites were determined with FIMO. 681 peaks characterized a common exhaustion profile, 738 peaks for a B6-specific exhaustion profile, and 737 peaks for a NOD-specific exhaustion profile. Motif enrichment analysis reveals that within the conserved regulatory elements between the strains, enrichment is equivalent with fewer than 10% of sites being polymorphic. Strain-specific profiles show complementary enrichment of bZIP and IRF motifs. NOD-specific exhaustion regions displayed higher diversity with 15-30% of bZIP and IRF sites being polymorphic. This indicates similar mediators are employed, but they will act on different genes due to the strain-specific accessible motif locations.