

**Title of Proposed Research:** Immunologic Dysregulations and Inflammation in the Pathogenesis of Frailty of Old Age. The Role of Chronic CMV Infection

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**A. Abstract**

Frailty in older adults is associated with immunologic dysregulations and a systemic inflammatory state. In chronic inflammatory conditions and infectious diseases, the T-cell receptor (TCR) repertoire becomes increasingly restricted as oligoclonal T cells accumulate. Because latent cytomegalovirus (CMV) infection has been shown to be associated with frailty, we have now hypothesized that in a subset of humans who eventually become frail, latent CMV infection leads to a chronic inflammatory state and, perhaps through frequent reactivation, causes an accumulation of CMV-specific T cells and restriction of the TCR diversity. Furthermore, we hypothesize that, regardless of CMV's role in frailty, an accumulation of senescent memory T cells and concomitant restriction in TCR diversity are associated with frailty. These immunologic dysregulations could play important roles in the pathogenesis of frailty. To test these hypotheses, we propose the following specific aims:

**Specific Aim 1.** To determine the relationships between T-cell phenotype alterations, CMV-induced immunologic parameters, and TCR diversity and frailty, in a cross-sectional case-control study (N = 194) within the Women's Health in Aging Study (WHAS).

**Specific Aim 2.** To determine whether the frequency of CMV reactivation is associated with frailty, by measuring CMV viral load in repository samples from multiple time points.

**Specific Aim 3.** To determine whether the immunologic alterations identified above antecede the onset of frailty, by performing a nested case-control study (N = 194) using longitudinal data in WHAS. We will develop a model based on these parameters to predict the development of frailty.

The long-term objectives of this research plan are to identify potential targets along the pathophysiologic pathway of frailty that are amenable to preventive and therapeutic interventions, and enable clinicians to identify at an early stage those older adults most vulnerable to develop frailty so that a preventive program can be started before the onset of frailty.