Immune Checkpoint Inhibitor Induced Diabetes Mellitus: A Unique Opportunity to Understand Beta-Cell Autoimmunity

Progress Report

Objective: To identify novel autoantibodies/autoantigens through use of proteome-wide programmable phage display technology (PhIP-Seq) in immune checkpoint inhibitor induced diabetes mellitus (CPI-DM) and Type 1 Diabetes Mellitus (T1DM) populations.

Experimental Progress:

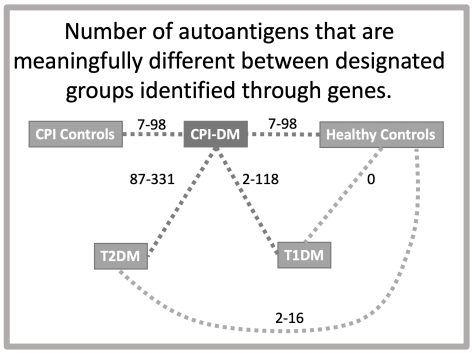
This project is composed of three stages: 1) completion of the PhIP-Seq experiment, 2) analysis of the PhIP-Seq data and 3) validation of any genes or peptides of interest.

At present, stage 1, the PhIP-Seq experiment, has been completed. Recall that PhIP-Seq utilizes a custom designed phage library containing over 700,000 unique phage, each displaying a 49 amino acid proteome segment that tile the full protein-coding human genome including all isoforms with 25 amino acid overlap. This allows for identification of putative autoantigens at both the gene and peptide level relative to chosen control groups.

A cohort of 1152 samples were simultaneously analyzed. Characteristics of the cohort are detailed to the right, but highlights include a collection of over 50 subjects with CPI-DM, over 200 subjects with T1DM, 25 subjects with T2DM, over 70 subjects treated with immune checkpoint inhibitors (CPI) without endocrine immune related adverse events and over 150 healthy controls. Additional subjects with other endocrine adverse events, non-endocrine adverse events and other autoimmune conditions comprise the rest of the samples.

Type of Subject	Sample Size
CPI-DM	
Single Time Point	23
Longitudinal Time Points	33
T1DM	
Single Time Point	202
Longitudinal Time Points	2
T2DM (all single time point)	25
Healthy Control (all single time point)	158
CPI Control (all single time point)	77

Stage 2, data analysis, is ongoing. There were three methods planned: 1) shared genes or peptides, 2) genes or peptides amplified across time and 3) particularly high expression in unique patients. Methods one and three are close to completion. Depending on the criteria used to define autoantigens of interest, there are variable numbers found. Parameters to optimize include the percent of samples within the disease cohort and control cohorts and fold change of the autoantigen relative to the background. These findings are summarized in the figure to the right. *The immediate next step is review of these genes for tissue specificity.* Thus far, with the current methodologies, there are potential autoantigens to follow up for CPI-DM but there has not been one apparent between healthy controls and T1DM. Further methods will be used to continue evaluating these samples, including Method 2, the investigation of genes across time, which will be carried out in the 35 patients with multiple time points. Particular attention will be paid to those subjects who have samples taken prior to development of diabetes. These same analyses will be completed on the peptide level.



Finally, in stage 3, validation of autoantigens of interest will be completed once the above detailed analysis has been finalized.

I expect that the timeline laid out in the proposal continues to be feasible and hope that with further interrogation critical autoantibodies/ autoantigens will emerge.