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]. While a wild type presenilin gene, *PSEN1*,regulates APP levels, a series of deletions in *PSEN1* causes an upregulation of APP through a mutated presenilin 1 protein (PSEN1) [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 in Alzheimer’s [3]. However, the mechanism by which *PSEN1* regulates gamma-secretase activity and APP production is currently unknown. One possibility is seen through the protein interactions between PSEN1 and UBQLN1, an ubiquitin protein associated with accumulation of APP and neurotoxicity in Alzheimer’s [4].

**Here we will test the hypothesis that UBQLN1-mediated ubiquitination is required to regulate PSEN1 and gamma-secretase activity in regards to APP accumulation.** Model mice and zebrafish will be used as model systems to study the role of ubiquitination in the formation of amyloid plaques and neurofibrillary tangles in Alzheimer’s.

Our ***long term goal*** is to identify the importance of UBQLN1 and its relationship with PSEN1 in those with Alzheimer’s. Understanding the interaction between PSEN1 and regulatory proteins such as gamma-secretase and UBQLN1 in Alzheimer’s disease is the main ***objective*** of this research. To do so, we will pursue the following three specific aims:

***Aim 1*:Identify a drug that inhibits UBQLN1 function of PSEN1 accumulation.**

**Approach**: Using PubChem and a direct target library, drugs targeting PSEN1, UBQLN1 and similar regulatory proteins of neurotoxicity can be isolated and tested in model zebrafish.

**Hypothesis**: A drug capable of inhibiting UBQLN1 will suppress PSEN1 accumulation, APP production and amyloid plaque formation.

**Rationale**: Treating mutant PSEN1 zebrafish with the identified compounds will restore wild type function to *PSEN1*, controlling the amount of neurotoxic plaques formed.

***Aim 2*:Determine the importance of UBQLN1 and other ubiquitination-inducing proteins.**

**Approach**: Use tandem affinity purification to identify brain-candidate proteins for CRISPR-Cas9 knockout to observe the effects on amyloid plaque formation in model mice.

**Hypothesis**: UBQLN1 and other ubiquitination-inducing proteins will be found essential to amyloid plaque formation, as observed in Alzheimer’s.

**Rationale**: Additional ubiquitination-inducing proteins will be identified as amyloid plaque regulators under mutated *PSEN1*, adding additional networks for PSEN1 and UBQLN1.

***Aim 3*:Identify essential phosphorylation sites in PSEN1 responsible for amyloid plaques.**

**Approach**: Use NetPhos 2.0 and Clustal Omega to determine the most conserved post-translational modification in PSEN1 linked to wild type PSEN1 function in humans.

**Hypothesis**: Phosphorylation at specific amino acid sites are required for wild type PSEN1 function.

**Rationale**: Altering the most conserved phosphorylation site will promote amyloid plaque formation, identifying the importance of certain post-translational modifications.

Regarding the specific aims, further research on *PSEN1* involvement in Alzheimer’s will not only reduce symptoms, but also isolate possible disease prevention techniques for the near future. While currently unknown, it is possible that stimulated downregulation of either gamma-secretase or UBQLN1 in disease patients could prevent APP accumulation. This suppression in APP would in turn control the neurotoxicity of the brain, while also eliminating the symptoms associated with the disease state. Understanding this connection between PSEN1 and its related protein interaction networks will then provide solutions to not only Alzheimer’s, but to other neurodegenerative diseases as well.

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