

AWARD NUMBER: W81XWH-15-2-0052

TITLE: Noninvasive Detection of AR-FL/AR-V7 as a Predictive Biomarker for Therapeutic Resistance in Men with Metastatic Castration-Resistant Prostate Cancer

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**RECIPIENT: University of Washington
Seattle, WA 98195**

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Fort Detrick, Maryland 21702-5012**

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| 14. ABSTRACT Subject: Primary and acquired resistance to abiraterone and enzalutamide represent critical problems in contemporary prostate cancer clinical care, and development of predictive biomarkers of response and resistance to abiraterone and enzalutamide remains an urgent and unmet need. Purpose: The overall goal of this Biomarker Development Award proposal is to enable near-term clinical use of a noninvasive test for prediction and assessment of response to abiraterone and enzalutamide in men with metastatic prostate cancer. Scope: A predictive biomarker of therapeutic resistance to the two agents is likely to generate therapeutic benefit to men with mCRPC by facilitating earlier treatment decisions regarding the type and sequence of therapy, given the availability of other FDA-approved therapies and experimental therapies. This predictive marker will also drive the development of novel therapeutic approaches designed to overcome resistance to abiraterone and enzalutamide. | | | | | |
| 15. SUBJECT TERMS castration resistant prostate cancer, AR-FL, AR-V7, biomarker, enzalutamide, abiraterone | | | | | |
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Subject: *Primary and acquired resistance to abiraterone and enzalutamide represent critical problems in contemporary prostate cancer clinical care, and development of predictive biomarkers of response and resistance to abiraterone and enzalutamide remains an urgent and unmet need.*

Purpose: The overall goal of this Biomarker Development Award proposal is to enable near-term clinical use of a noninvasive test for prediction and assessment of response to abiraterone and enzalutamide in men with metastatic prostate cancer.

Scope: A predictive biomarker of therapeutic resistance to the two agents is likely to generate therapeutic benefit to men with mCRPC by facilitating earlier treatment decisions regarding the type and sequence of therapy, given the availability of other FDA-approved therapies and experimental therapies. This predictive marker will also drive the development of novel therapeutic approaches designed to overcome resistance to abiraterone and enzalutamide.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).
Castration resistant, prostate cancer, AR-FL, AR-V7, biomarker, enzalutamide, abiraterone
3. **ACCOMPLISHMENTS:** The 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.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

| Specific Aim 1: To perform cross-institutional analytical validation of a blood-based assay in a CLIA-certified environment | Timeline | Site 1 (Initiating PI) | Site 2 (Partnering PI) | Site 3 (Partnering PI) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|----------------------------------|----------------------------------|----------------------------------|
| Major Task 1: Development of robust and standardized SOPs pertaining to the accurate and reliable detection of AR-FL/AR-V7 | Months | | | |
| Subtask 1: To conduct essential study planning activities including IRB and HRPO approval, 3-way collaborative research agreements, ordering of a common set of reagents, equipment readiness, protocol review, distribution of SOPs, personnel assignment, and review of documentation requirements. | 1-6 | Dr. Luo | Dr. de Bono | Dr. Plymate |
| <i>Milestone #1: HRPO approval received. Research agreements executed. Letter of Intent to FDA CDRH submitted.</i> | 3-6 | Dr. Luo | Dr. de Bono | Dr. Plymate |
| Subtask 2: Testing SOPs pertaining to the accurate and reliable detection of AR-FL/AR-V7. <ul style="list-style-type: none"> Determine the lower and upper detection limit and detection dynamic range. Determine assay sensitivity, primer specificity. Evaluate reproducibility among the test sites. Standardize analytical SOPs. Cell lines used: LNCaP, LNCaP 95 [ATCC/public sources, fingerprinted and mycoplasma tested] Human Anatomical Substances (HAS) used: peripheral blood samples [freshly collected from healthy individuals for cell spiking] | 4-12 | Dr. Luo (n=84) | Dr. de Bono (n=84) | Dr. Plymate (n=84) |
| Subtask 3: Development of robust SOPs for sample collection, processing, and transfer (Months 7-12). <ul style="list-style-type: none"> Distribution of existing preanalytical SOPs developed by Dr. Luo. Further optimization and standardization following comparison of two different SOPs. Human Anatomical Substances (HAS) used: peripheral blood samples [freshly collected from men with CRPC] | 7-12 | Dr. Luo (n=50) | Dr. de Bono (n=50) | Dr. Plymate (n=50) |
| Major Task 2: Correlation between CTC AR expression with contemporaneously acquired fresh CRPC biopsy expression, and with expression detected in cell-free exosome RNA. | | | | |
| Subtask 1: Correlation between CTC AR expression with contemporaneously acquired fresh CRPC biopsy expression. Human Anatomical Substances (HAS) used: biopsies collected from men with CRPC with CTC data. | 7-24 | Dr. Luo (n=30) | Dr. de Bono (n=20) | |
| Subtask 2: Correlation between CTC AR expression with expression detected in cell-free exosome RNA. Human Anatomical Substances (HAS) used: plasma samples collected from men with CRPC with CTC data. | 7-24 | Dr. Luo (n=50) | | |
| <i>Milestone #2: Co-author manuscript on analytical validity, implementation in certified labs, FDA initial briefing package submission.</i> | 12-24 | Dr. Luo | Dr. de Bono | Dr. Plymate |

| | | | | |
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| Major Task 3: Development of new CTC selection and molecular detection platforms | | | | |
| Subtask 1: Evaluation of new CTC selection platform for the purpose of detection of AR-FL/AR-V7. Cell lines used: LNCaP, LNCaP 95 [ATCC/public sources, fingerprinted and mycoplasma tested] Human Anatomical Substances (HAS) used: fresh blood samples collected from men with CRPC with CTC data. | 12-24 | | | Dr. Plymate (n=20) |
| Subtask 2: Evaluation of new molecular detection platforms. Cell lines used: LNCaP, LNCaP 95 [ATCC/public sources, fingerprinted and mycoplasma tested] Human Anatomical Substances (HAS) used: fresh blood samples collected from men with CRPC with CTC data. | 12-24 | Dr. Luo (n=20) | | |
| Specific Aim 2: To expand existing prospective clinical correlation studies to enable assay qualification and clinical validation. | | | | |
| Major Task 4: Clinical validation of the AR-FL/AR-V7 test | | | | |
| Subtask 1: Prospective recruitment of 300 patients with mCRPC initiating standard-of-care treatment with abiraterone, enzalutamide, or chemotherapy consenting for blood draw (baseline, 2 nd at the time of response if any, and 3 rd time at the time of progression), and optional biopsy (~n=50). Team A: Drs. Emmanuel Antonarakis and Channing Paller (JHU oncologists), and collaborating oncologists. Team B: Dr. Johann de Bono (ICR oncologist), and collaborating oncologists. Team C: Dr. Bruce Montgomery (UW oncologist), and collaborating oncologists. Human Anatomical Substances (HAS) used: fresh blood samples collected from men with CRPC with CTC data. Human Anatomical Substances (HAS) used: biopsies collected from men with CRPC with CTC data. | 12-30 | Dr. Luo (n=100) | Dr. de Bono (n=100) | Dr. Plymate (n=100) |
| Subtask 2: Biomarker implementation in certified labs Team: Drs. James Eshleman (JHU CLIA lab), Colin Pritchard (UW CLIA lab), Penny Flohr (ICR certified clinical lab) | 12-30 | Dr. Luo | Dr. de Bono | Dr. Plymate |
| Subtask 3: Data analysis Team Statistician: Dr. Hao Wang. | 30-36 | Dr. Luo | Dr. de Bono | Dr. Plymate |
| <i>Milestone #3: Manuscript on clinical validation</i> | 30-36 | Dr. Luo | Dr. de Bono | Dr. Plymate |
| | | | | |

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|----------------|---------------------|-------------|
| Specific Aim 3: To plan, coordinate, and facilitate multi-institutional clinical trials integrating AR biomarkers. | | | | |
| Major Task 5: Biomarker-embedded trial of enzalutamide and AKT inhibitor | | | | |
| Subtask 1: <ul style="list-style-type: none"> Recruit, consent, and enroll 140 patients/human subjects to Phase I/II trial. Evaluation of the association between CTC counts, AR-FL/AR-V7 expression, and PTEN status, and all these parameters to response to treatment. Human Anatomical Substances (HAS) used: peripheral blood samples. | 6-30 | | Dr. de Bono (N=140) | |
| Subtask 2: <ul style="list-style-type: none"> Collection and documentation of 20 pre and post-treatment biopsies from men enrolled in the trial for collaborative studies with Dr. Luo. Human Anatomical Substances (HAS) used: biopsies collected from men enrolled in the trial. | 6-12 | Dr. Luo | Dr. de Bono (N=20) | |
| <i>Milestone #4: Manuscript on clinical trial and biomarker qualification.</i> | 24-30 | Dr. Luo | Dr. de Bono | Dr. Plymate |
| Major Task 6: Alternative approaches | | | | |
| Subtask 1: <ul style="list-style-type: none"> Formulation of additional biomarker-driven clinical trials. | 24-36 | Dr. Luo (n=60) | Dr. de Bono | Dr. Plymate |
| Subtask 2: Additional studies according to FDA/EMA guidance | 24-36 | Dr. Luo | Dr. de Bono | Dr. Plymate |
| <i>Milestone #5: FDA and EMA full qualification package submissions.</i> | 30-36 | Dr. Luo | Dr. de Bono | Dr. Plymate |
| | | | | |

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

During year 1 we conducted essential study planning activities including IRB and HRPO approval, 3-way collaborative research agreements, ordering of a common set of reagents, equipment readiness, protocol review, distribution of SOPs, personnel assignment, and review of documentation requirements. IRB and HRPO documents were approved by appropriate authorities.

We next tested SOPs pertaining to the accurate and reliable detection of AR-FL/AR-V7.

- We determined the lower and upper detection limit and detection dynamic range.
- We determined assay sensitivity, primer specificity.
- We evaluated reproducibility among the test sites.
- Standardized analytical SOPs.

Cell lines used: LNCaP, LNCaP 95 [ATCC/public sources, fingerprinted and mycoplasma tested]

Human Anatomical Substances (HAS) used: peripheral blood samples [freshly collected from healthy individuals for cell spiking].

Initiated comparison between IHC for AR-V7 and CTC V7 correlation

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report

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

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to 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?

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

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report

What was the impact on other disciplines?

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

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an 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.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- transfer of results to entities in government or industry;*
- instances where the research has led to the initiation of a start-up company; or*
- adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?

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

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- improving public knowledge, attitudes, skills, and abilities;*
- changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- improving social, economic, civic, or environmental conditions.*

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.

Reproducibility between UW site and JHU and ICR has not been consistent. We have actively engaged in determining the source of the problem. It appears that the problems are most likely resulting from primer-dimer formation in during PCR.

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.

Nothing to Report

Significant changes in use or care of human subjects

Nothing to Report

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.”

- **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, one-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

- **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

- **Technologies or techniques**

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

Nothing to Report

- **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

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*

- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name: Dr. Stephen R. Plymate

Project Role: PI

Nearest person month worked: 2.4 Cal Months

Contribution to Project: oversees project and coordinates with partnering research sites

Funding Support: NIH, DOD, VA merit award

Name: Shihua Sun

Project Role: Research Scientist/Engineer III

Nearest person month worked: 3 Cal Months

Contribution to Project: assists with PCR

Funding Support: NIH, DOD

Name: Kathleen Haugk

Project Role: Research Scientist/Engineer III

Nearest person month worked: 6 Cal Months

Contribution to Project: processes patient samples, prepares and runs PCR analysis, communicates findings with partnering research sites

Funding Support: VA merit award

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?

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

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

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.