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Specific Aims – BG, Gap, and Aim #1

2/28/17

Ovarian cancer is the leading cause of gynecologic cancer in developed countries. Epithelial ovarian cancer (EOC) represents the majority of ovarian cancers, which are divided into two groups: slow growing type I tumors and rapidly growing type II tumors (1). Mutations in the tumor protein p53 gene (*TP53*) are some of the most common mutation in EOC, with a mutation rate of over 90% in type II tumors (2). *TP53* encodes for the protein p53, which regulates cell repair and apoptosis. Mutations in *TP53* result in decreased p53 function. Surprisingly, while mutations in *TP53* are generally rare in type I tumors, recent studies have found about a 50% mutation rate in mucinous carcinomas (3). *However, how TP53 mutation affects p53 function in mucinous carcinomas compared has not been explored.*

My **primary goal** is to understand how p53 function changes related to mutations in *TP53* in mucinous carcinomas*.*

My **hypothesis** is that *TP53* mutations in mucinous carcinoma result in decreased p53, but not complete inactivation, of p53 function.

My **long-term goal** is to understand why *TP53* mutations are common in mucinous carcinoma but not other type I tumors and how these mutations differ than those seen in type II EOC.

**Aim 1: Identify p53 expression levels in the ovaries of wild-type (WT) mice compared to *TP53* mutant mice**.

**Approach:** I will use CRISPR/Cas9 to knockdown *TP53* activity, and then perform a Western blot to analyze expression levels in the WT and mutant models. **Hypothesis:** Expression of p53 will increase in the *TP53* mutant mice compared to the WT mice. **Rationale:** This information would help provide a baseline for understanding how mutations in *TP53* affect overall p53 expression in the mouse ovary.

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) Ren, Y. A., Mullany, L. K., Liu, Z., Herron, A. J., Wong, K. K., & Richards, J. S. (2016). Mutant p53 promotes epithelial ovarian cancer by regulating tumor differentiation, metastasis, and responsiveness to steroid hormones. Cancer research, 76(8), 2206-2218.

(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.