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, a 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*:Isolate drug targets for wild type PSEN1 and UBQLN1 using a chemical genetics screen to test binding affinity.**

**Approach**: Using a chemical genetic database like PubChem, drugs targeting PSEN1, UBQLN1 and similar regulatory proteins of neurotoxicity can be isolated and tested.

**Hypothesis**: A drug capable of inhibiting either PSEN1 or UBQLN1 will reduce the production of APP while alleviating the formation of amyloid plaques.

**Rationale**: Finding a drug target that affects the binding between PSEN1 and UBQLN1 will help in procuring a solution to increased neurotoxicity observed during Alzheimer’s.

***Aim 2*:Identify additional proteins involved in the mutant *PSEN1* disease pathway through an RNAi screen.**

**Approach**: Conduct an RNAi screen in a *PSEN1* mutant background to identify gene and protein candidates for suppressing the formation of amyloid plaques and neurofibrillary tangles.

**Hypothesis**: UBQLN1 and other ubiquitination-inducing proteins will be found essential to the development of Alzheimer’s and its associated symptoms.

**Rationale**: Performing an RNAi screenin both model mice and zebrafish should illustrate the role of ubiquitination in human UBQLN1—which should regulate toxic gamma-secretase and APP levels.

***Aim 3*:Recognize other proteins that interact with PSEN1 and UBQLN1 during Alzheimer’s.**

**Approach**: Perform a Yeast 2-Hybrid screen using UBQLN1 and PSEN1 as baits to better interpret the protein interaction network.

**Hypothesis**: Ubiquitin ligases will be found to play a crucial role in neurotoxic protein accumulation.

**Rationale**: Understanding the role that ubiquitin ligases and other proteins have in the formation of amyloid plaques will provide insight to the causation of Alzheimer’s disease phenotypes.

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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