Understanding the mechanisms by which environmental factors influence the function of the immune system could provide new avenues for the prevention and/or treatment of immune-mediated diseases. One environmental sensor implicated in these diseases is the aryl hydrocarbon receptor (AhR), a ligand activated transcription factor. AhR ligands include 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), an environmental pollutant, diet-derived metabolites in cruciferous vegetables (e.g. indole-3- carbinol), and microbiota-derived metabolites. Our laboratory previously found that systemic activation of AhR by TCDD increases immunosuppressive CD4+ T-cells and prevents the development of type 1 diabetes (T1D) in NOD mice. In contrast, dietary indole-3-carbinol activates AhR in the intestine, increases a subset of proinflammatory CD4+ T-cells, shifts the gut microbiome, and promotes T1D. Given these contradictory data, we aim to understand how activation of the same receptor promotes divergent CD4+ T-cell subsets and T1D phenotypes. Our central hypothesis is that direct AhR signaling in CD4+ T cells and interactions with the gut microbiome drive organ intrinsic differences in T-cell subsets. To test this hypothesis, we will analyze CD4+ T-cell differentiation following TCDD and indole-3-carbinol exposures in NOD mice with transgenic T-cells specific for islet antigen and in gnotobiotic mice. The results will help elucidate how activation of AhR influences CD4+ T-cell differentiation.