Wilson disease (WD) is characterized by the inability to filter out copper from the body causing copper accumulation primarily in the liver and brain. This disease is caused by mutations in the copper transporting protein ATP7B, an ATPase residing in the trans-Golgi network [1]. Though small amounts of copper are necessary for energy pathways and iron metabolism, an excess of copper is toxic due to free radical formation and can lead to liver and brain damage. In previous research, copper toxicity has been linked to neural degeneration in Alzheimer’s, Parkinson’s, and Creutzfeldt-Jakob disease [2]. Some ATP7B mutations are linked to degeneration of the basal ganglia, a brain structure involved in functions such as movement coordination; however, *the function of ATP7B in regulating copper metabolism in the basal ganglia is not completely known* [3].

My **primary goal** is to learn more about the role of ATP7B in copper metabolism in the basal ganglia. I will use the fruit fly *Drosophila melanogaster* because it is an excellent model system to study neurodegenerative diseases [4]. I **hypothesize** that differential gene expression of copper-transporting and oxidative response proteins in the basal ganglia of mutant and wildtype ATP7 flies will occur in response to a high-copper diet. My **long-term goal** is to better understand the neurological WD phenotype for future treatments and insight into other neurodegenerative diseases.

Aim 1: Identify conserved amino acids in ATP7B that are important for copper metabolism function.

**Approach**: I will use MEME to discover conserved ATP7B sequence motifs in model organisms and humans. I will then screen through the known WD mutations in humans that cause symptoms associated with basal ganglia degeneration. From the conserved motifs and known WD mutations, I will use CRISPR/Cas9 to create flies with the ATP7 amino acid mutations that correspond to neurodegeneration in humans (ATP7 is the fruit fly homolog to ATP7B). I will then screen for decreased locomotion associated with copper toxicity in the fly brain following a copper-rich diet. **Rationale***:* Not all WD mutations affect the brain, so screening for mutations that cause problems in locomotion allows for a better correlation to the human WD phenotype. I **hypothesize** that mutations in conserved domains will affect the fly brain.

Aim 2**:** Identify genes that are differentially transcribed in the brain that are important for copper metabolism.  
**Approach**: I will use RNA-Seq on mutant and wildtype ATP7 fly brain tissue fed with a normal and a copper-rich diet to find differentially expressed genes in copper metabolism. I will then sort the genes by function through Gene Ontology. To confirm their role copper metabolism, I will use CRISPR/Cas9 to create fly knockouts of the differentially expressed genes and screen for the decreased locomotion phenotype associated with copper toxicity in the fly brain. **Rationale**: From this information I can determine genes involved in copper metabolism in flies. I **hypothesize** that there will be differentially expressed copper-transporting and oxidative response genes due to the ATP7 mutation in the brain.

Aim 3**:** Identify new protein interactors of ATP7 involved in copper metabolism in the brain.  
**Approach**: I will create TAP-tagged wildtype and mutant ATP7 flies in order to identify new interacting proteins. I will then use GO to determine the function of interacting proteins and then confirm their role in copper metabolism by using CRISPR/Cas9 to knockout the interacting proteins and screen for decreased locomotion. I will then compare the RNA-seq data and TAP results to expand the existing STRING interaction network to see if the differentially expressed transcripts translate into proteins that interact with ATP7. **Rationale**: I can determine if the differentially expressed genes function in copper metabolism interact with ATP7 and determine what functions they are involved in. I **hypothesize** that the differentially expressed interacting proteins encode novel copper metabolism and oxidative response proteins.  
  
The widespread and variable symptom display of WD often makes it difficult to characterize and without treatment, WD is fatal. If we are able to establish a method to test WD early on, it would save valuable time for individuals affected by this disease. By learning more about the phenotype of WD, we are gathering knowledge to potentially develop new drug or gene therapy treatments for WD and other neurological diseases.

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