Autoimmune regulator (AIRE) mutations result in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome characterized by defective central T cell tolerance and the production of many autoantibodies targeting tissue-specific antigens and cytokines. By studying CD3- and AIRE-deficient patients, we found that lack of either T cells or AIRE function resulted in the peripheral accumulation of autoreactive mature naïve B cells. Proteomic arrays and Biacore affinity measurements revealed that unmutated antibodies expressed by these autoreactive naïve B cells recognized soluble molecules and cytokines, including insulin, IL-17A and IL-17F, which are AIRE-dependent thymic peripheral tissue antigens targeted by autoimmune responses in APECED. AIRE-deficient patients also displayed decreased frequencies of regulatory T cells (Tregs) that lacked common TCRβ clones found instead in their conventional T cell compartment, thereby suggesting holes in the Treg TCR repertoire of these patients. Hence, AIRE-mediated T cell/Treg selection normally prevents the expansion of autoreactive naïve B cells recognizing peripheral self-antigens.

Tuesday, April 16, 2019
3:00 - 4:00 pm
Pelton Auditorium