**Specific Aims**

In the United States, Non-Small Cell Lung Cancer (NSCLC) accounts for 24% of all cancer related deaths, making the most common cause of cancer related death [1]. Lung cancer is composed of a wide variety of mutations, yet ALK gene inversion is a prominent driver of ALK associated with lung cancer [2]. Molecularly, ALK is a receptor tyrosine kinase protein. This means that when it receives signals from outside the cell, it will activate a number of other proteins involved in either cell survival or proliferation via phosphorylation. Within the past several decades, there has been a dramatic change in the manner that lung cancer has been treated. Specifically, targeted therapies have been capable of improving patient outcomes. However, it is unclear what ways ALK gains resistance to current therapies [3].

My **objective** is to determine the role of ALK in treatment resistance and how mutations in ALK differ between treatment responsive and treatment non-responsive mice. Mus Muscles will be utilized as a model organism due to their capacity to model ALK driven lung tumors and treatment. I **hypothesize** ALK mutations play a critical role in creating treatment resistance populations, and will have mutated binding sites. **My long-term goal** is to provide new understanding of ALK’s capacity to resist treatment, and ultimately provide new targeted ALK therapies that overcome common resistance mechanisms.

**AIM 1: Identify conserved sites in tyrosine kinase domain necessary for treatment response.**

**Approach**: Utilize NCBI Blast to determine various homologs for the ALK gene. Then align the sequences using ClustalOMEGA to identify conserved sites in tyrosine kinase domain. Using this information, use CRISPR/Cas9 to induce mutations at conserved sites across all species involved in molecule binding. Finally, screen for treatment resistant mutants in transgenic mice.

**Hypothesis**: Treatment resistance will be seen in all mutants, but mutations in the conserved treatment binding sites will display more resistance.

**Rationale**: The tyrosine kinase domain is the treatment binding site. Understanding the conserved regions in this domain will likely indicate amino acids necessary for ALK treatment response.

**References**

1. Non-Small Cell Lung Cancer. Medscape (2019 August). Retrieved from <https://emedicine.medscape.com/article/279960-overview>
2. Carper, Miranda B, and Pier Paolo Claudio. “Clinical potential of gene mutations in lung cancer.” *Clinical and translational medicine* vol. 4,1 (2015): 33. doi:10.1186/s40169-015-0074-1
3. Hrustanovic, Gorjan, and Trever G Bivona. “RAS signaling in ALK fusion lung cancer.” *Small GTPases* vol. 7,1 (2016): 32-3. doi:10.1080/21541248.2015.1131803