Chronic, low-grade inflammation is implicated in the pathogenesis of many common and disabling diseases in older adults. Most of these diseases are slowly progressive and have a clear association with advancing age. The etiologies that trigger chronic inflammatory activation in older adults are likely heterogeneous and include multiple chronic disease states, redox imbalance, senescent cells, and increased body fat. There is also evidence that age-related changes in the renin-angiotensin system (RAS) may contribute to the development of chronic inflammation observed in older adults. Angiotensin, the main RAS effector hormone, interacts with both angiotensin II type 1 receptor (AT₁R) and angiotensin II type 2 receptor (AT₂R). Both AT₁R and AT₂R are expressed on endothelial and immune system cells. An altered ratio between AT₁R and AT₂R induces inflammation in animal models. The effects of aging on the expression of AT₁R and AT₂R in humans and the contribution of changes in AT₁R and AT₂R to increased inflammation in older adults has not been previously studied. Our preliminary evidence suggests that frail older adults have up-regulation of AT₁R and down-regulation of AT₂R expression, and implicate for interleukin-6 (IL-6) in this imbalance.

We hypothesize that aging is associated with changes in AT₁R and AT₂R expression in immune system cells and that these changes are driven by age-related alterations in DNA methylation of AT₁R and AT₂R genes. Further, we hypothesize that these changes contribute to the increased production of inflammatory cytokines in older individuals, which in turn will further heighten the divergence in AT₁R and AT₂R expression.

To test our hypotheses, we will:

1. Measure changes in gene expression, protein synthesis, and specific gene DNA methylation of AT₁R and AT₂R in immune system cells from young, robust, and frail human subjects (20 in each group) using quantitative polymerase chain reaction (Q-PCR), western blot, confocal microscopy, and DNA methylation analysis.

2. Evaluate the contribution of AT₁R and AT₂R to cytokine production in older individuals by incubating immune system cells from the same individuals with specific AT₁R or AT₂R blockers and measuring cytokines with enzyme-linked immunosorbent assay and Bio-Plex cytokine assays at baseline and in response to treatment.

3. Assess the feedback of inflammation on AT₁R and AT₂R expression by incubating immune system cells from the same subjects with IL-6. Q-PCR and western blot will be used to quantify the change in expression of AT₁R and AT₂R in response to IL-6 treatment.

If we are successful in meeting our specific aims, important progress will have been made in understanding age-related molecular changes that may contribute to chronic inflammation late in life. Given that there are already available pharmacological agents that impact the RAS pathways, positive findings in this proposal could lead to a great variety of clinical translational studies. These studies would enable the study of these agents on the modulation of expression of AT₁R and AT₂R, and the related consequences of influencing their biologically active status and contribution to inflammation in older individuals. In addition, epigenetic changes in AT₁R and AT₂R genes that influence receptor expression may lead to much broader studies of age-related epigenetic change that influence molecular aging processes.

The ASP-American Geriatrics Society Foundation for Health in Aging Award will help me with the critical support needed to continue cutting-edge research in late life inflammation and frailty and it will facilitate my successful transition to an independent investigator.