Specific Aims

Alzheimer’s, a neurodegenerative disease often associated with dementia, is caused by a buildup of Amyloid Precursor Protein (APP), causing an increase in neurotoxicity that results in brain mass reduction [1]. A series of deletions in the presenilin 1 gene, *PSEN1*, cause the upregulation of APP through a mutated presenilin 1 protein (PSEN1) that, when in excess, leads to increased neurotoxicity [2]. When mutated, PSEN1 is unable to regulate the production of APP through gamma-secretase, an enzyme that uncontrollably cleaves APP into the toxic subcomponents of amyloid plaques that disrupt neural function observed through Alzheimer’s [3]. Though *PSEN1* involvement in APP production is known, current research has not determined if stimulated downregulation of gamma-secretase in disease patients could both positively impact and eliminate symptoms associated with Alzheimer’s.

**Here we will test the hypothesis that downregulation of gamma-secretase levels in mice model organisms with mutated *PSEN1* could prevent Alzheimer’s. Additional proteins involved with PSEN1 will be identified to observe their role in Alzheimer’s.** 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 more proteins may be involved with increased neurotoxicity than currently known.

Our ***long term goal*** of this study is to identify other proteins involved with PSEN1 in Alzheimer’s disease, to prevent increased neurotoxicity when gamma-secretase is upregulated. By piecing together *PSEN1* involvement with gamma-secretase, APP, and other involved proteins, future cases and symptoms 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 additional proteins targeted by PSEN1 in addition to gamma-secretase through datasets and gene expression analysis.** Though gamma-secretase is known to directly impact the levels of APP produced in the brain, isolating other proteins involved with PSEN1 in relation to Alzheimer’s will allow for further disease prevention. Using a GEO dataset, genes involved with upregulation of APP and *PSEN1* can be identified, and their proteins then further regulated to prevent influxes in neurotoxicity present during Alzheimer’s.

***2.* Further understand the role of PSEN1 in Alzheimer’s through an RNAi screen to inhibit genes with similar regulatory functions.** By restricting *PSEN1*, associations to Alzheimer’s symptoms can be drawn. Similarly, RNAi screens performed on a model mouse genome with mutated *PSEN1* can test if other genes are involved in suppression or enhancement of the disease phenotypes—identifying what future gene studies should be conducted.

***3.* Utilize RNA sequencing and tissue transcriptomics to identify additional target genes affected by mutated *PSEN1*.** By identifying additional targets of *PSEN1*, further prevention can be taken toward Alzheimer’s. Performing a bioassay followed by sorting with gene ontology, chemical genetic treatments for these novel cell targets can be identified and used to reverse the various symptoms of Alzheimer’s.

In regards to these specific aims, further research on *PSEN1* involvement in Alzheimer’s will not only reduce associated symptoms, but also isolate possible disease prevention techniques for the near future. Through increased regulation of APP production by identifying the involved proteins, PSEN1 production can be regulated, even in cases of mutated *PSEN1*. Doing so will decrease the amount of neurotoxicity present through Alzheimer’s, reducing the observed disease symptoms. Understanding this connection will then in turn also provide solutions to several neurodegenerative diseases in addition to Alzheimer’s.

References:

[1] Selkoe D (1994). "Cell biology of the amyloid beta-protein precursor and the mechanism of Alzheimer's disease". Annu. Rev. Cell Biol. 10: 373-403.[doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1146/annurev.cb.10.110194.002105](http://dx.doi.org/10.1146/annurev.cb.10.110194.002105).[PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [7888181](http://www.ncbi.nlm.nih.gov/pubmed/7888181).

[2] De Strooper, B. (2007). Loss-of-function presenilin mutations in Alzheimer disease. Talking Point on the role of presenilin mutations in Alzheimer disease.EMBO Reports, 8(2), 141–146. doi:10.1038/sj.embor.7400897

[3] Barnwell, E., Padmaraju, V., Baranello, R., Pacheco-Quinto, J., Crosson, C., Ablonczy, Z., … Sambamurti, K. (2014). Evidence of a Novel Mechanism for Partial γ-Secretase Inhibition Induced Paradoxical Increase in Secreted Amyloid β Protein. PLoS ONE, 9(3), e91531. doi:10.1371/journal.pone.0091531