



2026 IMPACT CIRCLE

Project Title: A Novel Metabolic Pathway and intervention for Sleep, Memory, and aging

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Unmet Need/Primary Question:

Sleep dysfunction has been shown to increase with age, contributing to cognitive decline, accelerated aging, and neurodegenerative diseases such as Alzheimer's disease (AD). Despite the growing need, there is a lack of widely accessible, simple, side-effect-free interventions to improve sleep and cognitive function.

Novel Hypothesis:

We hypothesize that astrocytes, key support cells of neurons, produce and export alanine to neurons, where it is converted into pyruvate for ATP production and glutamate for GABA synthesis, enhancing neuronal energy homeostasis and inhibitory neurotransmission, thereby promoting sleep and cognitive resilience. Our preliminary data in humans and flies suggests that this cycle, which we term the *Alanine-Astrocyte-Neuron (AAN) Shuttle*, regulates sleep, enhances memory, reduces neurodegeneration, and extends lifespan.

Project Proposal:

1) Epidemiological Analysis: We will analyze UK Biobank data (~250,000 individuals) to determine if plasma alanine levels correlate with sleep, cognition, lifespan, and neurodegeneration. **2) Intervention Studies:** We will test whether the combination of alanine and alpha-ketoglutarate (α -KG) improves sleep, memory, and neuronal function in animal models. **3) Cellular Mechanism:** Using cultured astrocytes and neurons, we will investigate whether astrocyte-derived alanine is a metabolic and neurotransmitter precursor in neurons, establishing the AAN Shuttle's role in neuronal function.

Description of Potential Impact:

- **Breakthrough in sleep and memory research:** This study could define a new metabolic pathway linking alanine metabolism, sleep efficiency, and cognitive resilience.
- **Potential therapeutic applications:** Alanine supplementation may provide a low-cost, safe intervention for sleep disorders, cognitive decline, and neurodegeneration.
- **Translational impact on human health:** By testing our hypothesis in multiple experimental models, we aim to pave the way for clinical trials exploring alanine-based metabolic therapies for human health.