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Specific Aims

Tourette syndrome is a non-debilitating disease that affects 1-10 in every 1,000 children worldwide. *Although current treatments do exist, the medications do not target any one gene or protein specific to the disease*. Medications on today's market include neuroleptic or antipsychotic medications. These treatments negate motor and vocal tics, attention deficits and compulsive feelings in patients with Tourette's, however they are not safe for children or for long-term usage. The cause of Tourette's has been linked to a single mutation in the *Hdc* gene. The *Hdc* gene encodes for histidine decarboxylase, a protein that aids in the conversion of histidine to histamine, a neurotransmitter in the brain. This mutation truncates the protein, making it unable to function within cells. Histamine regulates levels of another neurotransmitter, dopamine. In the brain, dopamine binds to receptors that affect motor control. Because the HDC can no longer function in patients with Tourette's, histamine and dopamine levels decrease in the brain. *The low levels of neurotransmitters and symptoms of Tourette's patients have not been directly linked to brain function.*

I am going to use zebrafish as my model organism for these experiments. Zebrafish are known to react quickly to light/dark changes within their environment. However, *Hdc* zebrafish mutants do not react normally to light/dark changes (Sundvik, 2011). Modafinil is a current drug on the market that has shown to oppose the biological characteristics of Tourette's syndrome. Modafinil works by raising the levels of histamine and dopamine in the brain. I propose that Modafinil regulates the expression of Hdc RNA and protein levels. My **primary goal** is to use a focused chemical genetic screen, similar to Modafinil, to identify drugs that regulate HDC function directly. This compound will potentially negate *Hdc* mutant phenotypes in zebrafish. Ultimately this research will help discover a new and safer treatment for children with Tourette's syndrome. This study will cover the **hypothesis** that biological levels of neurotransmitters can be affected to rescue Tourette phenotypes.

AIM 1: To determine other cellular targets of HDC function in the brain.
Approach: Perform RNA seq/GSEA analysis of wild type and *Hdc* mutant zebrafish to determine genes related to HDC activity in cell types.
Hypothesis: Novel targets can regulate histamine and dopamine levels and potentially be used for new treatments.

AIM 2: To identify chemical compounds which regulate *Hdc* gene function.
Approach: Initiate a focused genetic chemical screen of Modafinil-similar compounds on *Hdc* mutant zebrafish.
Hypothesis: New compounds that mimic Modafinil structure will bind and regulate HDC or neurotransmitter levels.

REFERENCES

Sundvik M, Kudo H, Toivonen P, Rozov S, Chen YC, Panula P. The histaminergeic system regulates wakefulness and orexin/hypocretin neuron development via histamine receptor H1 in zebrafish. 2011. FASEB J 2011; 25; 4338-47.