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TITLE: Genetic and Genomic Determinants of Homologous Recombination Repair Deficiency as Treatment Selection Markers for Lethal Prostate Cancer

PRINCIPAL INVESTIGATOR: Jun Luo

CONTRACTING ORGANIZATION: Johns Hopkins University, Baltimore, MD

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Jun Luo

E-Mail: jluo1@jhmi.edu

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

JOHNS HOPKINS UNIVERSITY,
3400 N CHARLES ST W400 WYMAN
PARK BLDG BALTIMORE MD 21218-
2680

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Purpose: to test the main hypothesis that patients with lethal prostate cancer can be categorized into three molecular groups according to homologous recombination deficiency (HRD) status defined by deleterious mutations in HRD genes: 1) germline/somatic HRD mutations; 2) somatic-only HRD mutations; and 3) no HRD mutations; and that these groups are clinically distinct with differential responses to systemic treatments including AR-targeting therapies and taxane chemotherapies.
Scope: The scope of the study will include prospective evaluation of men with potentially lethal prostate cancer receiving systemic treatments in order to capture a diverse cohort of men receiving contemporary treatment regimens for castration resistant prostate cancer. From clinical correlative analyses we will determine differential response to treatments including AR-directed vs taxane therapies on the basis of HRD status, and from RNA-seq analysis we will determine the gene expression profiles associated with the three HRD groups.
Major activities and findings: We have successfully initiated both laboratory and clinical portions of the study in spite of limitations posed by the pandemic. All regulatory documents are in place and approved by authorities. Due to the nature of the study and emphasis on prospective sample and data collection, major findings will be reported in the no-cost extension period.

15. SUBJECT TERMS

None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
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1. INTRODUCTION:

In this project, we will test the main hypothesis that patients with lethal prostate cancer can be categorized into three molecular groups according to homologous recombination deficiency (HRD) status defined by deleterious mutations in HRD genes: 1) germline/somatic HRD mutations; 2) somatic-only HRD mutations; and 3) no HRD mutations; and that these groups are clinically distinct with differential responses to systemic treatments including AR-targeting therapies and taxane chemotherapies. To test this hypothesis, we will conduct a prospective study of men with potentially lethal prostate cancer receiving these treatments in order to capture a diverse cohort of men receiving contemporary treatment regimens for castration resistant prostate cancer. First, we will define and categorize HRD status in a prospective cohort of men mainly using blood-based assays. Patient samples will be collected from an ongoing, IRB-approved study. Then, we will conduct clinical correlative analyses to determine differential response to the therapies. Finally, we will identify the surgical specimens linked to patients enrolled in this study, and conduct RNA-seq analysis to determine the gene expression profiles associated with the three HRD groups.

2. KEYWORDS:

Prostate cancer, CRPC, DNA repair, HRD, liquid biopsy, PARP inhibitor, androgen deprivation, taxane chemotherapy, check point blockade, abiraterone, enzalutamide, apalutamide, docetaxel, cabazitaxel, PSA response, progression-free survival, overall survival, RNA sequencing

3. ACCOMPLISHMENTS:

What were the major goals of the project

Major Task 1: Blood-based tumor/normal DNA sequencing in a prospective cohort

Subtask 1: To conduct essential study planning and organization activities including IRB and HRPO approval, ordering of reagents, equipment readiness, protocol review, SOP review, personnel assignment, and review of pre-defined statistical plan, leading to HRPO and site IRB approvals (months 1-6). Completed.
Subtask 2: To optimize a 103-gene panel for blood-based sequencing (Months 7-12). Completed (100%).
Subtask 3: To define germline/somatic HRD status for the prospective cohort (months 12-24). Ongoing (80%).

Major Task 2: To annotate clinical outcome data

Subtask 1: To collect and annotate treatment outcome data in the prospective cohort. (Months 7-30). Ongoing (90%).

Major Task 3: To conduct clinical correlative analysis by comparing

treatment outcomes in men with different HRD status

Subtask 1: Primary analysis (Months 24-30). Ongoing (50%)
Subtask 2: Post-hoc subgroup analysis (Months 30-36). Yet to start.

Major Task 4: To identify and prepare tissue specimens for RNA-Seq

Subtask 1: To retrieve tumor bank specimens from men enrolled in the prospective study (Months 6-24). Ongoing (90%).
Subtask 2: To further ascertain HRD status in tumor bank specimens (Months 18-24). Ongoing (90%)
Subtask 3: To conduct RNA-Seq analysis (Months 24-30). Yet to start.

What was accomplished under these goals?

1) Major activities: We have maintained clinical enrollment activities under a HRPO approved IRB protocol and enrolled 121 new patients. The prospective cohort of patients will reflect the current prostate cancer treatment landscape, and will allow us to capture treatment outcome to newer therapies including PARP inhibitors (Olaparib and rucaparib) and Lu-177 PSMA (Pluvicto), along with baseline clinical data and treatment outcome to other systemic therapies including AR-targeting therapies and chemotherapies. We dedicated substantial effort to annotate the clinical outcome data at an ongoing basis. We have completed some of the most labor-intensive components of the proposal including DNA extraction from more than 800 samples. Both germline (normal) and ctDNA (tumor) sequencing results are expected before the end of 2022.
2) Specific objective: We have three specific objectives for this period. First, we sought to intensify our patient enrollment efforts. Second, our objective for data collection was to continuously update treatment outcome data and DNA sequencing data. Third, in relation to major task #4, we sought to use existing data to guide specimen retrieval.
3) Significant results or key outcomes: We are behind schedule in laboratory data generation due to a number of challenges (supplies and reagents, equipment upgrade, the need to retrain personnel). In spite of limitations posed by the pandemic, we expect to be able to deliver the results and present the key outcomes during the no-cost extension period of the project.

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

We will continue to recruit patients into this study. We expect to generate data from the clinical specimens a few months into the no-cost extension period and will dedicate our efforts to data analysis. We expect to generate publishable findings in our final report.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

The project has two major components. The first component is clinical, and the second is laboratory in nature. The second component largely depend on the success of the first component. Although we were able to solve many pandemic-related challenges for the first component, the proposed laboratory studies are behind schedule. The delay was related to the challenge of preparing high quality DNA conforming with rigorous quality control standards, and the need to test reagents and lab supplies that tend to vary in quality during the pandemic. Supplies and reagents issues have been persistent, and required extra effort and time beyond our expectation. Data generation was also delayed by the need to upgrade the sequencing machine and the time needed to train technicians. Due to the delays we have requested a no-cost extension of the project for a year. This request was approved. During the extension period, we expect to generate reportable findings and complete all the tasks specified in SOW.

Changes that had a significant impact on expenditures

In Year 3, We added Dr. Channing Paller as a key personnel, listing her at 6% effort. This addition did not result in a significant impact on expenditures because we removed Dr. Emmanuel Antonarakis as a key personnel due to his move to another institution.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

Nothing to report

Books or other non-periodical, on(1)e-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

Nothing to Report.

ï **Website(s) or other Internet site(s)**

Nothing to Report.

ï **Technologies or techniques**

Nothing to Report.

ï **Inventions, patent applications, and/or licenses**

Nothing to Report.

ï **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	Role, contribution, and (ORCID ID)	Person Month
Luo, Jun	Principle Investigator, overall management (0000-0002-1414-473)	3
Paller, Channing	Co-Investigator, Oncology planning, (0000-0003-3658-1858). (Note, Dr. Paller is supported as a clinician and did not receive support from this grant although her estimated effort in the project is substantial. We have requested a change to list her as a key personnel)	1
Kanayama, Mayuko	Fellow, lab and clinical data management (0000-0002-1947-6311)	10
Chen, Yan	Technician, lab specimen recording and processing (N/A)	5

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS
COLLABORATIVE AWARDS:
QUAD CHARTS:

9. APPENDICES:

Nothing to report