



Schilling Lab

Alzheimer's disease (AD) is the leading cause of dementia in people over the age of 65, and the strongest genetic risk factor for late-onset AD is the APOE4 allele, which confers greater risk in women than in men. Much less appreciated is that APOE4 carriers also show accelerated skeletal fragility, and that patients receiving bone-targeted therapies such as bisphosphonates appear to experience slower cognitive decline. These observations point to bidirectional communication between bone and brain as an underrecognized contributor to AD risk. Work from the Schilling (and Ellerby) Lab recently demonstrated that APOE4 disrupts the female bone proteome even more profoundly than the hippocampus, and suppresses osteocyte perilacunar and canalicular remodeling (Advanced Science, 2026). Professor Schilling also directs the Buck Institute Proteomics and Metabolomics Cores, where five high-end mass spectrometers support deep comprehensive DIA proteomic profiling and spatial mass spectrometry imaging, and metabolomics (2 mass spectrometers). In this project, humanized APOE knock-in mice will be treated with bone-targeted agents, zoledronic acid and romosozumab, and matched bone and brain tissues will be profiled to determine whether improving skeletal health alters the AD-associated brain proteome. Findings can be extended to APOE-genotyped human bone tissue and to isogenic iPSC-derived cerebral organoids from the Ellerby laboratory. The postbaccalaureate trainee will learn quantitative proteomic sample preparation, data-independent acquisition on state-of-the-art instrumentation, and statistical and pathway analysis of large proteomic datasets, with the goal of identifying circulating mediators of the bone-brain axis that could be targeted therapeutically in AD.