The Honorable Tina Brozman Foundation Consortium Grant

Project Title: **Integration of Advanced Genomic and Bioengineering Approaches for Early Detection and Prevention of Ovarian Cancer.**

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LAY PROGRESS REPORT: YEAR 1

Ovarian cancer is responsible for the deaths of nearly 150,000 women worldwide each year and the 5-year survival rate has not improved in decades. The poor survival rate reflects the absence of effective treatment regimens and methods for early detection. We have assembled a multi-disciplinary team with diverse expertise to address this unmet medical need. It is now generally accepted that many ovarian cancers arise in the tips of the fallopian tubes. Our Consortium developed three inter-related projects that focus on two themes: (1) interrogating fluids in the vicinity of the fallopian tubes for the presence of genetic and protein biomarkers indicative of disease onset and (2) developing compounds that might eradicate the early tumor initiating cells that develop in the fallopian tube.

Specific Aim 1 of our Consortium continue to make progress in defining how cancer precursors in the fallopian tube develop, evolve, shed, and lead to tumor growth on the ovary. We recently reported that the incidence of tubal lesions in *BRCA1/2* mutation carriers was 6.3% and this was equally split among *BRCA1* (3.0%) and *BRCA2* mutation carriers (3.3%). We found that having multiple lesions in the fallopian tube fimbria may be an important predictor of disease progression. Using mathematical modeling in two studies, it appears that tubal precursors may progress to ovarian cancer within 6-7 years. This time frame represents our window of opportunity for prevention strategies. We are now asking whether we can detect other changes in the DNA (epigenetic changes) that might be detected even earlier than the current mutations found in fallopian tube precursors. With this data, we are asking whether cells or DNA from the early cancers in the fallopian tube are shed and can be detected using traditional Pap smears. This approach, called PapGene is very encouraging and we are collecting samples at multiple centers to test this concept. Our preliminary published results demonstrate the potential for DNA mutation-based diagnostics to detect ovarian cancer at a stage when it is more likely to be cured.

The goal of Specific Aim 2 is to develop tiny implantable sensors to measure ovarian cancer biomarkers over time in models of the disease, to understand when and where the biomarkers will appear. We are currently developing the Nanosensor implants to detect two well-established markers, CA-125 and HE4, and one new marker, CRAPB2. Several investigations are ongoing. One main focus is to make a more robust sensor for these markers that does not use antibodies, to allow for long-term measurements using the implants. We are currently developing this new class of sensor using machine learning to predict how the sensor will operate and determine how to improve the detection. We are also developing more conventional antibody-based sensors as well. Preliminary versions have now been synthesized for each biomarker.

Progress made in Specific Aim 3 established that in cultured mouse fallopian tube epithelial cells and human ovarian cancer cells with *BRCA1/2* inactivation a class of agents called BET inhibitors can significantly reduce the tumor-initiating cells. These findings set the stage for years 2 and 3 to look at whether BET inhibitors can eradicate tumor initiating cells in the fallopian tubes of animal models that recapitulate the human disease.

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Published Manuscripts Acknowledging Support from the Tina's Wish Foundation:

Visvanathan K, *et al*., Fallopian Tube Lesions in Women at High Risk for Ovarian Cancer: A Multicenter Study. Can Prev Res 2018; 11: 697-706.

Wu R, *et al*., Genomic Landscape and Evolutionary Trajectories of Ovarian Cancer Early Precursor Lesions. J Pathol 2019: *in press*.

Pisanic TR, *et al*., Methylomic Analysis of Ovarian Cancers Identifies Tumor-Specific Alterations Readily Detectable in Early Precursor Lesions. Clin Can Res 2018. Doi: 10.1158/1078-0432. CCR-18-1199.

Hooda J, *et al*., Early Loss of Histone H2B Monoubiquitylation Alters Chromatin Accessibility and Activates Key Immune Pathways that Facilitate the Progression of Ovarian Cancer. Can Res 2019: *in press*.

Wang Y, *et a*l., Evaluation of Liquid from Papanicolaou Test and Other Liquid Biopsies for the Detection of Endometrial and Ovarian Cancers. Sci Transl Med 2018; 10.

Williams, RM, *et al*., Noninvasive Ovarian Cancer Biomarker Detection via an Optical Nanosensor Implant. Sci. Adv. 4, eaaq1090 (2018).