



2024 IMPACT CIRCLE

Project Title: Developing a KIBRA-based Peptide Therapeutic for Memory Loss in Aging and Alzheimer's Disease

Investigator(s) and collaborations: Tara Tracy, PhD

Unmet Need: Most people have some degree of memory loss in normal aging, and memory loss in Alzheimer's disease is particularly life-altering and devastating for those who suffer from it. We do not yet have effective therapeutic options for age-related memory loss and dementia. Current efforts being tested by others in nationwide clinical trials are focused on slowing the progression of memory loss in Alzheimer's disease, but the possibility of having a therapeutic to recover brain function and memory after it is lost has not been explored. There is an urgent need for new therapeutic approaches to rescue the underlying dysfunction in the aging brain that causes cognitive decline in aging and disease.

The trillions of synapses in the brain function as the connection points between neurons that communicate and process information. Synapses are importantly responsible for encoding new memories in the brain. In age-related memory loss and dementia, synapses lose their plasticity and are no longer able to encode new memories as effectively as they used to. Our research on mice suggests that the KIBRA protein could be leveraged to repair synapse function and reverse the memory loss associated with Alzheimer's disease.

Primary Question: Can we deliver a synapse repair therapeutic into the brain that can improve memory in aging and in Alzheimer's disease?

Novel Hypothesis: We hypothesize that a synthetic peptide derived from the KIBRA protein can be delivered into the brain and can be sufficient to repair synapse function and restore memory encoding in aging and Alzheimer's disease.

Project Proposal: The term "synaptic plasticity" describes a change in the strength of synaptic connections in response to an experience. During a learning experience, synaptic plasticity occurs at individual synapses that are strengthened to encode a new memory for long-term storage in the brain. The KIBRA protein is critical for synaptic plasticity and for the encoding of new memories. In aging and in Alzheimer's disease, we found that lower KIBRA levels are associated with impaired synaptic plasticity and memory loss. We have designed a small synthetic peptide to mimic the KIBRA protein (KB_{pep}) and to restore its function at synapses. Last year, with funding from the Forever Healthy Foundation, we tested KB_{pep} by surgically injecting it directly into the brains of transgenic mice that model the toxicity and pathophysiology caused by tau protein in

Alzheimer’s disease and related dementias. KB_{pep} was injected into the aged mice after the onset of their cognitive impairments. When injected directly into the brain, KB_{pep} restored synaptic plasticity and memory in the mouse model of Alzheimer’s disease. This provided the first evidence that KB_{pep} is sufficient to repair synapse function and reverse Alzheimer’s disease-related memory deficits.

In this proposal, we aim to develop the translational potential of KB_{pep} as a therapeutic for memory loss. We propose to test the delivery and efficacy of KB_{pep} in the brain using a less invasive delivery route that does not require a direct surgical brain injection. Various small synthetic peptides have been tested in human clinical trials for different neurodegenerative diseases, and they can be delivered into the brain using less invasive approaches such as subcutaneous injection and intranasal application. Thus, we propose the following two aims:

Aim 1: Determine the delivery and efficacy of KB_{pep} in the brain via subcutaneous injection

Aim 2: Determine the delivery and efficacy of KB_{pep} in the brain via intranasal application.

Our proposed work will establish which route of administration enables the optimal delivery of KB_{pep} into the regions of the brain that are important for learning and memory. Chemically modified versions of the KB_{pep} will be tested that could further increase delivery of the peptide across the blood brain barrier. We will also confirm the extent to which the KB_{pep} that is delivered in the brain binds to target synaptic proteins that regulate synaptic plasticity.

Description of Potential Impact: The goal of this work is to establish a foundation for an optimal translational approach to deliver KB_{pep} into the brain. The findings from our proposed work could support our efforts to acquire NIH funding for preclinical studies on KB_{pep} in models of aging and Alzheimer’s disease. Our long-term goals are to develop a KIBRA-based therapeutic from the “bench-to bedside”, and to make an impact on the treatment of age-related memory loss.

Model for the effect of KB_{pep} on synapse dysfunction and memory loss in aging and Alzheimer’s disease

