**Data Studio**
1:30–3:00pm, Wednesday, November 20, 2019
Conference Room X393, Medical School Office Building, 1265 Welch Road, Stanford, CA

**Investigator:** Wei Jiang Instructor, Division of Human Gene Therapy, Department of Pediatrics

**Title:** The Role of T-cells in the Autoimmune Etiology of Narcolepsy

**Summary:**
Individuals with narcolepsy suffer from abnormal sleep patterns due to loss of neurons that uniquely supply hypocretin (HCRT), a wakefulness-promoting hormone in human brains. Previous studies found the associations of narcolepsy with human leukocyte antigen (HLA)-DQ6 allele and T-cell-receptor-alpha (TRA) J24 gene segment. These led to an autoimmune hypothesis for narcolepsy that the presentation of HCRT-derived peptides by DQ6-expressing antigen presenting cells to TRAJ24-expressing T-cells drives T-cell clonal expansion and downstream self-attacking immune responses against HCRT-producing neurons. Although T-cells from narcolepsy patients were recently reported to recognize HCRT peptides, autoimmunity-related evidence that HCRT-reactive T-cells have experienced in vivo clonal expansion is still absent.

We directly sequence T-cell-receptor (TCR) and selected phenotypic marker genes in over 5000 single ex vivo T-cells that are isolated from DQ6+ donors using DQ6-HCRT peptide tetramers. Statistical comparisons suggest that DQ6-HCRT(87–100) tetramers, a peptide composed of amino acids 87–97 from HCRT, identify significantly more expanded CD4+ T cells from 8 patients than from 8 DQ6 allele-matched healthy controls. We also identify related TRAJ24+ TCR clonotypes encoded by identical genes from 2 patients and 2 controls. TRAJ24-G-allele+ clonotypes only expand in the two patients, whereas a TRAJ24-C-allele+ clonotype expands in a control (the G/C SNP in TRAJ24 gene is narcolepsy-associated). In addition, clonally expanded TRAJ24-G-allele+ T-cells from the two patients exhibit an unconventional effector phenotype. Our identification of features distinguishing in vivo expansion of HCRT-specific TRAJ24+ T-cells in patients versus controls opens an avenue for further investigation of the autoimmune etiology of narcolepsy.

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