CURRENT RESEARCH AND SCHOLARLY INTERESTS

I. The laboratory’s research program focuses on the molecular mechanisms by which particular major histocompatibility molecules mediate the presentation of self antigens to induce autoimmunity. One of the principle disease models is the non-obese diabetic (NOD) mouse, a strain which spontaneously develops type 1 diabetes; and which is similar to the same disease in man. Current experiments focus on identifying the peptide fragments of proteins from the insulin producing beta cells which induce a T cell response leading to inflammation and destruction of the islet beta cells. Specific sequence polymorphisms in the class II MHC molecule, I-Ag7, result in the development of diabetes in individuals expressing this sequence polymorphism (as well as other susceptibility genes for type 1 diabetes). We have produced T cell hybridomas recognizing many of the peptide fragments of an important islet cell protein, glutamic acid decarboxylase 65. These T cell hybridomas have been used to produce transgenic mice, and we are currently analyzing these transgenic mice as well as their T cell receptors, which recognize GAD65 peptides bound by I-Ag7, to understand how this MHC class II molecule presents peptides in such a way as to induce an inflammatory response resulting in the destruction of the islets.

II. Other genes in the major histocompatibility complex encode the structural genes for tumor necrosis factor alpha and lymphotoxin alpha/beta. These molecules are critical in both the development of the immune system, and in the function of the immune system in the adult animal. Current studies focus on the effect of TNF alpha on signaling through the T cell receptor; on the development of CD4+, CD25+ regulatory T cells which are capable of suppressing normal immune responses, as well as autoimmune responses, and on the role of lymphotoxin in driving selective expression of chemokines which result in the development of autoreactive T cells in the spleen and lymph nodes.
### Publications

**PUBLICATIONS**

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- **The role of TNF-alpha in the pathogenesis of type 1 diabetes in the nonobese diabetic mouse: Analysis of dendritic cell maturation** *Proceedings of the National Academy of Sciences of the United States of America*
  
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- **Specific antigen vaccination to treat autoimmune disease** *Arthur M. Sackler Colloquium of the National Academy of Sciences on Therapeutic Vaccines*
  
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