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TITLE:	Clinical Qualification of DNA Repair Defects as Biomarkers in Metastatic Prostate Cancer Using Integrated Genomics and Tissue-Based Functional Assays
PRINCIPAL INVESTIGATOR:	Joaquin Mateo
CONTRACTING ORGANIZATION:	Vall d'Hebron Institute of Oncology
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Dr. Joaquin Mateo,

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

We and others previously described an enrichment for somatic and germline alterations in DNA damage repair (DDR) genes among men with metastatic prostate cancer. Several recent clinical studies have indicated many of these patients could benefit from precision medicine strategies with PARP inhibitors and DNA damaging agents. In this project, our teams would investigate genomic, transcriptomic and protein-related functional signatures for a more accurate sub-classification of prostate cancers associated to DDR defects, aiming for a more precise patient care. The project is divided in 3 main aims: 1) testing the prognostic value of somatic DDR defects in a retrospective cohort of tumor biopsies, 2) developing multi-omics signatures based on prospective analyses of metastatic biopsies and 3) clinical validation of these biomarkers in a clinical trial using carboplatin as DNA damaging chemotherapy.

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a. REPORT	b. ABSTRACT	c. THIS PAGE			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.*

   We and others previously described an enrichment for somatic and germline alterations in DNA damage repair (DDR) genes among men with metastatic prostate cancer. Several recent clinical studies have indicated many of these patients could benefit from precision medicine strategies with PARP inhibitors and DNA damaging agents. In this project, our teams would investigate genomic, transcriptomic and protein-related functional signatures for a more accurate sub-classification of prostate cancers associated to DDR defects, aiming for a more precise patient care. The project is divided in 3 main aims: 1) testing the prognostic value of somatic DDR defects in a retrospective cohort of tumor biopsies, 2) developing multi-omics signatures based on prospective analyses of metastatic biopsies and 3) clinical validation of these biomarkers in a clinical trial using carboplatin as DNA damaging chemotherapy.

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

   Genomics; Whole-exome sequencing; RNAseq; Precision Medicine; DNA repair; BRCA; PARP inhibitors; platinum chemotherapy; clinical trial.

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 correlate the presence or absence of somatic/germline alterations in DNA repair genes with overall survival from mCRPC, and specific response to taxanes, Abiraterone, Enzalutamide, and Rd223, in samples from a prospective study.

Major Task 1: Targeted NGS on all study samples	**Timeline (Months)**	**Completed (%)**
Preparation of tumor biopsies for DNA extraction	0-12	100%
Milestone 1.1 – Shipment of samples to UW Laboratory (batches)	3 to 15	25%
Library preparation for targeted NGS	3 to 20	25%
Sequencing of all samples from the PROREPAIR-B study	3 to 20	25%
Variant calling, bioinformatics analysis	3 to 20	25%

	Timeline (Months)	Completed (%)
Milestone 1.2 – Classification of each patients as "positive" or "negative" for each of the biomarkers of interest (BRCA1, BRCA2, ATM, PALB2)		
Sequencing data analysis board: identification of putative relevant calls for patient care and relatives' risk of cancer	3 to 20	25%
Statistical analysis: correlation of genomic biomarkers with previously annotated clinical outcome data	22	No
Milestone 1.3 – Data analysis and interpretation, Manuscript Preparation	24	No
Milestone 1. 4 - F2F meeting among participating sites to discuss progress	12	100%

Specific Aim 2. To optimize tissue-based tests of HR functionality samples for CRPC samples, and study the correlation with genomic aberrations in HR genes.

Major Task 2: Acquisition of bone marrow metastatic biopsies	**Timeline (Months)**	**Completed (%)**
Harmonization of tissue acquisition protocol among participating sites	1 to 2	100%
Collection of 100 metastatic biopsies, samples are sent to sites 2 and 3	3 to 22	40%
Milestone 2.1 – Sample acquisition completed	23	No
Major Task 3: Whole-exome sequencing studies		
DNA extraction from tumor and germline DNA	6 to 24	10%
Whole exome sequencing studies	12 to 26	No
Variant calling, bioinformatics analysis	12 to 28	No
Sequencing data analysis board: identification of putative relevant calls for patient care and relatives' risk of cancer	6 to 30	20%
Major Task 4: Expression profiling studies		
RNA extraction from frozen core of biopsies	6-24	No

RNA-seq studies	9 to 26	No
Bioinformatics analysis	12 to 28	No
Major Task 5: Immunofluorescence studies		
Sample preparation	8 to 30	20%
Immunofluorescence studies	10 to 30	20%
Milestone 5.1 – Integrated analysis of sequencing and IF data	32	No
Milestone 5.2 – Data analysis and interpretation, Manuscript Preparation	34	No

Specific Aim 3 To clinically qualify this HR functional test in a clinical trial of carboplatin in CRPC

Major Task 6: Clinical Trial Set Up	**Timeline (Months)**	**Completed (%)**
Clinical Trial Protocol Writing and Development	1 to 5	100%
Submission of clinical trial protocol to local ethics and regulatory bodies	5	100%
Set up of clinical sites participating in the trial		25%
Milestone 6.1 – First patient enrolled in the clinical trial	12	No
Major Task 7: Clinical Trial conduction		
Patient recruitment	12 to 30	No
Continuous data monitoring	12-36	No
Trial-related biopsy acquisition	12 to 30	No
Milestone 7.1 Recruitment completed for cohort 1	26	No
Milestone 7.2 Recruitment completed for cohort 2, stage 1	22	No

Recruitment for cohort 2, stage 2 (depending on results from stage 1)	23-30	No
Milestone 7.3 Recruitment completed for cohort 2, stage 2	30	No
Major Task 7: Biomarker studies in trials samples		
Preparation of trial related biopsies for NGS studies	12 to 30	No
Targeted sequencing in trial-related biopsies	12 to 30	No
Variant calling, bioinformatics analysis	12 to 30	No
Immunofluorescence studies	12 to 30	No
Sequencing data analysis board: identification of putative relevant calls for patient care and relatives' risk of cancer	12 to 30	No
Milestone 7.1 – Integrated analysis of clinical and biomarker data	34	No
Milestone 7.2 – Data analysis and interpretation, Manuscript Preparation	36	No

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.

Specific Aim 1 – To correlate the presence or absence of somatic/germline alterations in DNA repair genes with overall survival from mCRPC, and specific response to taxanes, Abiraterone, Enzalutamide, and Rd223, in samples from a prospective study.

Major Task 1: Targeted NGS on all study samples

HRPO approvals: The research for Aim 1 at Site 1 (UW) was determined to be not human subjects by the UW IRB, with HRPO concurrence on 10/17/2018. This facilitated use of de-identified samples from Site 2 in year 1 for optimization of the UW-OncoPlex sequencing assay in the context of limited sample quantity. HRPO approval was obtained at Site 2 (CNIO) on 9/30/19 for research on aims 1 and 2.

In year 1 Site 1 (UW) began receiving representative de-identified extracted DNA specimens from the Site 2 (CNIO) for UW-OncoPlex sequencing in batches to optimize sequencing protocols. In the first batch of 20 total extracted DNA samples 16 /20 were successfully sequenced and analyzed. Key DNA repair alterations detected in 4 patients so far, including bi-allelic *BRCA2* mutation or copy loss (n=2), *MLH1* (n=1) with associated MSI and hypermutation, and *ATM* mutation (n=1). While UW-OncoPlex sequencing did detect key alterations, the overall sample quality was poorer than expected, mostly likely due to very limited quantity of input DNA.

Many of the samples we anticipate sequencing have low amounts of residual DNA remaining (<250ng). There is availability of pre-capture libraries for most of the samples. To facilitate adequate performance on these low input samples we undertook three parallel development efforts in year 1 to modify and re-validate the UW-OncoPlex assay for clinical use with low-input samples anticipated from the PROREPAIR trial as part of this work.

The first approach was to validate pre-capture libraries from Site 2 for use with UW-OncoPlex. To evaluate and validate pre-capture libraries as a sample type for UW-OncoPlex pilot samples were sent to Site 1 (UW) from Site 2 (CNIO) with matched pre-cap libraries and extracted DNA. We are currently working closely with our bioinformatics team, wet-bench staff to work out the protocol to run and analyze these pre-cap library samples on our platform. Briefly, the samples are quantified on the Agilent Tape Station and pooled together for hybridization along with a HapMap control (NA12878). They are hybridized with latest UW-OncoPlex (version 6) capture, using an IDT xGen protocol. The pool is loaded on an Illumina instrument (PE101 + 8bp index read). Since the samples were previously barcoded with 6bp indexes, we added "NN" to the end of the sequences for the MiSeq samplesheet, which would allow demultiplexing and analysis of both the 6bp and 8bp indexes in the pool. Using this protocol we have successfully sequenced four pre-capture libraries, however the sequencing quality is not yet adequate using pre-capture libraries. To troubleshoot, we are attempting more pre-capture libraries with higher DNA quantity. In parallel we focused on testing samples with >250ng input DNA, prioritizing patients with radical prostatectomy first.

The second approach was to modify and re-validate the UW-OncoPlex sequencing assay for use with Nextera NextFlex enzymatic tagmentation-based sequencing library preparation rather than using DNA shearing with the Covaris. This NextFlex method allows the assay to take as little as 10ng DNA input rather than the 250ng input desired with Covaris shearing method. Also, less DNA is lost in wash steps using the NextFlex method. Briefly, to validate this method at Site 1, we selected a total of 57 tumor DNA samples that had been previously characterized by UW-OncoPlex and re-ran these using the Nextera low input protocol. All reportable mutations, copy number variants, and structural variants were identified using the Nextera protocol. Between run and within reproducibility was assessed for 3 tumor samples and for the NA12878 HapMap control with perfect concordance. MSI status was also 100% concordant. An example of the qualitive concordance of copy number calling is given in the Figure below.

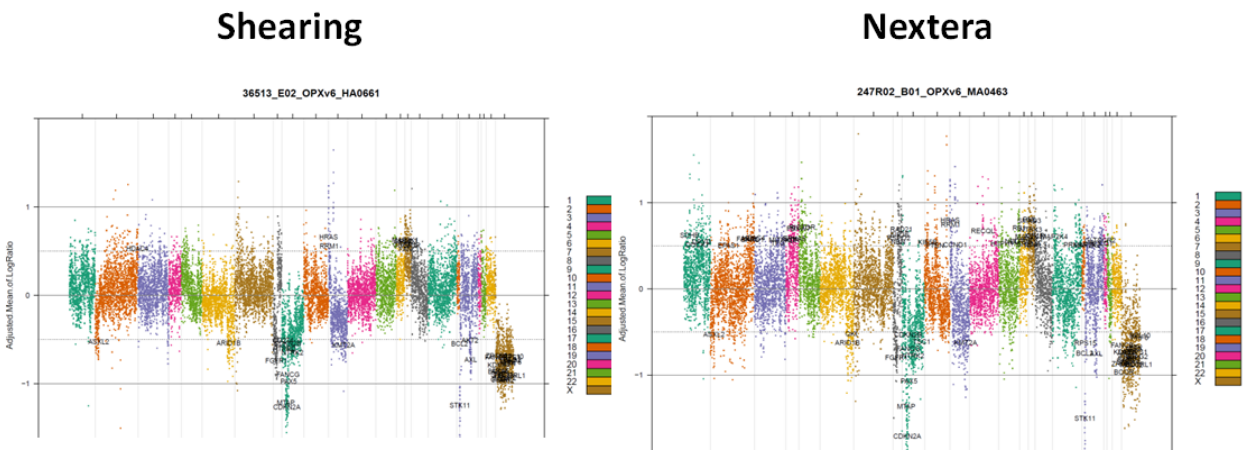


Figure: Comparison of copy number calling between the standard shearing and low input Nextera UW-OncoPlex sequencing. We observed high qualitative and quantitative concordance between the standard shearing-based library prep and Nextera low input library preparation for the UW-OncoPlex assay.

Finally, as a third approach if needed, we will explore testing plasma cell-free DNA for patients <250ng input DNA remaining. The CNIO group at Site 2 has frozen plasma available from most of these patients and is currently exploring whether it may be feasible to use these samples. The UW-OncoPlex assay has recently been extensively clinically-validated for use with plasma cell-free DNA in patients with metastatic prostate cancer (Schweizer et al. 2019 PMID:30865311, DOD support acknowledged).

Summary of progress on milestones related to Aim 1 in Year 1

Milestone 1.1 Shipment of samples From CNIO laboratory to UW laboratory (batches) (Month 3-15): Batches of de-identified samples were shipped for the purpose of assay and protocol optimization from Site 2 to Site 1 in year 1 (not human subjects research) while HRPO approval at site 2 was pending. The PROREPAIR-B trial in which aim 1 was based, was an already approved and completed protocol in Spain. There were some unanticipated delays in obtaining HRPO approvals at Site 2 (CNIO) due in part to requirements of independent evaluation of this work by our reference IRB, and review of several iterations of verified English translations from original study documents produced in Spanish between January and July 2019. After submission of the final required documents in July 2018, HRPO approval at Site 2 (CNIO) was granted on September 30th, 2019.

Since receiving HRPO approval at Site 2 (CNIO), 120 samples have been reviewed by a trained GU pathologist, macro-dissected from tumor sections and processed for DNA extraction at the CNIO Lab, after discussion with the Site 1 UW laboratory, and following progress in improving the UW-OncoPlex assay to work with samples with lower DNA quantity/quality as expected from PROREPAIR-B FFPE sample collection. Initial shipments are being organised according to quality/quantity starting with best samples from initial 120 extracted from October 28th with the 40 samples with better quality and quantity.

Even with some delay accumulated at site 2, we anticipate completion milestone 1.1 in year 2.

Milestone 1.2 – Classification of each patients as "positive" or "negative" for each of the biomarkers of interest (BRCA1, BRCA2,ATM, PALB2): Not due yet.

Milestone 1.3 – Data analysis and interpretation, Manuscript Preparation (24 months; Site 1, 2 and 3): Not due yet.

Milestone 1. 4 - F2F meeting among participating sites to discuss progress (12 months; Site 1, 2 and 3): A project Kick-Off meeting with three PIs (Pritchard, Olmos, and Mateo) and with some co-investigators (Cheng and Castro) was held in San Diego, CA in Oct 2018. An end-of-year 1 meeting to discuss progress was held Oct 25th 2019 in San Diego, California, that included the three PIs, according to the planned timelines.

Specific Aim 2 – To optimize tissue-based tests of HR functionality samples for CRPC samples, and study the correlation with genomic aberrations in HR genes.

Major Task 2: Acquisition of bone marrow metastatic biopsies

For Site 2 (CNIO): IRB approval for the participation of site 2 at this major task (2.2) was received on November 26th, 2018 with the approval to proceed with aim 1. As outlined in the section above HRPO approval for aim 1 and 2 was received September 30th, 2019.

For Site 3 (VHIO), the research protocol for acquisition and analysis of patient biopsies was approved by the local ethics board. As of 15th Oct 2019, 76 patients have been consented for consideration of biopsies. After discussion of suitability with interventional radiology, 27 patients have successfully undergone a metastatic biopsy procedure, collecting at least 1 fresh frozen core and 1 FFPE core for the study. Additionally, archival prostate primary tumor biopsy material has been retrieved from the diagnostic hospital for 52/74 cases. Saliva samples for correlative germline analyses were collected for all patients at the time of consent.

We consider we are on track towards the planned goal of 100 biopsies by the end of Year 2.

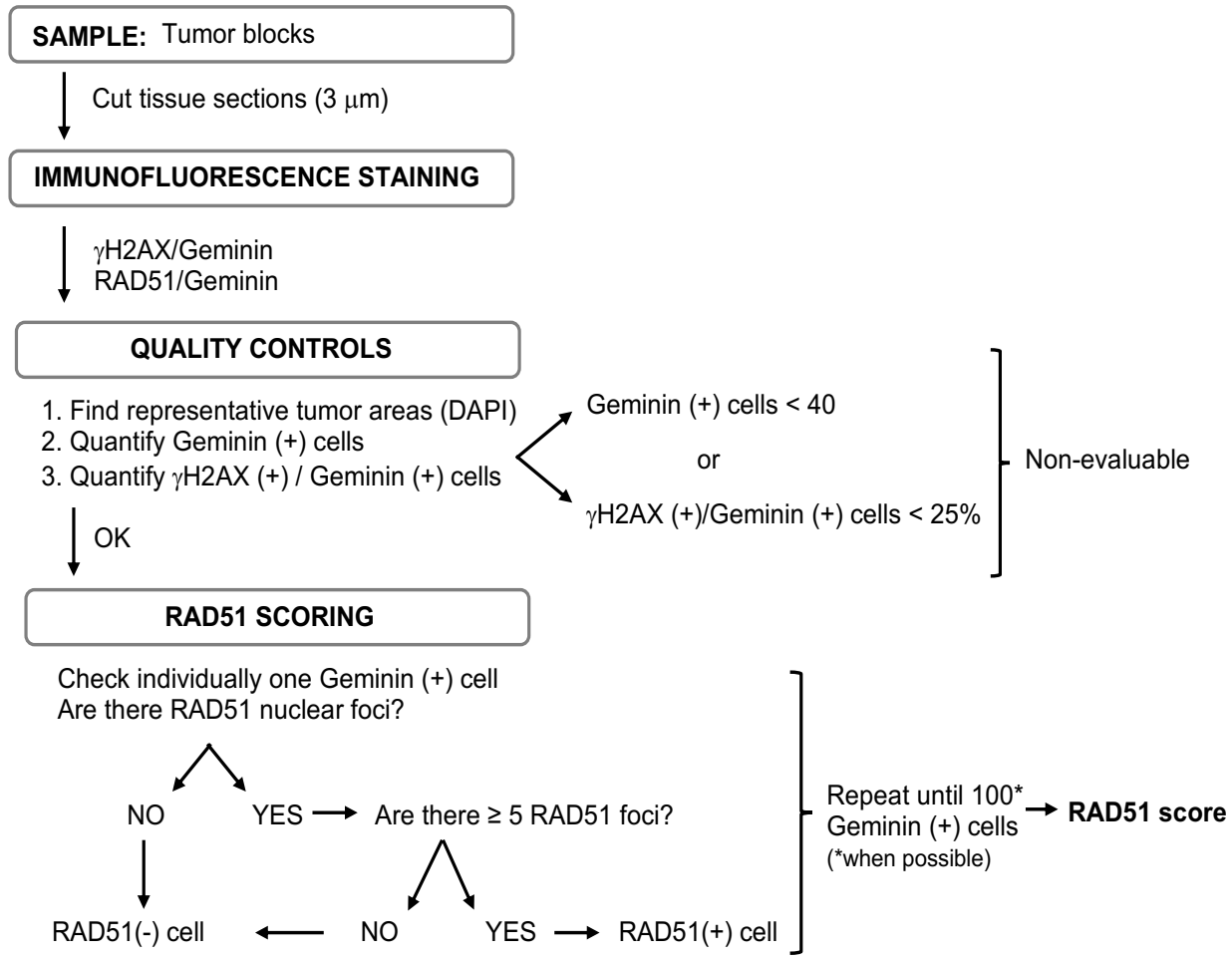
Major Task 3: Whole-exome sequencing studies

Major Task 4: Expression profiling studies

Major Tasks 3 and 4 were meant to start during Q3-Q4 YEAR 1 respectively but we have planned to first optimize our sequencing pipelines using the archival prostate tumors retrieved before using the study biopsies, considering the little material available. We plan to start the WES and RNAseq studies during first half of Y2. This should not impact completing the task according to the planed timeline.

Major Task 5: Immunofluorescence studies

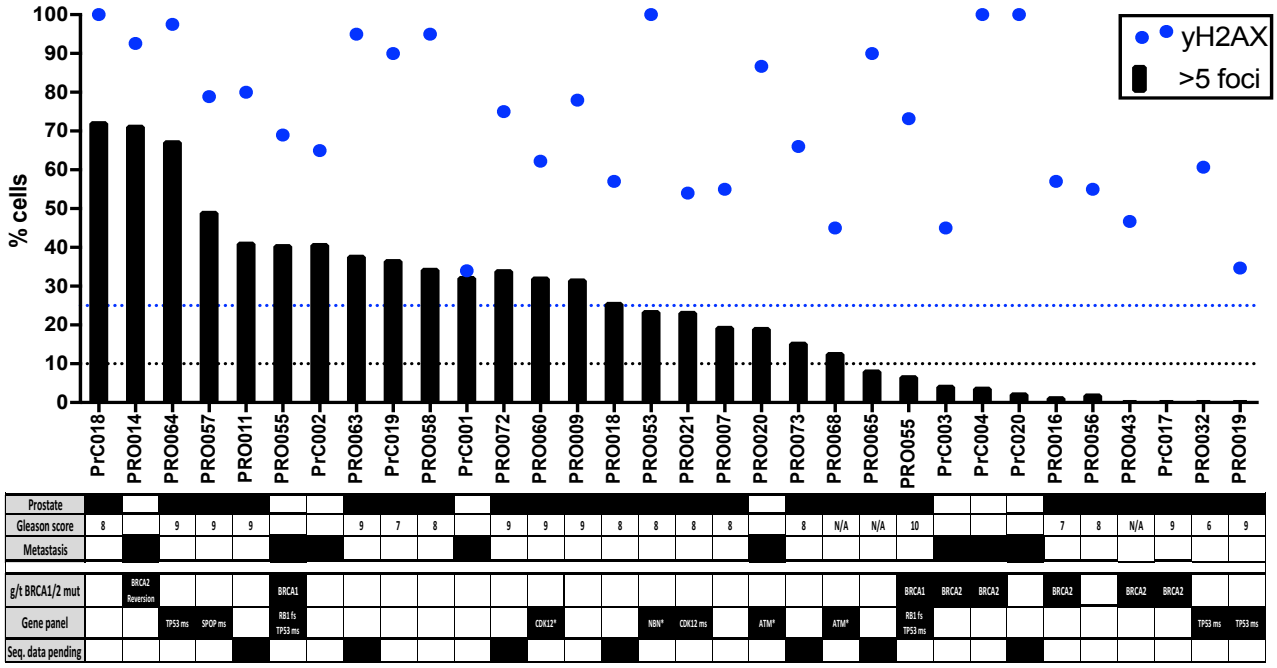
As planned, we are re-optimizing an IF-based test initially developed in breast cancer patient-derived xenoimplant models and then validated in breast cancer biopsies (Cruz et al, Ann Onc 2018; Castroviejo-Bermejo et al, EMBO Med 2019). We are using FFPE slides from prostate cancer primary and metastatic biopsies. An overview of the assay procedure and interpretation workflow is presented below:



Firstly, we conducted technical tests using different slide thickness and antibody concentrations. We have now established an SOP to process samples using 3-micron thick sections (minimum 4 sections per sample).

Up to 15th Oct 2019, we have analyzed 32 primary or metastatic samples from patients participating in the study from Site 3, and explored correlations with mutations in DNA repair genes, although sequencing data for some of these samples is still pending as described above for Major Task 4.

Preliminary results on this pilot cohort of 32 samples are presented below, suggesting the assay is capable of identifying prostate cancers with *BRCA2* mutations:



We are ahead of schedule for the completion of Major Task 5, and anticipate significant development during Year 2 as Tasks 3 and 4 advance.

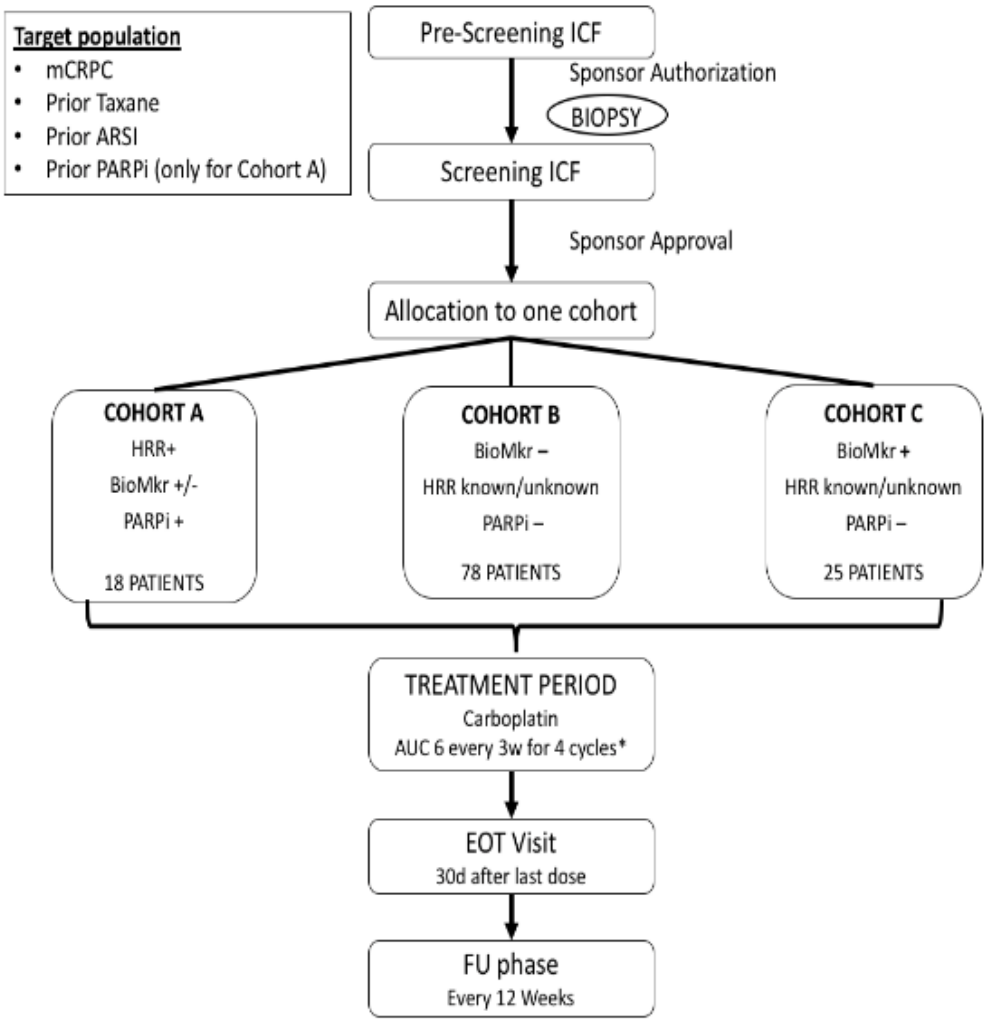
Summary of progress on milestones related to Aim 2 in Year 1

Milestone 2.1 – Sample acquisition completed (month 23): Not due yet.
Milestone 5.1 – Integrated analysis of sequencing and IF data (*month 32*): Not due yet.
Milestone 5.2 – Data analysis and interpretation, Manuscript (month 34): Not due yet.

Specific Aim 3 – To clinically qualify this HR functional test in a clinical trial of carboplatin in CRPC

Major Task 6: Clinical Trial Set Up

In year 1, initial versions of the clinical trial protocol and patient informed consent form have been completed as 30th of June 2019 and has been submitted to CDMRP representatives for pre-approval review on July 9th, 2019, and are awaiting feedback from the HRPO office. In addition, the protocol was submitted simultaneously to site 2 reference IRB (CEI Provincial de Málaga) and the AEMPS (Spanish regulatory agency) and initial review and proposed amendments were received by October 15th. Currently, the CNIO team is working to address the comments from both IRB and. AEMPS. Meanwhile we are still waiting from HRPO feedback on the clinical trial. The clinical trial design is summarized in the figure below:



In parallel, set up of clinical sites participating in the trial is now ongoing; we have collected feasibility questionnaires from 19 sites in Spain that have expressed interest in participating in the clinical trial. An initial 10 has been confirmed and will be activated as soon as we have received IRB, AEMPS and HRPO final approval. These centres are the following:

- Hospitales Universitarios Virgen de la Victoria and Regional de Málaga (CNIO clinical site)
- Hospital Universitario Vall D'Hebron, Barcelona (Site 3)
- Hospital Universitario 12 de Octubre, Madrid
- Hospital Universitario La Princesa, Madrid
- Hospital Provincial de Castellon
- Instituto Valenciano de Oncología, Valencia
- Centro Oncológico de Galicia, La Coruña
- Hospital Clínico San Carlos, Madrid
- Hospital Universitario de Santiago, Santiago de Compostela

- Hospital del Mar, Barcelona

Additional potential sites that may be activated in a second round of the study if required, but not selected to this first round were:

- Instituto Oncológico de Donostia, San Sebastian
- Hospital universitario de Navarra, Pamplona
- Hospital Clinico de Barcelona
- Hospital Universitario Puerta del Hierro, Madrid
- Instituto Catalan de Oncología, L'Hospitalet
- Instituto Catalan de Oncología, Badalona

While we were aiming for the first patient to be enrolled in the trial by beginning of Year 1, due to the delay in the approval of documents for Site 2, we now envision first patient would be recruited by mid-Year 2.

Major Task 7: Clinical Trial conduction

Major Task 8: Biomarker studies in trials samples
Tasks 7 and 8 are planned for Years 2 and 3 of the award, and hence have not been yet initiated as they depend on clinical trial activation.

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.

- **Site 1 (UW):** Gavin Ha, PhD recent junior faculty member recruit at the Fred Hutchinson Cancer Center who had collaborated with the Pritchard site on the UW-OncoPlex assay was awarded a 2019 Prostate Cancer Foundation Young Investigator Award.

- **Site 2 (CNIO):** Elena Castro, MD, PhD, investigator at site 2 was awarded a Juan Rodés Clinician Scientist fellowship from ISCIII (Spanish NIH) to continue working in the area of this project and DNA repair in Prostate Cancer

- **Site 3 (VHIO):**

1) Alejandro Athie, PhD, postdoctoral researcher at Site 3 participating in this project, was selected for the AACR Worskshop "Translational Research for Basic Scientists" in Boston, November 2018.
2) Sara Arce, laboratory technician at Site 3 participating in this project, has been awarded a PhD fellowship to conduct her PhD in part related to this project under the mentorship of PI J. Mateo.

How were the results disseminated to communities of interest?
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.

- **Site 1 (UW):** Nothing to report.

- **Site 2 (CNIO):** This project has been discussed at a two different Patient Engagement Events hold in Málaga in November 2018 (attendance: 32 patients and relatives) and Madrid in June 2019 (attendance 45 patients and relatives). The first engagement was co-organized by CNIO, our clinical site at Málaga and an the Málaga branch of the Spanish Coalition Against Cancer (AECC), the largest Spanish cancer charity devote to patient advocacy, cancer patient support, cancer prevention and research. The second event was co-organized by the CNIO team and the CRIS foundation, a cancer research charity.

- **Site 3 (VHIO):** This project was discussed at a Patient Engagement Event hold in Barcelona in April 2019 (attendance: 54 patients and relatives). This engagement, co-organized by VHIO and ProstateNet, a patient advocacy group, aims to discuss ongoing and completed clinical and translational research projects with patients, to raise awareness about the importance of cancer research. Such events are organized twice a year in Barcelona.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

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

Site 1 (UW): For Aim 1, now that HRPO approval has been granted at Site 2 and we have optimized and re-validated the UW-OncoPlex assay for use with low input samples, we anticipate completing UW-OncoPlex testing for all PROREPAIR-B samples in year 2.

For Aim 3, we anticipate beginning to receive samples for targeted sequencing from Site 3 in year 2.

Site 2 (CNIO): For aim 1, Site 2 (CNIO) is increasing communication with Site 1 (UW) where samples will be analyzed in order to ensure completion of this aim in year 2. Extra resources (more pathology and technicians' hours) to accelerate samples review and initial processing at CNIO have been put in place.

For aim 2, after HRPO approval at our site activation for this aim, we will accelerate oru contribution the recruitment of patients and samples for aim 2. We will also plan to start with the RNA expression analyses along the second part of year 2.

For aim 3, we expect to receive regulatory approval and ethics approval in the first 2 months of year 2, and pending on HRPO feedback and approval we aim to activate the first study site and to enroll the first patient before the 6thmonth of Year 2.

Site 3 (VHIO): For aim 2 we anticipate continuing to make good progress on the IF studies and between expression profiling work. For aim 3 we anticipate the patient recruitment on the biomarker trial.

4. IMPACT: D*escribe 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).

In year 1, we have had successes in two key areas that impact the field. The first, is in the successful implementation of a novel RAD51 immunofluorescence-based assay to look for functional homologous recombination DNA repair deficiency. This assay is already showing great promise as a functional biomarker and has generated interest at national meetings. The second is in the successful clinical validation of the UW-OncoPlex assay for use with low-input DNA. The failure rate of clinical tumor samples using comprehensive NGS panels in clinical trials of HRD and other DNA repair defects is increasingly recognized as a major impediment to research in this area. Our work improves the performance and will reduce sample failure rates so that more patients can be tested for key mutation-based biomarkers and qualify for precision therapy.

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:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

At the present we anticipate keeping the initial plans despite some delays in obtaining HRPO approvals. We may need to extent the duration of aim 3 if HRPO approval for the trial are delayed.

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.

In year 1 there was some unanticipated delay at Site 2 (CNIO) in obtaining HRPO approval for aims 1 and 2 as described above. The development of the clinical trial in aim 3 may also be delayed by

the HRPO review process. Site 2 is trying to keep in close communication with the DoD Science officer assigned to our award as well as to the HRPO.
As described above, at Site 1 we have developed protocols and alternative strategies for use with low input DNA quantity as many of the PROREPAIR-B samples have limited DNA for clinical sequencing. In parallel, we are prioritizing sequencing of samples from patients with high input DNA. This groundwork achieved in year 1 was accomplished to facilitate more rapid completion of sequencing of PROREPAIR-B samples now that HRPO approvals are in place.

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.

Due to a misunderstanding of whether site 2 could start spending money to hire staff prior to initial HRPO approval, a trial manager was not hired until February 2019 to start developing the Aim 3 clinical protocol.

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
Not applicable

Significant changes in use or care of vertebrate animals
Not applicable

Significant changes in use of biohazards and/or select agents
Not applicable

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).*

Schweizer MT, Gulati R, Beightol M, Konnick EQ, Cheng HH, Klemfuss N, DeSarkar N, Yu EY, Montgomery RB, Nelson PS, and **Pritchard CC**. Clinical determinants for successful circulating tumor DNA analysis in prostate cancer. Prostate; 79: 2019; 701-708; published; acknowledgement of federal support (yes).

Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, Cieslik M, Benelli M, Robinson D, Van Allen EM, Sboner A, Fedrizzi T, Mosquera JM, Robinson BD, DeSarkar N, Kunju LP, Tomlins S, Wu YM, Nava Rodrigues D, Loda M, Gopalan A, Reuter VE, **Pritchard CC, Mateo J**, Bianchini D, Miranda S, Carreira S, Rescigno P, Filipenko J, Vinson J, Montgomery RB, Beltran H, Heath EI, Scher HI, Kantoff PW, Taplin ME, Schultz N, deBono JS, Demichelis F, Nelson PS, Rubin MA, Chinnaiyan AM, Sawyers CL. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci; 116: 2019; 11428-11436; published; acknowledgement of federal support (yes).

Schweizer MT, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Konnick EQ, Mostaghel EA, Hsieh AC, Nelson PS, Yu EY, Montgomery RB, True LD, Epstein JI, Lotan TL, and **Pritchard CC**. Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations. JCO Precis Oncol. 2019; PMID: 31123724; published; acknowledgement of federal support (yes).

Khani F, Wobker SE, Hicks JL, Robinson BD, Barbieri CE, De Marzo AM, Epstein JI, **Pritchard CC**, Lotan TL. Intraductal carcinoma of the prostate in the absence of high-grade invasive carcinoma represents a molecularly distinct type of in situ carcinoma enriched with oncogenic driver mutations. *J Pathol*; 2019; PMID:30993692; published; acknowledgement of federal support (yes).

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).*

BOOK CHAPTER (in press): Germline and Somatic Defects in DNA Repair Pathways in Prostate Cancer. Book Title: Prostate Cancer - Cellular and Genetic Mechanisms of Disease Development and Progression. Authors: Sara Arce, Alejandro Athie, **Colin C. Pritchard, Joaquin Mateo**

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.)*

SITE 1 (UW)

Name: Pritchard, Colin
Project Role: Initiating PI
Research Identifier: cpritch (eRA Commons)
Nearest person month worked: 1.20 calendar months
Contribution to Project: Colin Pritchard coordinates UW-OncoPlex sequencing and focuses on interpreting the sequencing data for this project. He is guiding experiments and participating in manuscript preparation and review.

Name: Cheng, Heather
Project Role: Co-Investigator
Research Identifier: hhcheng (eRA Commons)
Nearest person month worked: 0.35 calendar months
Contribution to Project: Heather Cheng reviews sequencing data at molecular tumor boards to identify relevant findings for patient care and relatives' risk of cancer.

Name: Salipante, Stephen
Project Role: Co-Investigator
Research Identifier: stevesal (eRA Commons)
Nearest person month worked: 0.60 Calendar Months
Contribution to Project: Stephen Salipante directed the development and implementation of the data analysis pipeline, assists with UW-OncoPlex data interpretation, and in guiding and preparation of manuscripts.

Name: Beightol, Mallory
Project Role: Research Tech
Research Identifier: N/A
Nearest person month worked: 2.40 Calendar Months
Contribution to Project: Mallory Beightol is responsible for preparing genomic libraries and UW-OncoPlex sequencing for this project.

SITE 2 (CNIO)

Name: David Olmos
Project Role: Principal Investigator
Nearest person month worked: 12
Contribution to Project: Dr. Olmos is the PI of this award. Work in Aim 1 ethics and HRPO approvals, documents translations. Work in aim 2 related to ethics and HRPO approval. Work in aim 3 developing the clinical trial protocol, contacting and selecting sites.
Funding Support: Ramón y Cajal grant from Spanish Ministry of Science, and this award.

Name: Elena Castro
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 12
Contribution to Project: Work in Aim 1 ethics and HRPO approvals, documents translations. Work in Aim 3 developing patient informed consent and supporting protocol development.
Funding support: Juan Rodés clinician scientist fellowship from Instituto Salud Carlos III (ISCIII) and this award

Name: Mónica Balsells
Project Role: Senior trial Manager
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 9

Contribution to Project: Work in Aim 1 ethics and HRPO approvals, documents translations. Work in aim developing protocol, and documents, translations, site contact, feasibility questionnaires, development of case report form and study manual procedure for sites, as well as contracts.
Funding support: this award

Name: Ana Maria Gutierrez Pecharroman
Project Role: Pathologist (MD)
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Work in Aim 1 pathology review of samples from PROREPAIR-B.
Funding support: CNIO core funds

Name: Teresa Garcés del Rey
Project Role: Pathology Technician
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 3
Contribution to Project: Work in Aim 1 gathering samples, building samples database before September 30th, and processing samples 8 sectioning and DNA extraction from October 1st
Funding support: CNIO core funds

SITE 3 (VHIO)

Name: Joaquin Mateo
Project Role: Principal Investigator
Nearest person month worked: 12
Contribution to Project: Dr. Mateo is the PI of this award. Work in Aim 2 Patient Recruitment and Sample Acquisition.
Funding Support: Prostate Cancer Foundation, European Commission H2020 Program and this award.

Name: Alejandro Athie
Project Role: Postdoctoral Researcher
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 6
Contribution to Project: Optimization of NGS protocols and bioinformatic analysis for Aim 2.
Funding Support: this award.

Name: Sara Arce
Project Role: Laboratory Technician
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 6
Contribution to Project: Task 5

Name: Violeta Serra
Project Role: Collaborator

Nearest person month worked: 2
Contribution to Project: Dr Serra collaborates with Dr Mateo in development of Task 5.
Funding Support: Spanish Ministry of Science, Asociacion Española contra el Cancer

Name: Cristina Cruz
Project Role: Collaborator
Nearest person month worked: 1
Contribution to Project: Dr Cruz collaborates with Dr Mateo in development of Task 5.
Funding Support: Asociacion Española contra el Cancer

Name: Raquel Perez-Lopez
Project Role: Collaborator
Nearest person month worked: 3
Contribution to Project: Dr Perez-Lopez oversees patient evaluation for pursuing biopsies and has participated in set up of Aim 3.
Funding Support: Prostate Cancer Foundation

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.

Colin Pritchard

Previously Pending Now Active

Title: The Pacific Northwest Prostate Cancer SPORE
Effort: 1.20 Calendar Months (10.00% effort)
Supporting Agency: Fred Hutch through National Institute of Health
Contracting/Grants Officer: Lillian Furlong
Address of Funding Agency: 1100 Fairview Ave N, POB 19024, National Institute of Health, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152
Performance Period: 09/01/2019 – 08/31/2020
Level of Funding: $170,437
Project Goals: The proposed plan builds on our prior SPORE work, taking advantage of our experience to prospectively recruit a population-based PCa cohort with germline mutations (index cases) and their male first degree relatives (high risk cohort) with the goal of conducting a PCa early detection study that will incorporate germline DNA sequencing to characterize risk, novel PCa

biomarkers, clinical and PCa-specific outcomes data. Univariate, stratified, and multivariate analyses will be completed to evaluate sensitivity and specificity of new biomarkers. The Cox proportional hazards model will be used to calculate hazard ratios, 95% CIs, and p-values to examine the association of individual and combinations of germline genetic biomarkers and with PCa outcomes. The overall goal is to identify and validate prognostic genetic-epigenetic biomarkers and begin to translate these findings into better patient management by investigating novel screening and detection approaches for men at high risk for aggressive PCa.
Specific Aims: AIM 1: Determine factors associated with uptake of genetic testing among mPC cases and identify clinical, pathologic and molecular predictors of gDRG status. (Corollary: Men with mPC and gDRG will be offered targeted clinical trials proposed in SPORE Project 4.)
AIM 2: Conduct a high-risk prostate cancer early detection study incorporating imaging, novel biomarkers and statistical modeling in at-risk male gDRG carriers. In addition to collecting critical information about test-ing outcomes, this aim will establish a protocol for high-risk prostate cancer screening in this population.
AIM 3: Develop processes for and identify barriers to cascade genetic testing from index cases to their at-risk first-degree relatives (FDRs).
Overlap: N/A
Role: PI

Previously Active Now Closed

Title: Advanced development and validation of targeted molecular counting methods for precise and ultrasensitive quantitation of low prevalence somatic mutations
Effort: 0.60 Calendar Months (5.00% effort)
Supporting Agency: National Institute of Health
Contracting/Grants Officer: Angela Walters (angela.walters@nih.gov)
Address of Funding Agency: National Institute of Health, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152
Performance Period: 05/01/2015 – 04/30/2019
Level of Funding: $736,710 Direct Costs
Project Goals: This grant will focus on development of single molecule molecular inversion probe technology for clinical molecular diagnostics.
Specific Aims: Aim 1: We will develop and optimize a smMIP panel enabling highly-multiplexed, ultrasensitive detection of low-prevalence cancer-associated mutations.
We will develop and optimize a smMIP panel to target a broad range of cancer-associated gene exons and isolated substitution and indel mutation hotspots (>800 hotspots and >50 fully tiled genes), with broad application to clinical testing and cancer research in mind. This panel will be used in subsequent Aims.
Aim 2: Detection of minimal residual disease (MRD) in acute myeloid leukemia (AML) by smMIPs.
We will apply the smMIP panel to detect ultra-rare, heterogeneous disease-associated mutations as biomarkers of MRD, the key prognostic variable in predicting AML relapse. Limits of detection, analytic measurement range, reproducibility, and false positive rate will be determined using defined dilutions of sequenced cell lines and specimens from healthy individuals. Performance of smMIPs will be directly compared to existing, gold-standard clinical methodology (flow cytometry) for MRD detection in at least 50 patient specimens, and for prediction of AML relapse in

longitudinal specimens derived from 10 patients.
Aim 3: Detection of cancer-associated mutations in circulating cell-free tumor DNA using smMIPs. The smMIP panel will be used to identify a broad range of ultra-rare cancer-associated mutations from the cell-free DNA of cancer patients, a promising analyte for non-invasive detection of therapeutically actionable mutations, estimation of prognostic outcome, and surveillance for cancer or recurrence. We will determine performance characteristics (defined in Aim 2) using cell-free DNA from 50 healthy individuals and 60 cancer patients, spanning a spectrum of malignancy, and including matched germline and tumor DNA to facilitate identifying true somatic mutations. We will catalog and quantitate cancer-associated mutations in the cell-free DNA of patients with active and quiescent disease.
Overlap:
Role: Co-Investigator; PI: Stephen Salipante

Title: Non-invasive detection of AR-FL/AR-V7 as a predictive biomarker for therapeutic resistance in men with metastatic castration-resistant prostate cancer
Effort: 1.20 Calendar Months (10.00% effort)
Supporting Agency: Department of Defense (DOD) US Army
Contracting/Grants Officer: Jennifer Shankle (Jennifer.e.shankle.civ@mail.mil)
Address of Funding Agency: 820 Chandler St, Fort Detrick, MD 21702-5014
Performance Period: 08/01/2018 – 09/29/2019
Level of Funding: $58,830

Project Goals: The overall objective of this Biomarker Development Award application is to establish a critically important and standardized non-invasive assay for measuring AR-FL/AR-V7 in patients initiating treatment with abiraterone or enzalutamide. To further improve the assay, to enable clinicians to offer the assay to patients with metastatic prostate cancer as part of the standard of care, and to facilitate anti-cancer drug development by integrating the assay into clinical trials of novel AR-directed therapies.
Specific Aims: Aim 1: To perform cross-institutional analytical validation of a blood-based assay in a certified environment (CLIA or international equivalent).
Aim 2: To plan, coordinate, and facilitate multi-institutional clinical trials integrating AR biomarkers.
Overlap:
Role: Co-Investigator; PI: Plymate, Stephen

Heather Cheng

Previously Pending Now Active

Title: The Pacific Northwest Prostate Cancer SPORE
Effort: 1.40 Calendar Months (11.60% effort)
Supporting Agency: Fred Hutch through National Institute of Health
Contracting/Grants Officer: Lillian Furlong
Address of Funding Agency: 1100 Fairview Ave N, POB 19024, National Institute of Health, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152

Performance Period: 09/01/2019 – 08/31/2020
Level of Funding: $170,437
Project Goals: The proposed plan builds on our prior SPORE work, taking advantage of our experience to prospectively recruit a population-based PCa cohort with germline mutations (index cases) and their male first degree relatives (high risk cohort) with the goal of conducting a PCa early detection study that will incorporate germline DNA sequencing to characterize risk, novel PCa biomarkers, clinical and PCa-specific outcomes data. Univariate, stratified, and multivariate analyses will be completed to evaluate sensitivity and specificity of new biomarkers. The Cox proportional hazards model will be used to calculate hazard ratios, 95% CIs, and p-values to examine the association of individual and combinations of germline genetic biomarkers and with PCa outcomes. The overall goal is to identify and validate prognostic genetic-epigenetic biomarkers and begin to translate these findings into better patient management by investigating novel screening and detection approaches for men at high risk for aggressive PCa.
Specific Aims: AIM 1: Determine factors associated with uptake of genetic testing among mPC cases and identify clinical, pathologic and molecular predictors of gDRG status. (Corollary: Men with mPC and gDRG will be offered targeted clinical trials proposed in SPORE Project 4.)
AIM 2: Conduct a high-risk prostate cancer early detection study incorporating imaging, novel biomarkers and statistical modeling in at-risk male gDRG carriers. In addition to collecting critical information about test-ing outcomes, this aim will establish a protocol for high-risk prostate cancer screening in this population.
AIM 3: Develop processes for and identify barriers to cascade genetic testing from index cases to their at-risk first-degree relatives (FDRs).
Overlap: N/A
Role: Co-Investigator

Stephen Salipante

Previously Pending Now Active

Title: Understanding Staphylococcus aureus host-bacterium interactions that drive chronic infection in CF patients
Effort:
Supporting Agency: Vertex Pharmaceuticals Inc
Contracting/Grants Officer: Vicky Tepley
Address of Funding Agency: 50 Northern Avenue, Boston, MA 02210
Performance Period: 10/01/2019 – 09/30/2024
Level of Funding: $750,000
Project Goals: The major goals we propose are we hypothesize that polygenic mutations arising in S. aureus during CF infections can increase bacterial tropism for host airway cells and produce phenotypes that promote persistent infection. We will test this hypothesis and identify genes involved using a novel, cross disciplinary approach combining methods from evolutionary biology, population genetics, genomic sequencing, and genome editing.
Specific Aims: Aim 1: Identify spontaneous mutations in S. aureus that promote increased persistence phenotypes in CF. (Years 1-2)
Aim 2: Define variants associated with persistence phenotypes in S. aureus isolates from chronic CF

infection. (Years 1-2)
Aim 3: Determine the function of mutations associated with persistence phenotypes in S. aureus using high throughput genome editing techniques.
Overlap: N/A
Role: PI

Previously Active Now Closed

Title: Clinical Effects of Evolved Variation in Infecting Bacterial Populations
Effort: 0.66 Calendar Months
Supporting Agency: National Institute of Health
Contracting/Grants Officer: Tyrone A Smith
Address of Funding Agency: National Institute of Health, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152
Performance Period: 9/20/2018 – 8/31/2019
Level of Funding: $439,587
Project Goals: Chronic infections cause progressive dysfunction of infected organ, and marked variation in the rate of disease progression is apparent in patients with similar risk factors and within individual patients at different times. Understanding the mechanisms responsible for stable or accelerated clinical decline could suggest novel approaches to slow disease. This project investigates the contribution of genetic variation that evolves Pseudomonas aeruginosa strains to disease severity in cystic fibrosis. This work will provide proof of principle for a new idea to explain disease variability that could have implications for many chronic infections, and suggest new treatments
Overlap: N/A
Role: Co-Investigator

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.*

Organization Name: Vall D'Hebron Institute of Oncology (VHIO)
Location of Organization: Barcelona, Spain
Partner's contribution to the project: Collaboration

Organization Name: Centro Nacional Investigaciones Oncologicas (CNIO)
Location of Organization: Madrid, Spain
Partner's contribution to the project: Collaboration

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.