Von Hippel Lindau disease is a rare genetic disorder that effects 1 in 36,000 individuals. It is characterized by tumors and cysts that grow throughout the body, called hemangioblastomas. Hemangioblastomas can form on the brain, retinas and spinal cord while cysts may develop on pancreas and kidneys [1]. The VHL gene is a tumor suppressor, which regulates downstream genes that play a role in cell division, and thus mutations in the VHL gene lead to uncontrolled cell division or tumors. For many Von Hippel Lindau patients, renal cell carcinoma is the leading cause of death [2], however *it is unclear what role the VHL gene plays in kidney function throughout development.*

The **primary goal** is to determine how the VHL gene functions during kidney development. My **hypothesis** is that the VHL box domain is responsible for normal kidney development because all homologs of VHL that have mesonephros and metanephros excretory systems contain the VHL box domain while those that have pronephros or no excretory system do not. I will use zebrafish as a model organism because they have mesonephros excretory systems, as well as being easily amendable to study kidney development in genetic studies. The **long-term goal** of my research is to elucidate how VHL regulates kidney development to be used better understand how loss of VHL leads to renal cell carcinoma.

**AIM 1:** **Identify conserved amino acids in VHL responsible for kidney development.**

**Approach:** I will align the protein sequences for all VHL homologs using Clustal Omega to identify conserved regions in species with complex versus simple excretory systems. I will then use CRISPR to mutate particular regions of amino acids in zebrafish and determine if these mutations give rise to kidney tumors.

**Hypothesis:** Loss of specific amino acids in the VHL domain leads to kidney tumors.

**Rationale:** Conserved amino acids in the VHL domain only in complex excretory systems will be important for kidney function.

**AIM 2: Identify a small molecule that restores function in VHL mutant zebrafish with kidney tumors.**

**Approach:** I will perform a chemical genetic screen using a diversity-oriented library on parental VHL mutant zebrafish generated in AIM 1. I will then observe whether their progeny displays a reduction in kidney tumor formation. **Hypothesis:** A small molecule screen will identify a drug that can rescue the kidney tumor phenotypes from CRISPR mutants constructed in AIM 1.

**Rationale:** By identifying a chemical compound that restores VHL function in kidney development, it could potentially be used clinically to restore VHL function in renal cell carcinoma.

**AIM 3: Identify novel VHL protein interactions important for kidney development.**

**Approach:** To identify novel VHL protein interactors that function specifically in kidney development, I will run a TAP Tag assay on wildtype and VHL mutant zebrafish kidney samples. I will sort my data based on Gene Ontology terms to identify factors that are involved in cell proliferation and angiogenesis.

**Hypothesis:** I will identify novel protein interactions only observed between wildtype and VHL mutant zebrafish that are important for tumor proliferation and kidney localization.

**Rationale:** Protein interactors of VHL that specifically function on kidney tissue development would likely be identified using this method.

From all of the results from this research, I expect to determine if the VHL box domain is important for complex excretory system development. By understanding role of VHL in normal kidney development, researchers in the future will be able to better develop treatment for Von Hippel Lindau patients.

1. Wong, M., Chu, Y.-H., Tan, H. L., Bessho, H., Ngeow, J., Tang, T., & Tan, M.-H. (2016). Clinical and molecular characteristics of East Asian patients with von Hippel–Lindau syndrome. *Chinese Journal of Cancer*, *35*, 79. <http://doi.org/10.1186/s40880-016-0141-z>
2. Von Hippel-Lindau Syndrome: Genetics Home Reference. Retrieved from < [https://ghr.nlm.nih.gov/condition/von-hippel-lindau-syndrome#](https://ghr.nlm.nih.gov/condition/von-hippel-lindau-syndrome) >