Verdin Lab

The Verdin Lab investigates how diet, exercise, metabolism, and chronic inflammation influence the aging process and contribute to diseases such as Alzheimer's. Our research seeks to define the molecular and metabolic pathways that regulate aging and to uncover novel targets that promote healthy longevity. Possible research projects include:

Targeting CD38-Mediated NAD+ Depletion in APOE4-Associated Alzheimer's Disease:
This project aims to investigate how CD38 expression in human brain pericytes drives NAD+ depletion and cellular dysfunction in Alzheimer's disease, particularly in individuals with the APOE4 genotype—the strongest genetic risk factor for late-onset AD. Our preliminary data demonstrate that CD38 deletion attenuates amyloid-β burden in AD mouse models and that APOE4 carriers show significantly elevated CD38 expression. We will explore how pharmacological inhibition of CD38 using our novel brain-penetrant compound NTX-748 can restore NAD+ levels, reduce AD-associated cellular pathology, and potentially slow disease progression.

To achieve our goals, we will utilize human iPSC-derived pericytes and choroid plexus organoids from isogenic APOE2, APOE3, and APOE4 lines, modeling the genetic diversity of AD patients. We will employ cutting-edge techniques including spatial metabolomics to map NAD+ depletion patterns, single-cell RNA sequencing to identify AD-specific transcriptional signatures, proteomics to measure amyloid and tau pathology markers, and functional assays of mitochondrial dysfunction and cellular senescence—key hallmarks of AD pathology. These methods will enable us to examine how APOE genotype influences vulnerability to AD through CD38-mediated mechanisms, advancing precision medicine approaches for this devastating disease.

Decoding How SIRT5 Protects the Myelin Sheath from Mitochondrial Stress in Alzheimer's Disease:
Mitochondrial dysfunction is one of the earliest hallmarks of Alzheimer's disease (AD). As mitochondria lose efficiency with age, they generate reactive metabolites that chemically modify proteins and impair neural function. In the brain, these modifications compromise the myelin sheath—the protective layer that enables fast and coordinated nerve signaling—ultimately contributing to cognitive decline. This project investigates how SIRT5, a mitochondrial enzyme that removes these harmful modifications, safeguards myelin integrity. When SIRT5 activity is lost, these modifications accumulate, driving myelin destabilization and neuroinflammation, processes strongly linked to AD and related dementias.

The SPARC project will explore how mitochondrial metabolism and protein regulation intersect to maintain myelin structure and neuronal communication through integrated cellular, genetic, and biochemical approaches. This project provides a unique opportunity to bridge mitochondrial metabolism, protein modification, and Alzheimer's pathology, ideal for students eager to explore how metabolic dysfunction drives neurodegeneration.