



SU2C-Ovarian Cancer Research Fund Alliance-National Ovarian Cancer Coalition Ovarian Cancer Dream Team:

“DNA Repair Therapies for Ovarian Cancer”



[This abstract was provided by the scientists when their application was accepted.]

Large-scale genomic studies have demonstrated that half of high-grade serous ovarian carcinomas have alterations in homologous recombination DNA repair (HR). Loss of HR causes genomic instability, hyperdependence on alternative DNA repair mechanisms and relative sensitivity to certain types of DNA-damaging chemotherapy.

Conversely, restoration of HR can be a potent mechanism of therapeutic resistance. Specifically, HR-deficient (HRD) ovarian cancers are dependent on DNA repair processes requiring the enzyme PARP1, thus accounting for their hypersensitivity to PARP inhibitors (PARPi).

PARPi have demonstrated activity in ovarian cancer with germline or somatic BRCA1 or BRCA2 (BRCA1/2) mutations as well as those lacking BRCA1/2 mutations but presumably containing other HR defects.

Multiple PARPi are currently in clinical development for the treatment of HRD ovarian cancers. Three PARPi have recently received FDA approval for ovarian cancer (olaparib, rucaparib, niraparib). Inherited mutations in 11 DNA repair genes account for >20% of ovarian cancer and lead to clinically actionable levels of risk. Surgical prophylaxis decreases the mortality of women with inherited mutations in BRCA1 and BRCA2, but many women at high genetic risk are not identified until after a cancer diagnosis, leading to a missed opportunity to save lives.

Thus, focusing on DNA repair pathways could improve ovarian cancer mortality not only through development of novel therapeutic strategies, but also through identification and surgical prophylaxis of women at risk.

There is a critical need for 1) better biomarkers for identifying ovarian cancer patients who will benefit from PARPi therapy, 2) validated drug combinations that can inhibit HR and thereby extend PARPi use to include HR-proficient ovarian cancer, and 3) development of high throughput genetic testing strategies for ovarian cancer risk with attendant recommendations for risk reduction.

Through this SU2C Dream Team, we have assembled a team of experts in basic, translational, and clinical investigation of DNA repair and ovarian cancer to address these needs. Our program is designed to include novel therapeutic interventions for OC and to deliver near-term patient benefit. Our program has had high impact because it is highly translational, integrating the basic science of DNA repair with clinical disciplines in the area of DNA repair-targeted therapies and cancer prevention. Our preliminary data suggest that we may be able to successfully identify ovarian





Scientific Abstract

patients who respond well to PARPi monotherapy and to identify and treat other patients who are otherwise resistant to PARPi treatment through the use of novel drug combinations.

