Jeremy Racine, Ph.D., Final Project Report

Type 1 diabetes (T1D) is an autoimmune disease resulting from complex interactions between many genes. However, particular genes within what is known as the major histocompatibility complex (MHC; designated HLA in humans) are master controllers of immune responses represent the primary contributors to T1D susceptibility. Through contributions from DRC, I have successfully created a new mouse model (now published in Diabetes) that will allow the creation of multiple HLA-trait-specific pre-clinical mouse models for therapy development. Work is now ongoing to combine multiple HLA genetic traits together in different combinations to represent different subsets of T1D patients. Additionally, a special version of these mice, that lack a functional immune system, is being generated. These mice will be able to receive blood samples from T1D patients, such that potential therapies can be tested directed on immune cells from patients prior to translation to the clinic.

As a proof of principle for creation of new trait specific models, I also published on two new models expressing the human T1D susceptibility genetic traits HLA-A*0201 and HLA-B*3906. These models can be used to develop therapies for patients carrying these specific genetic traits. Using one of these new models, I have tested a novel therapy attaching peptides to microspheres and delivering them to mice expressing HLA-A*0201. While delivery of this therapy reduced diabetes incidence an older (faulty) pre-clinical model, the treatment failed to reduce diabetes incidence in the new, more clinically relevant model developed during this project. This finding leads to the following questions:

1) Does this therapy require an increased dosing schedule before clinical translation? Since the DRC funding has ended, I found that changes to the dosing schedule were not effective, leading to question number 2.

2) Does the delivery mechanisms of these peptides have to be changed prior to clinical translation? Prior to testing microsphere delivery, our group had conjugated these peptides to cells derived from the first-generation HLA-humanized mouse model and showed success with these four peptides. Since the funding for the DRC has ended, we tested a cell-based-delivery system, but this too did not translate to the new model, leading to question 3.

3) Does the number of specific peptides delivered need to be increased from the currently tested four peptides? The immune system in these newly created mice can see and respond to a wider array of antigens from the islets than the first-generation model, so we should be able to discover additional important targets of the immune system that went previously unidentified. Work is now being done to expand the number peptides used in our therapy, and to identify the important contributors to disease development.

Therapies previously developed with older generation humanized mice may not translate to the clinic, as was the case observed with our potential therapy. These new DRC funded mice will allow researchers to design better therapies that are more likely to translate to clinical success.

Additionally, I am in the process of creating NSG versions of these mice so that human immune cells from T1D patients can be transplanted into these mice.

This work has been published, click here to read the full report.