Project Summary
This proposal will focus on the functional consequences and underlying mechanisms of genetic variation in thymic involution, one of the hallmarks of immunologic aging. Vaccine failure in the elderly has been attributed at least in part to thymic involution because of a decreased pool of naïve T cells leading to a decline in the capacity of aged individuals to mount immune responses to neoantigens. However, decreased production of naïve cells is associated with expansion of pre-existing memory cells. It is therefore possible that thymic involution and concomitant decline in naïve T cells production allows the establishment of a larger pool of memory cells capable or responding rapidly to infection, and thus providing improved immunity to adult individuals of reproductive age. Understanding the significance, functional consequences and underlying mechanisms of thymic involution is therefore of critical importance to human health.

To identify mechanisms involved in thymic involution and establish models of delayed or accelerated thymic involution, we took advantage of genetic variation among inbred mouse strains. Our published and preliminary data indicate that a novel regulatory axis in hematopoiesis, consisting of Prdm16, which enhances the ligand-induced activity of peroxisome proliferator activated receptor-gamma (PPARγ) and through this activity regulates signaling by the cytokine TGF-β2, affects thymic involution. Mouse strain-dependent coding variation in Prdm16 regulates the activity of this mechanism. To unequivocally address the role of this locus *in vivo*, we generated mice where the DBA/2 allele of *Prdm16* was knocked in into the C57BL/6 background ($B6^{Prdm16/D2}$ mice). In control mice, the C57BL/6 allele of *Prdm16* was knocked into the C57BL/6 background ($B6^{Prdm16/B6}$ mice). These mice, as well as $Tgfb2^{+/-}$ mice and congenic and transgenic mice with delayed or accelerated thymic involution, will be further examined in this proposal.

The specific aims of this proposal are:
Specific aim 1: To analyze thymic involution in $B6^{Prdm16/D2}$ and $B6^{Prdm16/B6}$ mice.
Specific aim 2: To analyze the mechanism of delayed thymic involution
Specific aim 3: To analyze immune function in mice with delayed or accelerated thymic involution