2026 IMPACT CIRCLE

Project Title: The Bone–Brain Connection: Unlocking a New Paradigm for Alzheimer's Disease and Osteoarthritis

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Unmet Need/Primary Question:
Today, medicine treats aging as a collection of separate problems. A person with Alzheimer's disease sees a neurologist who looks only at the brain. A person with osteoporosis sees an orthopedist who looks only at the bone. Yet most older adults do not have just one condition, they often have **multi-morbidities**. This fragmented approach means we are missing critical connections between diseases. We urgently need a new way of thinking about the aging body, treating the person as a whole. ***"What happens in your bones doesn't stay in your bones. What happens in your brain doesn't stay in your brain."*** Alzheimer's disease (AD) affects **6.7 million Americans**, and osteoarthritis (OA) affects **32 million**, both striking women disproportionately, both without effective long-term treatments. Clinical data show that patients with osteoporosis or hip fracture have significantly elevated risk of developing Alzheimer's disease, and OA patients show measurable loss of whole brain volume and increase of dementia. These are signals of a deeply connected biology that science has largely overlooked.

Our team pioneered a field-changing concept: the bone–brain axis: a two-way biological communication highway between the skeleton and the nervous system. Bone cells (osteocytes) and brain cells (neurons) look strikingly similar, share molecular signaling pathways, and may age and decline in parallel. We showed that bone deterioration can begin before visible brain changes appear in Alzheimer's models. The key breakthrough came from studying **APOE4**, a strong genetic risk factor for Alzheimer's disease, carried by approximately 25% of the population and increasing AD risk by up to 12-fold. We discovered that APOE4 causes severe bone fragility specifically in females, and that molecular disruption in bone is actually **greater than in the hippocampus** (the brain's memory center) at the same age. This work is accepted for publication in ***Advanced Science*** 2026.

Novel Hypothesis:
We hypothesize that **bone health and brain health are molecularly coupled through the APOE pathway and other inter-organ signals**, and that interventions targeting bone may simultaneously protect the aging brain. We propose that FDA-approved bone medicines **bisphosphonates** such as alendronate (Fosamax®) and zoledronic acid (Reclast®), already taken by tens of millions of patients worldwide for osteoporosis, may also be **reducing the risk of dementia**. Large epidemiological studies from Hong Kong and Taiwan already suggest this is the case. Our research will rigorously test this hypothesis and uncover the molecular mechanisms.

Project Proposal:
With Impact Circle funding we will conduct the following focused research program:
A) Bisphosphonate Intervention Study in Alzheimer's Mouse Models. We will treat 3xTg Alzheimer's mice, a well-established model carrying three human AD mutations, with FDA-approved bisphosphonates (alendronate and/or zoledronic acid) and use our state-of-the-art proteomics platform to measure molecular changes in both bone and brain. This directly tests whether a bone drug already prescribed to millions can protect the aging brain.
B) Human Tissue Validation. Leveraging our access to the NIH BioBank, we will begin validating key findings in human bone and brain tissues from AD patients (APOE4 risk factor carriers versus non-carriers).

Description of Potential Impact:
For donors personally: Alzheimer's disease and osteoporosis together affect a majority of people over 70. If you or someone you love has been diagnosed with either condition: this research is directly relevant. A bone scan or a fracture may one day serve as an early warning system for Alzheimer's risk, years before memory symptoms appear. And a medicine already sitting in medicine cabinets may turn out to protect the brain. **For translation:** Bisphosphonates have been prescribed since the 1990s with over 150 million prescriptions dispensed in the U.S. (from 2005 to 2009). If our hypothesis is confirmed, the path to a clinical trial can be short. We would repurpose a safe, affordable, widely available drug for a devastating disease (AD) that currently has no cure. **For future funding:** This project is designed as the pilot data engine for a major NIH R01 grant application. Impact Circle funding will directly enable us to compete for $2–3 million in federal funding within 2 years. **For the field of aging:** This work represents a genuine paradigm shift from treating organs in isolation to understanding the aging person as a whole, interconnected system.

A New Paradigm: Health of One Organ Improves Health of Other Organs