Ovarian cancer is the leading cause of gynecologic cancer death in developed countries. Ovarian cancer represents the large variety of disease where tumors develop in the ovary (1). Mutations in the tumor suppressor protein p53 (*p53)* gene are the most frequent genetic events found in ovarian cancer patients (2). p53 functions as a transcription factor during the cell cycle regulation, apoptosis, and elimination of tumor cells throughout the body (3). It is also involved in facilitating DNA damage repair within the genome (4). In the ovary, mutations in *p53* often result in the overexpression of the protein, consequently altering its ability to bind DNA and associated factors (5). *However, the specific role of p53 in DNA repair in the ovaries has not been examined.*

My **primary goal** is to identify mutations in *p53* specifically associated with ovarian tumors to assess how these changes affect DNA repair mechanisms in the ovary. My **hypothesis** is that *p53 regulates* the expression of DNA repair genes in the ovary, leading to novel protein interactions and tumor development. I will use a mouse model because the ovary structure is well defined and gene knockdown experiments are relatively easy. My **long-term goal** is to understand of the role of *p53* in DNA repair in the ovary to order to develop more effective therapeutics and prevention strategies for the ovarian cancer.

**Aim 1: Determine which amino acids in *p53* are specifically mutated in ovarian tumors.**

**Hypothesis:** Specific amino acid mutations in *p53* will cause in tumor development in the females but not the males.

**Approach:** ClustalOmega will be used to determine specific amino acids in *p53* that are conserved across the mice with ovaries but not in mice without ovaries. CRISPR/Cas9 will then be used to knockout these conserved amino acids in the female and male organisms**.** Knockouts that result in tumors in the female mice only will be used as the ovarian cancer model for future experiments.

**Rationale:** Knockouts that result in tumors only in the females will identify amino acids in *p53* that are ovarian specific.

**Aim 2: Determine gene expression changes related to DNA repair in ovarian cancer tissue.**

**Hypothesis:** Mutations in *p53* will result in the decreased expression of select DNA repair genes in the ovary, thus disrupting proper DNA damage repair and promoting tumor development.

**Approach:** RNA-seq will be conducted on ovary and testis tissue samples from wild type and p53 mutant mice generated in Aim1. Global gene expression levels will be analyzed and compared to wild-type mice. Genes with decreased expression specific to the *p53* mutant ovary tissue will be identified, Gene ontology will then be used to identify those associated with DNA repair and other biological processes.

**Rationale:** Mutations in p53 has differential downstream effects on global gene expression specifically in the ovary. Understanding gene expression patterns of DNA repair genes specifically in the ovary can provide insight into the role of *p53* in ovarian tumor development.

**Aim 3: Identify DNA repair proteins that interact with p53 specifically in the ovary.**

**Hypothesis:** Specific DNA repair proteins with decreased expression found in ovarian cancer will interact with p53 exclusively in the ovary..

**Approach:** Wild type and *p53-*mutant mice ovary and testis tissue will be used to identify interacting proteins using co-immunoprecipitation. Mass spectrometry will be used to identify interacting proteins, which will be compared between wild type and p53 mutant ovary and testis tissues in order to identify p53-interacting proteins in the wild type ovary tissue only. These p53-interacting proteins will be compared to the DNA repair proteins with decreased expression found in aim 2 to identify any matches.

**Rationale:** Novel ovarian p53-interacting proteins will be identified from the wild type ovary tissue sample when compared to the testis and *p53*-mutant ovary and testis tissues. Somep53-interacting proteins in the wild type ovary tissue are likely downregulated in the *p53-*mutant model.

Understanding the role of *p53* in ovary-specific DNA repair machinery could provide key insight into the cause and treatment of ovarian cancer.

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