AWARD NUMBER: W81XWH-19-1-0686

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

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REPORT DATE: October 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2023	Annual	01Sep2022-31Aug2023

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-19-1-0686

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

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 conducted sequencing analysis and completed clinical data assembly. 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 final 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
Unclassified	Unclassified	Unclassified	Unclassified	11	19b. TELEPHONE NUMBER *(include area code)*

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

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:** Provide a brief list of keywords (limit to 20 words).

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 (90%).

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 (95%).

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 (70%)
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 (95%).
Subtask 2: To further ascertain HRD status in tumor bank specimens (Months 18-24). Ongoing (95%)
Subtask 3: To conduct RNA-Seq analysis (Months 24-30) (70%).

What was accomplished under these goals?

1) Major activities: We have maintained clinical enrollment activities under a HRPO approved IRB protocol and enrolled 114 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 and whole exome sequencing of more than 800 samples. We will have the full set of sequencing data for analysis pending data from a small subset of DNA samples with suboptimal quality/quantity.
2) Specific objective: We have three specific objectives for this period. First, we sought to continue 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 identify tissue specimens and complete initial RNA sequencing analysis.
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, personnel turnover). In spite of these limitations posed by the pandemic, we expect to be able to deliver the results and present the key outcomes during the final 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 dedicate our efforts to data analysis. We expect to generate publishable findings in our final report.

4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to report

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period 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. We have been able to overcome many pandemic-related challenges and have now generated sequencing data and assembled clinical data. The delay in final results was related to the delay experienced in the last reporting period and further disruptions to bioinformatic support during this period, primarily due to personnel turnover. Due to the delays we have requested a 2nd no-cost extension of the project for a year. This request was approved. During the final extension period, we expect to generate reportable findings and complete all the tasks specified in SOW.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

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: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

ï **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

Books or other non-periodical, on(1)e-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report.

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

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report.

ï **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

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

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

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
Rabizadeh, Daniel	Bioinformatics (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?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what

has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Nothing to report