

PRESENTATION TITLE: *Targeting genome instability as an essential vulnerability in ovarian cancer*

ABSTRACT: Ovarian cancer is the most lethal of all gynecologic malignancies in North America. The most common form of cancer of the ovary is epithelial ovarian cancer (EOC) and approximately 70% of EOC patients present with a high-grade serous (HGS) histotype. The etiology of most EOCs is unknown although 10% are attributed to the inheritance of genetic factors such as mutations in the BRCA1 and BRCA2 genes in HGS EOC, which significantly increases risk. The standard of care for ovarian cancer consists of a combination of surgery and chemotherapy consisting of platinum alkylating agents and the microtubule poison paclitaxel. While many women initially respond, most will relapse and eventually die of their disease. Our goal is to improve the current treatment for ovarian cancer to ensure better outcomes with improved quality of life. Ovarian cancers display high intra-tumoral heterogeneity, but all suffer from aneuploidy and our research has shown that this distinct feature can actually be exploited as the ‘Achilles heel’ of these atypical cells. Importantly, we have shown that blocking Ran in cells with aneuploidy leads to their death but that normal cells can tolerate the loss of Ran. Our research has allowed us to understand the molecular basis for this differential sensitivity and we have begun to develop small molecules able to selectively inhibit Ran function and have demonstrated their efficacy *in vitro*. This research builds on the strong models we have generated as well on extensive collaborations between fundamental, translational and clinical researchers.