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TITLE: Real-Time Assessment of Homologous Recombination Deficiency During Ovarian Cancer Treatment

PRINCIPAL INVESTIGATOR: Elizabeth Swisher

CONTRACTING ORGANIZATION: University of Washington Seattle, WA 98195

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1. INTRODUCTION

BRCA1 and *BRCA2* (*BRCA*) are critical genes in the *BRCA*-Fanconi anemia pathway which repairs double strand DNA breaks via homologous recombination. Defective homologous recombination repair (HRR) confers increased sensitivity to platinum based chemotherapy and is synthetically lethal with PARP inhibitors. We and others have demonstrated that secondary somatic reversion mutations can restore *BRCA* function in *BRCA*-mutated ovarian carcinoma (OC). These reversion mutations correlate with platinum and PARP inhibitor resistance but are difficult to detect in clinical samples with current methods. In addition to the difficulty in identifying reversion to wildtype mutations in patients with HRR mutations, another barrier to predicting responsiveness to PARP inhibitors in the clinical setting is the need for pre-treatment biopsies to assess HRR status in real-time. We propose that assays that reveal the dynamic HRR status in tumors will lead to improved prediction of which women will benefit from PARP inhibitor therapy and provide essential information that will lead to better personalized therapies. To overcome the challenge of needing repeat biopsies, we propose to develop an HRR assay in cell-free DNA (cfDNA); this "liquid biopsy" will provide real-time assessment of HRR during therapy

2. KEY WORDS

Ovarian cancer, cell free plasma DNA, circulating tumor DNA, BRCA1, BRCA2, DNA repair, homologous recombination deficiency, next generation sequencing, liquid biopsy

3. ACCOMPLISHMENTS

Our first major task was to obtain DoD HRPO approval, which was accomplished on schedule.

Our second major task was to optimize a next generation sequencing assay to detect reversion mutations in tumor tissues using next generation sequencing. We performed high depth targeted NGS in cases with known reversion mutations identified by laser capture microdissection purification of neoplastic cells followed by Sanger sequencing. The identification of novel indel or single nucleotide substitutions that restore the open reading frame is relatively easy and was possible to do with our usual bioinformatics pipeline. However, the detection of secondary reversion to wildtype sequencing occurring on the mutant allele is challenging. We used tumor tissues with a variety of neoplastic purities to determine the lower limit of reliable detection of reversion to wildtype somatic mutations. We spent some time using different bioinformatics strategies to correct for neoplastic purity using allelic ratios both intragenic and across the genome. Despite these efforts, we were not able to get the threshold for reliable detection of reversion to wildtype below a minimum of 70% neoplastic purity. That means that for less pure tumor samples tested by NGS, one cannot rule out the presence of a sub-clonal reversion to wildtype somatic mutation.

Our third major task was to develop, optimize and test a cfDNA assay to identify HRR status. We designed a cfDNA NGS assay using IDT probes for target identification. We are closely collaborating with investigators in the University of Washington on development of this assay, so that it will be CLIA ready for clinical application at the conclusion of the project. First we tested the performance of the assay on high quality tumor DNA to compare with our standard tumor targeted NGS assay. In this quality control step, no mutations were missed with the new design. We've included unique molecular identifiers (UMIs) in our pipeline, which are small molecular tags that are added to each molecule prior to amplification that facilitate identification of amplification errors from true low-level variants. When combined with bioinformatic digital error correction, our sensitivity is significantly increased to the <0.2% variant range.

We are evaluating the assay both for standard single nucleotide subsitutions and indels, but also for larger copy number variations (CNV) and again, we have not missed any known mutations as evidence by the table below.

_miniOnco_Dataset	BROCA Sample	Gene	Expected Mutation(s) in overlapping genes based on BROv10
169R01_A01_MONCv1_NA0250	56_H05_BROv7_HA0198	PMS2	partial deletion exon 2
169R02_B01_MONCv1_NA0250	6624_H03_BROv8_HA0215	MSH2	exon 7 duplication
169R03_C01_MONCv1_NA0250	9659_C08_BROv8_HA0255	MSH2	exons 3-16 deletion
169R04_D01_MONCv1_NA0250	LMG2140	MLH1	exon 10 deletion
169R05_E01_MONCv1_NA0250	18224_H03_BROv10_HA0323	BRCA1	exon 17 deletion
169R06_F01_MONCv1_NA0250	23438_F05_BROv10_HA0410	BRCA1	exon 13 duplication
			exons 12 and 13
169R07_G01_MONCv1_NA0250	LMG1847	PALB2	deletion
169R08_H01_MONCv1_NA0250	LMG2145	BRCA1	exons 21-24 deletion

Now that we are confident in the performance of our design using high purity tumor DNA, we have begun testing on cfDNA samples from patients with OC. We have optimized our cfDNA collection and DNA extraction process. We have just tested our first batch of cfDNA samples

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.

We will test a number of cfDNA samples and compare results in our cfDNA NGS assay to direct tumor sequencing to identify sensitivity and specificity of cfDNA for tumor DNA alterations.

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

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 (e.g. ORCID ID):	0000-0003-2331-0434
Nearest person month worked:	1
Contribution to Project:	Dr. Swisher is directing all aspects of the project including IRB oversight, sequencing analyses, and data interpretation
Name:	Maria Harrell, PhD
Project Role:	Staff scientist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Dr. Harrell was overseeing all experiment and coordinating efforts between the Swisher Laboratory and Lab Medicine Department. She left the Swisher laboratory in March 2017 and has been recently replaced by Christopher Pennil MSc
Name:	Marc Radke
Project Role:	Staff scientist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Mr. Radke identify specimens, purify DNA including from plasma and perform all library preparations.
Name:	Chris Pennil., MSc.
Project Role:	He is now overseeing all experiment and coordinating efforts between the Swisher Laboratory and Lab Medicine Department and took over Dr. Harrell's role on the project.

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Name:	Mallory Beightol
Project Role:	Ms. Beightol is a senior technician in the Clinical Molecular Genetics Laboratory. She perform cfDNA library preps and sequencing.
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Name:	Colin Pritchard MD, PhD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Together with Dr. Swisher, Dr. Pritchard oversees assay development and validate the assay in a CLIA environment.
Name:	Stephen Salipante MD, PhD
Project Role:	Computational biologist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Salipante has developed the pipeline to assess somatic reversion mutations and to identify homologous recombination mutations in cell- free plasma DNA. He will perform the bioinformatics analyses for all samples.

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