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The Iddm14 gene is Tcrbv-13S1A1: Prevention of Autoimmune Diabetes in the Rat with an Allele-Specific Depleting Antibody That Recognizes the Vβ13a T Cell Receptor Beta Chain

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Presenter Information
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To identify new intervention strategies for autoimmune type 1 diabetes (T1D), we investigated several rat models of the disorder. We dissected the powerful Iddm14 diabetes susceptibility locus in eight T1D susceptible vs. resistant rat strains by single nucleotide polymorphism (SNP) haplotyping. We identified an allele of a T cell receptor (TCR) beta chain gene, Tcrb-V13S1A1 (encoding V13βa) as a candidate gene. In three separate trials, treating LEW.1WR1 rats, which are susceptible to T1D, with a depleting anti-Vβ13 monoclonal antibody reduced diabetes frequency from 75% (N=50) to 17% (N=30, p<0.001. Anti-Vβ13 monoclonal antibody also prevented T1D in spontaneously diabetic BBDDP rats. We then analyzed the phenotype of infiltrating T cells recovered from the cultured islets of LEW.1WR1 rats exposed to a diabetogenic trigger. Within 5 days, up to 22% of CD4+ T cells recovered from islets were V13β+, most of these CD25+FoxP3-. We also recovered Vβ13 transcripts from pre-diabetic islets and observed a limited number of Jβ variant transcripts, indicating an oligoclonal TCR response to pancreatic beta cells. These data indicate that, in susceptible rats, V13βa on diabetogenic T cells is required to recognize a critical T1D autoantigen. Interestingly, the diabetogenic and non-diabetogenic alleles of Vβ13 have non-conservative sequence differences in both CRR1 and CDR2. The data suggest that it is possible to prevent T1D in the rat with a very narrowly targeted deletional therapy. Preliminary data suggest that a specific alpha chain may preferentially pair with Vβ13a. We are currently generating rat T cell hybridoma clones with which to analyze the interaction of putative autoantigens with a diabetogenic TCR.