Diabetes Autoimmunity Study in the Young

COMIRB Protocol # 92-080 **5/6/2021**

This project, called Diabetes Autoimmunity Study in the Young (DAISY) has established two unique cohorts of very young
children who are at increased (up to 20-fold) risk of developing type 1 diabetes (T1D):
1) a cohort of siblings and offspring of persons with T1D and their family members ; and
2) a cohort of newborns with T1D associated genetic markers, identified through a cord blood screening of 50,000 general
population children without a relative with T1D and their family members.
This protocol is designed to explore the determinants of b-cell autoimmunity and T1D, and to develop genetic and
autoantibody testing methods suitable for future programs of general population screening and T1D prevention.

- **Specific Aim 1. Determine the natural history of islet autoimmunity and to explore the heterogeneity of diabetes and other autoimmune phenotypes in young adults through follow-up of the existing cohort for 5 more years.**
- We will follow already established cohort of youth at high risk of T1D and other autoimmune diseases (current n=1149, median age 17.2 y, IQR 13.5-20.2 y). We will estimate overall burden of pre-clinical and clinical T1D, celiac, thyroid, adrenal, rheumatic and parietal autoimmune disease in Colorado by age 25. This will inform future screening and prevention programs. We will further explore the apparent heterogeneity of IA and its implications for adult-onset diabetes. Selected hypotheses include:
- Hypothesis 1.1: Persistent IA triggered after the age of 6 y results in T1D diagnosis in early adulthood
- Hypothesis 1.2: Transient childhood IA does not increase the risk of diabetes in early adulthood
- Hypothesis 1.3: Sedentary life-style and insulin resistance predict faster progression from persistent IA to T1D

- **Specific Aim 2. Validate candidate proteomic biomarkers of IA and T1D, in a nested-case study of 213 youth with persistent IA and 213 controls.**
- So far, none of the `omics biomarkers reported to predict progression from IA to T1D have been confirmed by independent studies. Using targeted proteomics we will validate candidate peptides/proteins reported from several discovery studies. Selected hypotheses:
- Hypothesis 2.1: A reproducible set of proteomic biomarkers will predict development of IA independently of demographic factors and HLA class II genotypes.
- Hypothesis 2.2: A reproducible set of proteomic biomarkers will predict the rate of progression from IA to T1D independently of demographic factors, HLA class II genotypes.

- **Specific Aim 3. Develop an integrated comprehensive model of the relapsing-remitting process leading to T1D in youth using prospectively collected DAISY `omics data.**
- Integrative Bayesian modeling, based on a small set of disparate features e.g., gene variants, proteins, or metabolites, will be used to generate individualized prediction algorithms in IA progressors vs. non-progressors to identify potential pathways. Selected hypotheses:
- Hypothesis 3.1: A limited number of features derived from high-resolution `omics data can reliably predict development of IA on an individual basis
- Hypothesis 3.2: A limited number of features and time-points derived from high-resolution `omics data can reliably predict the rate of progression from IA to T1D on an individual basis

- The proposed studies are important to reach our overarching goals: to find the environmental causes of T1D, develop primary prevention, and inform public health screening for several autoimmune disorders in children and adolescents. We will continue to make every effort to share DAISY resources with multiple investigators studying T1D and other autoimmune diseases through an open-source database/ repository.

- Hypothesis 2.2: A reproducible set of proteomic biomarkers will predict the rate of progression from IA to T1D independently of demographic factors, HLA class II genotypes.

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