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**Specific Aims**

The adaptive immune system is the body’s most powerful tool in fighting off infections. In individuals with severe-combined immunodeficiencies (SCIDs), T and B cells are greatly decreased or absent. One such SCID is Omenn syndrome. Omenn syndrome causes the low B and T cell counts typically found in SCIDs. What makes Omenn syndrome unique among SCIDs is that there is an oligoclonal population of adaptive immune cells that are autoreactive, causing autoimmune symptoms. The immunodeficiency found in individuals with Omenn syndrome is caused by a mutation in a gene called *RAG1*. *RAG1* encodes the RAG1 protein, which is involved in the production of the receptors that adaptive immune cells use to determine their specific target. The mutation is typically “leaky”, allowing some T and B cells to be produced, but not as many as in a healthy individual. *The causes of the autoimmune symptoms of Omenn syndrome are, as of now, yet to be fully explained.*

**We seek to test the hypothesis that a combination of deficiencies in RAG1 and the transcription factor AIRE creates a small oligoclonal population of immune cells that are self-reactive.** AIRE is a transcription factor that activates genes involved in the negative selection of self-reactive immune cells. Recently, two individuals with Omenn syndrome were found to also have deficiencies in AIRE. The **primary goal** of this research will be to demonstrate that RAG1 and AIRE deficiencies produce the phenotype found in patients with Omenn syndrome. The **long term goal** is to identify the cause of the AIRE deficiency in these patients.

**Specific Aim:** To determine if all individuals with Omenn syndrome are deficient for AIRE.

**Approach:** We will use a microarray to determine gene expression in individuals that are confirmed to have Omenn syndrome. We will focus on detecting levels of expression of RAG1 and AIRE.

**Specific Aim:** To demonstrate that deficiencies in RAG1 and AIRE are sufficient to produce an oligoclonal population of self-reactive adaptive immune cells.

**Approach**: We will use the CRISP-Cas9 system to produce populations of mice that are deficient in RAG1, AIRE, and both. The external phenotype of each of these populations will be assessed. T cells and B cells from each will be collected to determine the variety and specificity of their receptors.

**Specific Aim**: To detect if there is a mutation in the AIRE gene or associated regions that would correspond to its deficiency in individuals with Omenn syndrome.

**Approach**: We will use next-generation sequencing methods to sequence a population of MM mice, a strain that has the characteristic Omenn syndrome phenotype, and a population of normal mice. We will analyze the sequences of the AIRE gene for mutations and, if present, analyze them to determine if they could cause the observed phenotype.

As of yet, no study has been done to confirm that AIRE deficiency causes the autoimmune symptoms present in Omenn syndrome. This research could confirm this link, which could aid in treatment of individuals with the disease. While Omenn syndrome is a rare disease, understanding the mechanism of its function could also advance our understanding of immunodeficiencies and autoimmune diseases individually