#### AWARD NUMBER: W81XWH-17-1-0070

**TITLE:** Mutator Phenotypes that Better Predict PARP Inhibitor Response in Ovarian Carcinomas

PRINCIPAL INVESTIGATOR: Elizabeth Swisher

| CONTRACTING ORGANIZATION: | University of Washington |
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|                           | Seattle, WA 98195        |

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| AUTHOR(5) Elizabeth Swisher Elizabeth Swisher Elizabeth Swisher Elizabeth Swisher Elizabeth Swisher E-Mail: swisher@@uw.edu T.PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Washington 4333 BrodNin Ave NE Box 359472 Seattle, WA 98195 S.SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) US.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012 ISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited IS.SUPPLEMENTARY NOTES IA ABSTRACT Approved for Public Release; Distribution Unlimited IA ABSTRACT Approved for Public Release; Distribution Unlimited IA ABSTRACT Approved for Public Release; Distribution Unlimited IA ABSTRACT Approved for DNA repair, and cancers associated with BRCA1 or BRCA2 genes, BRCA1 and BRCA2 function in DNA repair, and cancers associated with BRCA1 or BRCA2 genes, BRCA1 and BRCA2 function in DNA repair, and cancers recombination does not work right, cancer cells rely on other types of DNA repair that result in more errors in replicating DNA, leading to characteristic patterns of DNA alterations. Whole genome sequencing and detect patterns of alterations in the BRCA2 to rBRCA2 genes, BRCA1 and BRCA2 function in DNA repair. When homologous recombination does not work right, cancer cells rely on other types of DNA repair that result in more errors in replicating DNA, leading to characteristic patterns of DNA alterations. Whole genome sequencing and detect patterns of alterations in the BRCA2 to rBRCA2 mutations, but who also have a good chance of responding to PARP inhibitor.  15.SUBJECT TERMS Ovarian cancer, BRCA1, BRCA2, whole genome sequencing, mutator, DNA repair, and cancer should be treated with a PARP inhibitor. In this manner, we can disently work and cancer who do not have BRCA1 or BRCA2 is PARP inhibitor.  15.SUBJECT TERMS Ovarian cancer, BRCA1, BRCA2, whole genome sequencing, mutator, DNA repair, bornologous recombination deficiency.  16.SUBJECT TERMS Ovarian cancer, BRCA1, BRCA2, whole genome sequencing,   | Carcinomas                    |                                     |                                |                                   |                           |  |  |
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## 1. INTRODUCTION

PARP inhibitors (PARPi) have clear therapeutic utility for cancer treatment in individuals with germline mutations in *BRCA1* or *BRCA2* (*BRCA*). These drugs also have activity in a subset of ovarian, peritoneal or fallopian tube carcinoma (OC) without germline mutations. However, the best way to predict which patients with *BRCA*-wildtype OC will respond to PARPi therapy is not defined. Loss of heterozygosity (LOH) as a maker for homologous recombination deficiency (HRD) does not optimally separate responders from non-responders amongst *BRCA*-wildtype OC. ARIEL2 is a monotherapy PARPi trial in platinum-sensitive OC and was powered to identify predictive biomarkers for PARPi response in women without germline *BRCA* mutations. We hypothesize that specific mutator signatures can be identified by whole genomic sequencing that identify HRD and are more predictive of response to PARPis than current diagnostic tests using LOH profiling. Our objective is to develop an HRD test that that will predict benefit from PARPi therapy and provide insight into which genetic alterations lead to HRD and PARPi response.

#### 2. KEY WORDS

Ovarian cancer, BRCA1, BRCA2, whole genome sequencing, mutator, DNA repair, signature, homologous recombination deficiency

#### **3. ACCOMPLISHMENTS**

Our first major task was to submit IRB exemption request to our IRB and then submit to the DoD HRPO. This task was successfully accomplished with receipt of human subjects expemption based on non-identifiability of the samples to be studied.

Our second major task is to develop and optimize the bioinformatics pipeline. We have done that successfully collaborating with Serena Nik-Zainal PhD, a well-known expert and developer of mutational signatures at the University of Cambridge.

Our third major task is to complete whole genome sequencing (WGS) on ARIEL2 samples. We are currently in the middle of that process. During this reporting period we identified the company providing the best price and quality sequencing (MedGenome). We wanted to test the quality of our WGS from formalin fixed paraffin embedded (FFPE) tumor sections from ARIEL2 samples using a small set of cases before we run the entire batch. We chose 8 cases and sent matched germline and tumor DNA to Macrogen. We got back very high quality data from 7 of 8 samples. Using Dr. Nik-Zainal's pipeline, we analyzed the samples according to the following algorithm:

- Caveman for substitutions plus additional post-hoc filtering to deal with FFPErelated artefacts and any new sequencing artefacts
- Pindel for insertions/deletions under 100bp
- Brass for structural variation
- ASCAT for copy number, ploidy and aberrant cell fraction

Per Dr .Nik-Zainal, these were the highest quality FFPE samples she has seen using her bioinformatics pipeline and were essentially indistinguishable from fresh frozen samples. Furthermore, the fail rate is usually been about 1/3 with FFPE samples, so we are very encouraged by our first test set. Whilw, this test set is too small to make any definitive conclusions about the relationship between signatures and response, it is encouraging that 2 of 3 cases with high HRDetect scores had measurable response to the PARP inhibitor rucaparib.



**Figure 1.** Preliminary mutational signature analysis of first 7 ARIEL2 FFPE cases. Of the first three cases with high HRDetect scores two had a partial response to rucaparib (AR2.021 and AR2.149. In contrast, of the next 4 cases with low HRDetect scores, only one had a partial response (AR2.060) and that tumor had too low neoplastic purity to provide a reliable score. Furthermore, that case has a high microhomology-mediated deletion score, which is one of our signatures of interest in detecting HRD. With a larger sample set, we will compare performance of HRDetect with the microhomology mediated deletions scores as well as with the other mutational signatures to identify the best predictor of PARPi response.

#### **Opportunities for training and professional development has the project provided?** Nothing to report

#### **Dissemination of Results**

Nothing to report

#### Plans during the next reporting period.

Now that we have confidence in the quality of the WGS data from ARIEL2 FFPE specimens, we will extract DNA and send to Macrogen for the remaining 110 cases. We already know mutational and methylation status. We will then correlate mutational signatures with PARPi response in collaboration with statisticians at Clovis Oncologycore known HR genes.

#### 4. IMPACT

#### Impact on the principal discipline

Nothing to report

**Impact on other disciplines** Nothing to report

**Impact on technology transfer** Nothing to report

**Impact on society** Nothing to report

5. CHANGES/PROBLEMS Changes in approach Nothing to report

**Problems or delays and plans to resolve them:** Nothing to report

**Changes that had a significant impact on expenditures** Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents Nothing to report

6. PRODUCTS

**Publications, conference papers, and presentations** Nothing to report

Website(s) or other Internet site(s) Nothing to report

**Technologies or techniques** Nothing to report

**Inventions, patent applications, and/or licenses** Nothing to report

Other Products Nothing to report

## PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

## • What individuals have worked on the project?

| Name:                                     | Elizabeth Swisher MD   |
|---|--|
| Project Role:                             | PI   |
| Researcher Identifier<br>(e.g. ORCID ID): | 0000-0003-2331-0434  |
| Nearest person month worked:              | 1  |
| Contribution to<br>Project:               | Dr. Swisher is directing all aspects of the project including IRB oversight, recruitment, sequencing analyses, and data interpretation                                   |
| Name:                                     | Maria Harrell, PhD   |
| Project Role:                             | Staff scientist  |
| Researcher Identifier<br>(e.g. ORCID ID): |  |
| Nearest person month worked:              | 2  |
| Contribution to<br>Project:               | Dr. Harrell was overseeing all sequencing including quality control.<br>She left the Swisher laboratory in March 2017 and has been replaced<br>by Christopher Pennil MSc |
| Name:                                     | Marc Radke   |
| Project Role:                             | Staff scientist  |
| Researcher Identifier<br>(e.g. ORCID ID): |  |
| Nearest person month worked:              | 1  |
| Contribution to<br>Project:               | Mr. Radke performs all DNA preparations and quality control prior to whole genome sequencing and monitors data transfer with Macrogen                                    |
| Funding Support:                          |  |
| Name:                                     | Chris Pennil., MSc.  |
| Project Role:                             | He now oversee all sequencing including quality control and took<br>over Dr. Harrell's role on the project   |
| Researcher Identifier<br>(e.g. ORCID ID): |  |
| Nearest person month worked:              | 2  |

| Name:                                     | Nithisha Khasnavis MSc   |
|---|--|
| Project Role:                             | Ms. Khasnavis is leading the bioinformatics on the project including developing and refining the WGS pipeline. |
| Researcher Identifier<br>(e.g. ORCID ID): |  |
| Nearest person month worked:              | 6  |

## Has there been a change in the active other support of the PD/PI(s) or senior/key personnel

since the last reporting period? No, Nothing to report

### What other organizations were involved as partners?

Nothing to report

Appendices

None