

"Integrated Genetic Analysis of Epithelial Ovarian Cancer"

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Abstract: Mutation of the genome underlies the development and progression of ovarian cancer. These alterations are responsible for the aberrant growth, invasion, escape from cell death, and resistance to treatment. Therefore the translational focus of this project is the characterization of such mutations, through which we can identify the primary alterations that are responsible for the etiology of ovarian cancer. We have developed several genomic technologies and methods of analysis to identify such genomic modifications and have applied them to 48 tumors thus far. We have begun the analysis of the various types of data, including copy number, methylation and gene and miRNA expression, and are in the process of identifying candidate tumor suppressors and oncogenes. The gene candidate analysis will be tightly integrated with the analysis of associated clinical data. This set of candidates will be validated with a high throughput program of functional characterization. Gene candidates that associate with such clinical variables as survival will be tested in mice. Gene candidates that are implicated in Carboplatin resistance will be tested in a culture system. Genes that are functionally validated will be sequenced in the tumor set to identify point mutations that can affect structure and function. Informatic analysis will also be used to identify the pathways targeted by genomic alteration. The integrated approach presented in this project will identify critical target genes and reveal their mechanisms of action that underlie the etiology of ovarian cancer.