Ovarian cancer is the leading cause of gynecologic cancer death in developed countries. Epithelial ovarian cancer (EOC) embodies the majority of ovarian cancer (1). Mucinous epithelial ovarian cancer (mEOC), a type I EOC tumor characterized by a mucus-like filling, responds poorly to platinum-based drug treatment compared to the more common type II subtypes of EOC (2). Mutations in the tumor protein p53 (TP53) are common in type II EOC tumors, but are rarely seen in type I tumors. Interestingly, mEOC has been found to be an exception, as recent studies have revealed up to a 50% TP53 mutation rate in these type I tumor (3). TP53 encodes for p53, a protein which functions as a tetrameric DNA-binding transcription factor that regulates growth arrest, apoptosis, DNA repair, and elimination of damaged or emerging tumor cells throughout the body (4). In the ovary, mutations in TP53 either result in the loss of p53 or, more commonly, in the overexpression of mutant p53, consequently altering the DNA-binding ability of p53 or changing in the interaction of p53 with other proteins (5). *However, the location of TP53 mutation and subsequent effects on p53 expression and function in mEOC has not been explored.*

My **primary goal** is to identify the location of TP53 mutations in mEOC and how this effects p53 expression and function compared to other EOCs. My **hypothesis** is that TP53 mutations in mEOC result in the interaction between mutant p53 and other proteins that cause downstream development of mEOC. My **long-term goal** is to use understand of p53 function in mEOC to develop more effective therapeutics for this unique type of EOC.

**Aim 1: Determine which regions of TP53 domains are mutated in during mEOC tumor development.**

**Approach:** Domain analysis was conducted on both human p53 and *Mus musculus* p53 using SMART and PFAM database, revealing high domain conservation between the two species*.* CRISPR/Cas9 will be used to knockout the most conserved areas of the different domains in *Mus musculus*, as well as amino acid 273, which is a commonly mutated region in other EOC subtypes. Mice that EOC will undergo a platinum-based drug treatment to isolate mice with mEOC specifically.

**Rationale:** There are three major domains in TP53, but it is unknown which is associated with mEOC development. Knockouts that result in a mEOC phenotype will provide insight into the location of TP53 mutations in the disease.

**Hypothesis:** Specific mutations in amino acid sequences within a specific domain will affect p53 expression and function and cause development of mEOC.

**Aim 2: Evaluate p53 expression levels in mEOC models to determine the effect of TP53 mutation on p53 expression.**

**Approach:** RNA-seq will be conducted on cells dissociated and isolated from ovary tissue samples in the mEOC+ mouse models developed in Aim 1. p53 expression levels will be analyzed and compared to p53 expression in wild-type mice.

**Rationale:** p53 expression in mEOC has not yet been established. Mutations in TP53 can result in both loss or overexpression of p53, which have different downstream effects on tumor development. Understanding expression patterns of p53 in mEOC can provide insight into the progression of these tumors in the ovary.

**Hypothesis:** TP53 mutation results in overexpression of mutant p53 in mEOC compared to wild-type mice.

References:

(1) Kroeger Jr, P. T., & Drapkin, R. (2017). Pathogenesis and heterogeneity of ovarian cancer. Current Opinion in Obstetrics and Gynecology, 29(1), 26-34.

(2) Hess, V., A'hern, R., Nasiri, N., King, D. M., Blake, P. R., Barton, D. P., ... & Kaye, S. B. (2004). Mucinous epithelial ovarian cancer: a separate entity requiring specific treatment. Journal of clinical oncology, 22(6), 1040-1044.

(3) Rechsteiner, M., Zimmermann, A. K., Wild, P. J., Caduff, R., von Teichman, A., Fink, D., & Noske, A. (2013). TP53 mutations are common in all subtypes of epithelial ovarian cancer and occur concomitantly with KRAS mutations in the mucinous type. Experimental and molecular pathology, 95(2), 235-241.

(4) Oros Klein, K., Oualkacha, K., Lafond, M.-H., Bhatnagar, S., Tonin, P. N., & Greenwood, C. M. T. (2016). Gene Coexpression Analyses Differentiate Networks Associated with Diverse Cancers Harboring TP53 Missense or Null Mutations. Frontiers in Genetics, 7, 137. http://doi.org/10.3389/fgene.2016.00137

(5) Muller, P. A., & Vousden, K. H. (2013). p53 mutations in cancer. Nature cell biology, 15(1), 2-8.