Specific Aims

Alzheimer’s, a neurodegenerative disease often associated with dementia, has been associated with a buildup of Amyloid Precursor Protein (APP)—causing an influx in neurotoxicity, resulting in reduction in brain mass. Through current genomic and proteomic research, the increased production of APP associated with Alzheimer’s has been linked to both presenilin genes, *PSEN1* and *PSEN2*; however, modern bioinformatics has indicated how the preseniln 1 protein (PSEN1) directly leads to increased APP production. Several deletions in the PSEN domain of *PSEN1* deregulate production of gamma-secretase of the presenilin complex, causing the overproduction of APP observed in Alzheimer’s. Though *PSEN1* involvement in APP is known, current research has not tested if induced gamma-secretase regulation could positively impact, slow, or eliminate symptoms associated with Alzheimer’s disease. Preliminary data suggests upregulation of the presenilin complex could associate with regular levels of APP production, preventing Alzheimer’s all together.

**Here we will test the hypothesis that *PSEN1* production of PSEN1 is a direct causation of increased APP production and development of Alzheimer’s. Testing regulation of gamma-secretase levels in model mice organisms will indicate if stimulation of *PSEN1* in those with Alzheimer’s could inhibit or reverse disease symptoms.** This hypothesis has been produced through current research indicating the linkage between *PSEN1* involvements with gamma-secretase regulation and neurotoxic APP production. Studies indicate that gamma-secretase regulation in those diagnosed with Alzheimer’s could reduce the amount of neurotoxic APP produced, causing Alzheimer’s disease prevention.

Our ***long term goal*** of this study is to isolate a direct cause of Alzheimer’s disease, while working to cure those with or developing Alzheimer’s. By piecing together *PSEN1* involvement with both gamma-secretase, APP, and the presenilin complex, future cases of Alzheimer’s should be treatable. Isolating this connection between *PSEN1* and Alzheimer’s disease is the main ***objective*** of this research. To do so, we will pursue the following three specific aims:

***1.* Identify cellular targets of the presenilin complex in addition to gamma-secretase.** Though gamma-secretase is known to directly impact the levels of APP produced in the brain, isolating other cellular targets involved in the presenilin complex in relation to Alzheimer’s will allow for further disease prevention.

***2.* Understand how the presenilin complex is involved in Alzheimer’s through RNAi to inhibit regulatory function.** By restricting the presenilin complex, *PSEN1* involvement with Alzheimer’s disease can be found. Our goals are to identify other precursors to Alzheimer’s disease through interference of gene function—defining just how crucial the presenilin complex is to regulation and prevention of Alzheimer’s disease.

***3.* Isolate signals that upregulate gamma-secretase in mutated *PSEN1* in model mice organisms.** By testing signal regulation in mice, treatment for deregulated *PSEN1* can be discovered—producing mechanisms of disease prevention in humans. Through use of phylogeny and the conserved binding domain of PSEN1, various signals can be tested in several organisms to accurately replicate Alzheimer’s disease prevention in humans.

In regards to these specific aims, further research in regards to *PSEN1* involvement in Alzheimer’s disease will not only reduce associated symptoms, but also isolate possible disease prevention techniques for the near future. Through increased regulation of APP production by means of induced signals, PSEN1 production can be regulated, even in cases of mutated *PSEN1*. Such knowledge on PSEN1 involvement in the presenilin complex will not only prevent future cases of Alzheimer’s, but also provide solutions to other neurodegenerative diseases.