­­Von Hippel Lindau (VHL) disease is a rare genetic disorder that effects I in 36,000 individuals. It is characterized by tumors and cysts that grow throughout the body called hemangioblastomas. Hemangioblastomas can form on brain, retinas and spinal cord while cysts may develop pancreas and kidneys [1]. In patients with VHL, there is loss of function in tumor suppressor gene called VHL. VHL acts as an E3 ubiquitin ligase to degrade HIF-α, which activates genes downstream that play a role in controlled cell division. For those that have VHL disease, renal cell carcinoma is the leading cause of death [2]. It is known that during development, the human kidney goes through 3 levels of development [3]. *However, the role of VHL in these 3 different levels of kidney development is unknown.*

The **primary goal** of my research is to determine the region of the VHL gene that is responsible for progression through different levels of kidney development. **Hypothesis:** The region of the VHL gene that is responsible for mesonephros kidney development is the VHL box domain. The **long-term goal** of my research is to use the knowledge of the region of VHL important for normal kidney function to be used better understand the function of VHL in renal cell carcinoma.

**Aim 1:** Determine the region of VHL responsible for complex kidney development

**Approach:** I will align the protein sequences for the homologs of VHL using Clustal Omega to observe conserved regions. I will then use CRISPR to mutate these target areas in an organism with mesonephros kidneys, like zebrafish.

**Rationale:** I will be able to observe the amino acids that are conserved in organisms with more complex kidneys. This information will tell me the link between VHL and complex kidney development.

**Hypothesis:** The conserved region in organisms with complex kidney development will be in their VHL box domain.

**Aim 2:** Identify a small molecule that restores function in knockout zebrafish

**Approach:** I perform a chemical genetic screen using a diversity-oriented library on my knockout zebrafish and wildtype zebrafish embryos.

**Rationale:** By identifying a chemical compound that restores VHL function in development, it’s structure could be used to find a drug restore VHL function in renal cell carcinoma.

**Hypothesis:** The small molecule will restore the structure and function of the alpha helical VHL box domain.

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) >
3. Romagnani, P., Lasagni, L., & Remuzzi, G. (2013). Renal progenitors: an evolutionary conserved strategy for kidney regeneration. *Nature Reviews Nephrology*, *9*(3), 137-146.