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