Down syndrome is caused by a trisomy of chromosome 21 (having three copies instead of two copies) [1]. This extra copy of chromosome 21 is a result of abnormal cell division during development. Several neuronal defects are observed in affected individuals in their developmental years [2]. Down syndrome cannot be cured, and symptoms will stay with individuals for the rest of their lives. The current support and treatment can only help affected individuals manage their symptoms. Although several genes may be involved, the *DYRK1A is one* gene that has been associated with cognitive defects in Down syndrome [2]. *DYRK1A* encodes a kinase that plays a role in neural development and neuronal differentiation [3]. Interestingly, *DYRK1A* also mediates cell proliferation [4], *­and it is unclear if the levels of DYRK1A protein may mediate cell division events during neural development.*

My **primary goal** is to determine how *DYRK1A* modulates the cell cycle during neural development. I **hypothesize** that the *DYRK1A* kinase downregulates cell cycle factors leading to reduced cell proliferation during critical neural development periods. I will use wild-type and *DYRK1A* mutant zebrafish (*Danio rerio*) as a model because the *DYRK1A* domains are well-conserved, and their transparent nervous systems allow for the visualization of neural proliferation. My **long-term goal** is to analyze how neural development is impacted by cell cycle modulation.

**Aim 1: Identify the specific *DYRK1A* domains that are necessary for cell cycle processes in the brain.**

**Approach:** First, NCBI BLAST will be used to determine the homologs of *DYRK1A* with diverse nervous systems. The homolog sequences will be aligned using ClustalOMEGA, and highly conserved domains will be determined. I will then create *DYRK1A* mutants by using CRISPR/Cas9 to knockout the identified domains one at a time. The neural proliferation in the mutant zebrafish will be compared with the neural proliferation in the wild-type zebrafish.

**Rationale:** *DYRK1A* is known to reduce neuronal development and is also known to have phosphorylating capabilities through its P-kinase regions. Removing regions of the gene that may play a role in mediating the cell cycle in neurons is a priority as these will phenocopy the human disease.

**Hypothesis:** Knockout of the P-kinase region in species with diverse nervous systems will be necessary for mediating cell division in neurons.

**Aim 2: Identify genes in the brain that are expressed differently within the *DYRK1A* mutants**

**Approach:** Brain tissue samples will be taken from both wild-type and the *DYRK1A* mutant zebrafish from Aim #1. The gene expression profiles of wild-type and P-kinase knockout mutants will be determined by conducting RNA sequencing on these tissue samples. Through GO analysis, the differentially expressed genes will be sorted into categories such as neurogenesis, neural cell differentiation, and neural cell proliferation.

**Rationale:** Identifying genes that are differentially expressed in *DYRK1A* mutants will elucidate the interactions of *DYRK1A* that play a role in neural cell proliferation.

**Hypothesis:** Wild-type and *DYRK1A* mutant zebrafish will differ in gene expression profiles related to neural cell proliferation. Specifically, the *DYRK1A* mutants without the P-kinase domain will have increased expression of neural cell proliferative genes.

**Aim 3: Determine DYRK1A protein interactions that regulate the cell cycle in neurons in the brain**

**Approach**: I will determine the difference in protein interactions between DYRK1A protein with and without the P-kinase domain. By using BioID, proteins that interact with DYRK1A will be tagged in brain samples of wild-type and mutant zebrafish without a P-kinase domain. Using affinity chromatography, the proteins that are tagged from both samples will be purified and analyzed using mass spectrometry. Next, we can identify the proteins and group them by gene ontology groups such as neurogenesis, neural cell differentiation, and neural cell proliferation to understand the biological and functional relationships with DYRK1A.

**Rationale**: Identifying DYRK1A protein interaction changes in the brain between wild-type and DYRK1A mutants will further elucidate the biological processes that mediate neural cell proliferation.

**Hypothesis**: DYRK1A interacts with proteins that are implicated in mediating neural cell proliferation through its P-kinase domain.

Through these specific aims, I expect to elucidate how the specific domains, gene expression profiles, and protein interactions of DYRK1A are involved in mediating cell division and neural proliferation in the brain. This research is especially crucial because it can lead to a better understanding of the biological mechanisms that lead to the pathology of neurodegenerative diseases such as Down syndrome.

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