Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is a recessive autoimmune disease where patients suffer from various endocrine and ectodermal disorders.[[1]](#endnote-1) APECED is caused by a loss of function in the AutoImmune Regulator (AIRE), which is a transcription factor that plays a crucial role in maintaining self-tolerance. [[2]](#endnote-2) AIRE’s primary role is to maintain self-tolerance by promoting expression of self-antigens in the thymic epithelial cells which kill self-reactive immune cells before they enter circulation. [[3]](#endnote-3) When AIRE is lost, self-reactive immune cells survive and give rise to autoimmune disease. Recent studies have also identified populations of extra Thymic AIRE expressing Cells (eTACs) in secondary lymphoid organs, such as lymph nodes and the spleen.[[4]](#endnote-4) While AIRE promotes the expression of tissue specific antigens (TSAs) in both thymic and extrathymic cells, the specific antigens expressed differ between the thymic cells and eTACs. [[5]](#endnote-5) *Despite these findings, the role of AIRE in promoting transcription of these unique TSAs in eTACs remains unclear.*

My **primary goal** is to uncover the mechanisms through which AIRE promotes the expression of unique antigens in eTACs. My **hypothesis** is that the AIRE transcription complex in eTACs involves different cofactors from those in the thymus which leads to different TSA expression.

**Aim 1: Determine which AIRE domains are necessary for TSA expression in eTACs.**

**Approach:** Deletion constructs with only the HSR, SAND, or PHD domains from AIRE will be inserted into a Cre/*lox* system for inducible gene expression in mice to allow controlled expression of the altered AIRE protein in only eTACs.[[6]](#endnote-6) The expression pattern of eTACs with each individual AIRE domain, along with wild type mice, will be analyzed using RNA-seq.

**Rationale:** By analyzing the changed expression patterns in eTACs with different domains of AIRE, we can understand which domains are necessary for the expression of specific TSAs.

**Hypothesis:** The expression patterns will differ between wild type and single AIRE domains.

1. Kisand, Kai and Peterson, Pärt. 2015. Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy. Journal of Clinical Immunology. pp 463-478. [↑](#endnote-ref-1)
2. Finnish-German APECED Consortium. 1997. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nature. https://www.ncbi.nlm.nih.gov/pubmed/9398840/​ [↑](#endnote-ref-2)
3. Owen et al. 2013. Kuby Immunology. 7th edition. [↑](#endnote-ref-3)
4. Gardner et al. 2008. Deletional Tolerance Mediated by Extrathymic Aire-Expressing Cells. Science. Vol 231. pp. 843-847. [↑](#endnote-ref-4)
5. Gardner et al. 2008. Deletional Tolerance Mediated by Extrathymic Aire-Expressing Cells. Science. Vol 231. pp. 843-847. [↑](#endnote-ref-5)
6. Inducible Gene Expression and Gene Modification in Transgenic mice. http://jasn.asnjournals.org/content/11/suppl\_2/S95/F2.expansion [↑](#endnote-ref-6)