**Myostatin-Related Muscle** **Hypertrophy** (MRMH) is a single gene disorder characterized by an increase in muscle mass and strength. Patients with MRMH are able to live a normal life with no other functional or cognitive effects. Mutations in the MSTN gene lead to failure to produce a functional myostatin protein, a member of the TBFB superfamily which are important for tissue development throughout the body. Myostatin plays a role in keeping muscle growth in check by inhibiting myoblast (cells that eventually develop into muscle fibers) differentiation. Myostatin is initially in the form of two inactive subunits and is only activated when cleaved by Protease, a specific type of enzyme [1]. The active COOH-terminal dimer of Myostatin then binds to the activine type ll receptor, which recruits Alk-3 or Alk-4 [2]. These are co-receptors that activate a cell signaling cascade that then induces the activation of transcription factors, thus inducing myostatin related gene regulation. When these transcription factors are applied to myoblasts, myostatin genes inhibit their differentiation into mature muscle fibroblasts [1]. *While the process is well characterized, the effects on other body systems, besides muscular, are not well defined*. Alk-4, otherwise known as ACVR1B, also plays roles in cell growth, differentiation and death [2]. Because Alk-4 is not recruited when the myostatin gene is mutated, it’s control over other cell systems is compromised. Alk-4 malfunction has been a known contributor to the development of lung cancer [3].

**Long term goal:** Discover if people with Myostatin-Related Muscle Hypotrophy have a higher risk of developing lung cancer.

**Hypothesis:** A mutation in the myostatin gene effects the function of Alk-4 and will decrease control of differentiation and apoptosis in cells, which would lead to higher lung cancer prevalence.

**Specific AIMS 1:** Confirm that Alk-4 is present within lung tissues

**Approach:** Take a lung tissue sample of the model organism. Perform immunostaining and label for the protein ALK-4 with fluorescent markers. Observe the fluorescent tag in a tissue sample.

**Hypothesis:** The Alk-4 protein labeled with the fluorescent antibody will be present in the musculature, and in the lung tissue as well.

**Rational:** Because Alk-4 is present in the lung sample, we can assume that it is part of regulating tissue differentiation and apoptosis in the lungs.

**Specific AIMS 2**: Characterize the effects of an absent Alk-4 in the lungs

**Approach:** Conditionally knockout the Alk gene in a mouse. During maturity, observe if tumors develop in the lungs. After, dissect the lungs and observe the extent of tumors.

**Hypothesis:** In the absence of Alk-4 and no mechanism to control cell growth, tumors will grow excessively in the lungs.

**Rational:** If, without Alk-4 present, tumors develop in the lungs, we can determine that there is a direct correlation between the two. Thus linking Alk-4 directly to the suppression of tumors in the lungs.

References

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2.    Schiaffino, S., & Mammucari, C. (2011). Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: insights from genetic models. *Skeletal Muscle*, *1*, 4. <http://doi.org/10.1186/2044-5040-1-4>

3. ALK: A Specific Oncogenic Driver

<https://www.biooncology.com/pathways/alk/what-is-alk.html?cid=ale_PS_00005363_1&utm_source=bing&utm_me>