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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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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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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 BBDP 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.