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**What Genes Make Ovarian Cancer Resistant to Carboplatin Chemotherapy?**

**Grantee:** Jeremy Chien, PhD (need headshot)

**Institution:** University of New Mexico Health Science Center (South Region)

**Area of Focus:** Tumor Biochemistry and Endocrinology

**Grant Term:** 7/1/2014 to 6/30/2019

**The Challenge:** Resistance to chemotherapy is the main cause of ovarian cancer-related death. We don't fully understand why sometimes the drugs don't work or why they stop working.

**The Research:** Jeremy Chien, PhD, and his lab are looking for the genes linked to carboplatin resistance. Carboplatin is a chemo drug made with platinum that's used for new and recurrent tumors. It kills cancer cells by damaging their DNA and stopping them from dividing to make more cancer.

The team is taking complementary approaches to better their chances of identifying possible drug-resistant genes. They created a custom cDNA library from 10 ovarian tumors of different subtypes that were resistant to platinum-based chemotherapy. They're also growing carboplatin-resistant cancer cells in the lab.

Using highly efficient RNA sequencing, they're analyzing up to 200 sections of DNA in almost 400 samples. They're searching for pieces of genetic code that are more common in both primary ovarian tumors that start off as chemo-resistant as well as recurrent tumors that have become resistant.

**The Goal and Long-term Possibilities:** The data that results from Chien's work will be a valuable resource to help figure out what causes chemotherapy resistance in tumor cells and what can be targeted to overcome it. This could form the basis for more effective chemo, which prevents recurrence for ovarian and other types of cancer and which increases survival.

**ORIGINAL**

Resistance to chemotherapy is the final step in tumor evolution and the main cause of cancer-related death. Accordingly, how resistance is facilitated in tumor cells and which “facilitators” can be targeted to overcome chemotherapy resistance are clinically relevant questions. To address these questions, we will test the hypothesis that tumor-derived RNA transcripts, some of which are selected in the course of drug treatment, contribute toward carboplatin resistance. In Aim 1, we will apply innovative genetic screens to identify tumor-derived transcripts that contribute carboplatin resistance in ovarian cancer cell lines. In Aim 2, we will apply next-generation sequencing technologies to identify tumor-derived transcripts that are enriched in primary tumors with intrinsic resistance or recurrent tumors with acquired resistance. We will apply two innovative approaches in functional genetic screens: (1) We will use custom retroviral cDNA library generated from 10 chemotherapy-resistant ovarian tumors; and (2) Using this library, we will perform genetic screens in carboplatin-sensitive ovarian cancer cell lines grown on mesothelial-derived matrix to identify tumor-specific transcripts that contribute to carboplatin resistance. These approaches (the use of custom library from chemotherapy-resistant tumors and carboplatin resistance selection of cancer cells grown on the mesothelial-derived matrix) have never been done in functional genetic screens for drug resistance and therefore are innovative. The use of custom cDNA library will allow us to determine the extent to which tumor-specific variant transcripts contribute to carboplatin resistance, and cell cultures on mesothelial-derived matrix will allow us to test cooperativity between tumor-intrinsic factors and tumor-extrinsic microenvironment. Using next-generation sequencing of tumor transcriptomes, we will also identify novel transcripts, variant transcripts, and non-coding RNAs that are enriched in primary ovarian tumors with intrinsic resistance to chemotherapy or in recurrent tumors with acquired resistance to chemotherapy. Collectively, these studies will directly address how altered or tumor-derived RNA transcripts contribute to chemotherapy resistance and the clinical relevance of novel and variant transcripts in chemotherapy resistance.