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Defining and Modulating BRCAness to Improve the Precision of Prostate Cancer Therapy

PRINCIPAL INVESTIGATOR:
Peter S. Nelson, MD

CONTRACTING ORGANIZATION:
Fred Hutchinson Cancer Center, Seattle, WA

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Peter S. Nelson, MD

E-Mail: pnelson@fredhutch.org

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Fred Hutchinson Cancer Center
1100 Fairview Ave N
PO Box 19024, Mailstop J6-500
Seattle, WA 98109-1024

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14. ABSTRACT

Purpose: This proposal is focused on exploiting a specific subtype of metastatic CRPC, termed *Homology Directed DNA Repair Deficient* (HDR-D) prostate cancer (PC) to enhance treatment outcomes, reduce morbidity and improve survival. HDR-D represents at least 20% of metastatic PC and is most commonly identified through the genomic analysis of biopsies from metastatic tumors and identifying mutations in *BRCA1*, *BRCA2* and related genes.

Scope: This proposal is designed to address two challenges: First, to improve the accuracy of detecting PCs with functional HDR-D for appropriate treatment allocation. It is clear from prospective studies that simply evaluating the mutation status of HDR-associated genes lacks precision for predicting treatment responses: a high percentage (>50%) of biomarker 'positive' patients fail to respond. Second, to increase the number of men with PC that could benefit from therapeutics targeting HDR-D by promoting 'conditional haploinsufficiency' converting HDR-competent tumors to a 'BRCAness' phenotype.

Major Findings: (1) We have developed a new assay, termed OncoplexHRD, that represents a read out of functional HDR-D. This assay is suitable for tissue based analyses or circulating tumor DNA (ctDNA); (2) We developed a composite assays for functional HDR-D that incorporates mutation signatures – termed iHRD, and demonstrated strong associations with responses to platinum chemotherapy and PARPi; (3) We determined that inherited mutations in DNA repair genes are rare in men with low risk prostate cancer; (4) We determined that TP53 is an inherited prostate cancer predisposition gene, and that TP53 can influence metrics usually associated with HDR-D such as LOH scores; (5) We determined that aggressive prostate cancers with BRCA2 loss exhibiting neuroendocrine features respond to PARPi, concordant with typical adenocarcinomas with HDR-D; (6) We confirmed that HR gene mutations ascertained in analyses of primary prostate cancers are generally concordant with events identified in metastatic biopsies or ctDNA – confirming that primary tumors can serve as a relevant source for ascertaining HDR-D status and allocating appropriate treatment; (7) We identified a pattern of structural DNA alterations that associate with HDR-D, adding an additional parameter for clinical testing for determining HDR-D in patients.

15. SUBJECT TERMS

Prostate cancer, metastasis, castrate-resistant prostate cancer, DNA repair, homology-directed DNA repair deficiency, PARP inhibitor, chemotherapy, biomarker

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1. INTRODUCTION

This proposal is focused on exploiting a specific subtype of metastatic CRPC, termed *Homology Directed DNA Repair Deficient* (HDR-D) prostate cancer (PC) to enhance treatment outcomes, reduce morbidity and improve survival. HDR-D represents at least 20% of metastatic PC and is most commonly identified through the genomic analysis of biopsies from metastatic tumors and identifying mutations in *BRCA1*, *BRCA2* and related genes. Recent clinical studies have determined that mCRPCs with these mutations are responsive to two types of therapy, PARP inhibitors and platinum-based chemotherapy. However, the current biomarkers, based on identifying gene mutations, are imprecise: many men determined to be biomarker positive do not respond, and the gene mutation-based biomarkers fail to identify other patients that will respond. Further, only about 20% of men with CRPC have a tumor with functional HDR-deficiency, consequently many men will not benefit from the 'synthetic lethality' treatment approaches that leverage this important tumor vulnerability.

This proposal is designed to address two challenges: First, to improve the accuracy of detecting PCs with functional HDR-D for appropriate treatment allocation. It is clear from prospective studies that simply evaluating the mutation status of HDR-associated genes lacks precision for predicting treatment responses: a high percentage (>50%) of biomarker 'positive' patients fail to respond. Second, to increase the number of men with PC that could benefit from therapeutics targeting HDR-D by promoting 'conditional haploinsufficiency' converting HDR-competent tumors to a 'BRCAness' phenotype.

2. KEYWORDS.

Prostate cancer, metastasis, castrate-resistant prostate cancer, DNA repair, homology-directed DNA repair deficiency, PARP inhibitor, chemotherapy, biomarker

3. ACCOMPLISHMENTS.

Project Goals:

This is a partnering PI award with research sites at Fred Hutchinson Cancer Center and the University of Washington (FH). The Aims, applicable sub-tasks, and work accomplished to date for each site are listed below:

TITLE: DEFINING AND MODULATING BRCAness TO IMPROVE THE PRECISION OF PROSTATE CANCER THERAPY	**Timeline (Months) 1-36**	**FHCRC** (Nelson)	**UW Lab. Medicine** (Pritchard)	**Completed (%) Year 1 Annual Report**
AIM 1. Develop and test clinical grade assays that define prostate cancers with functional homology directed DNA repair deficiency to improve sensitivity and specificity relative to HR gene mutations.				
Subtask 1: Obtain institutional (Fred Hutch / UW) IACUC and IRB review and approvals.	1	Nelson Team	Pritchard Team	100%
Subtask 2: Submit compliance documents from institutional offices to DOD ACURO/HRPO for review, and obtain approvals.	2	Nelson Team	Pritchard Team	100%
Subtask 3: Initiate study start-up procedures (staff training).	1-2	Nelson Team	Pritchard Team	100%
Subtask 4: Identify biospecimens from mCRPC models with germ-line and/or somatic defects in HRR.	2-12	Nelson Team		100%
Subtask 5: Extract DNA, complete genomic	3-24		Pritchard	50%

sequencing, and identify variants conferring HRR-D and variants with uncertain significance.			Team	
Subtask 6: Identify and obtain tumor biospecimens and ctDNA samples from patients with mCRPC with and without HRR-D	2-34	Nelson Team	Pritchard Team	50%
Subtask 7: Develop a NextGen assay targeting relevant DNA repair genes and genomic parameters of HRR-D (tumor and ctDNA)	2-6		Pritchard Team	100%
Subtask 8: Sequence tumor and ctDNA from patient biospecimens and identify aberrations in DNA repair: genes and genomic scars.	3-34		Pritchard Team	70%
Subtask 9: Identify and obtain biospecimens collected from patients on clinical trials of therapies exploiting HRR-D	3-34	Nelson Team	Pritchard Team	60%
Subtask 10: Sequence tumor and ctDNA from patient biospecimens from HRR-D directed therapy and identify aberrations in DNA repair: genes and genomic scars.	3-34		Pritchard Team	60%
Subtask 11: Confirm metrics of sensitivity and specificity using tumor tissue and ctDNA.	4-12		Pritchard Team	100%
Subtask 12: Determine concordance and discordance of assay performance comparing minimally-invasive assessments with tumor assessments for clinical trial participants.	12-34		Pritchard Team	70%
Subtask 13: Determine assay performance in longitudinal assessments of tumor responses and assessing resistance mechanisms.	24-35		Pritchard Team	30%
Subtask 14: Submit data for CLIA/CAP approval of assays.	18-24		Pritchard Team	50%
Milestone #1: Prepare and submit manuscript detailing the performance characteristics of assays for accurate determination of HRR-D.	24	Nelson Team	Pritchard Team	50%
Milestone #2: Prepare and submit manuscript detailing the utility of orthogonal assays of HRR-D to impact patient care: identification of appropriate patients for treatment and monitoring responses.	30-34	Nelson Team	Pritchard Team	50%
AIM 2. Identify specific combinations of DNA repair gene and metabolic parameters that confer functional homology directed DNA repair deficiency.				
Subtask 1: Identify combinations of HR related genes with single copy loss and concurrent parameters indicating HRR-D – PDX lines.	1-6	Nelson Team		100%

Subtask 2: Identify combinations of HR related genes with single copy loss and concurrent parameters indicating HRR-D – tumor biospecimens.	1-12	Nelson Team		100%
Subtask 3: Identify variations in metabolic gene expression and activity.	3-14	Nelson Team		50%
Subtask 4: Develop models with combinations of single copy loss genes and metabolic alterations.	4-18	Nelson Team		50%
Subtask 5: Evaluate effects of metabolites and metabolic parameters on HRR-D and treatment responses.	6-24	Nelson Team	Pritchard Team	50%
Subtask 6: Conduct preclinical cell line and PDX studies evaluating gene combinations and agents altering metabolic parameters: 6 drug/treatment studies – 4 lines x 3 arms x 8 mice/arm = 576 mice.	6-30	Nelson Team		50%
Milestone #3: Prepare and submit manuscripts detailing the effects of haploinsufficiency and metabolic features inducing conditional HRR-D.	12-24	Nelson Team	Pritchard Team	50%
AIM 3. Identify pharmacological agents that promote HRR-D and that enhance the effects of genotoxic drugs and PARPi.				
Subtask 1: Test 3 PARPi for effects against tumors with HRR-D due to biallelic HRG loss and against tumors with multiple-monoallelic loss.	6-18	Nelson Team		50%
Subtask 2: Test platinum therapy for effects against tumors with HRR-D due to biallelic HRG loss and against tumors with multiple-monoallelic loss.	8-20	Nelson Team		30%
Subtask 3: Test drug combinations that a) induce HRR-D and b) target HRR-D for effects against tumors with HRR-D due to biallelic HRG loss and against tumors with multiple-monoallelic loss.	8-34	Nelson Team		30%
Subtask 4: Evaluate tumors resisting therapy for mechanisms of treatment resistance.	12-35	Nelson Team		20%
Milestone #4: Prepare and submit manuscripts detailing the effects of inducing HRR-D with targeting HRR-D.	32-26	Nelson Team	Pritchard Team	0%
Milestone #5: Prepare and submit final report.	36	Nelson Team	Pritchard Team	0%

Accomplishments Toward Goals:

To accomplish the Specific Aims, we developed a bi-institutional collaboration between Dr Peter Nelson (PI; Fred Hutchinson Cancer Center, Seattle, Washington USA) and Dr Colin Pritchard (PI; University of

Washington, Seattle, Washington USA).

1) Major Activities:

The major activities conducted during Year 1 of this project are outlined above in the SOW according to each Specific Aim and Subtask partitioned by partnering site. The activities centered on accomplishing these aims/objectives. The results of these activities are detailed below.

2) Specific Objectives:

The specific objectives followed the Specific Aims: AIM 1. Develop and test clinical grade assays that define prostate cancers with functional homology directed DNA repair deficiency to improve sensitivity and specificity relative to HR gene mutations; AIM 2. Identify specific combinations of DNA repair gene and metabolic parameters that confer functional homology directed DNA repair deficiency; AIM 3. Identify pharmacological agents that promote HDR deficiency and that enhance the effects of genotoxic drugs and PARPi.

3) Significant Results or Key Outcomes, Including Major Findings, Developments, and Conclusions:

AIM 1. Develop and test clinical grade assays that define prostate cancers with functional homology directed DNA repair deficiency to improve sensitivity and specificity relative to HR gene mutations.

Progress to Date: The major activities for this aim focused on developing a clinical-grade assay for ascertaining HRD status in prostate cancer. In the first year, HRPO and internal IRB protocol approvals were obtained, a research coordinator hired, and validation of the assay commenced with both prospective and retrospective molecularly-characterized prostate cancer biospecimens.

Protocol Approvals and Study Start Up: During the first year we obtained both HRPO and internal IRB approvals for the work. HRPO approval numbers E02119.1a and E02120.1a, approved 2/14/2022. Internal approval Fred Hutch IRB, IR# 8130, RG5118000, UW Study: DEFINING AND MODULATING BRCAness TO IMPROVE THE PRECISION OF PROSTATE CANCER THERAPY: UW IRB STUDY00014494. A research coordinator was hired and study training performed.

OncoPlex Assay Background: UW-OncoPlex is a ~3Mb, 362-gene comprehensive cancer sequencing panel developed by the Pritchard group which has been in continuous clinical use in the CLIA-laboratory setting for prostate cancer patients since 2011, with over 15,000 total patients tested to date. In collaboration with Dr. Nelson, the OncoPlex assay has been validated for prostate cancer use in *both* tumor tissue and for circulating cell-free DNA (ctDNA) (PMID:30865311, PMID:27324988, PMID:24189654). OncoPlex currently detects single nucleotide variants, all sizes of indels, copy number variants, structural rearrangements, total mutation burden (TMB), and microsatellite instability (MSI) (PMID:24987110). OncoPlex has unique features designed to accurately detected DNA repair gene mutations, including capture of introns in *BRCA1/2* and in MMR genes.

OncoPlexHRD Development: Homologous recombination deficient (HRD) cancers accumulate large deletion and duplication events that lead to genomic LOH which can serve as a biomarker for detection of HRD. We modified OncoPlex to measure LOH mutational signatures for HRD through analysis of paired tumor and normal samples (OncoPlex v7 update) by adding 3,076 single 120bp IDT lockdown capture probes at sites of

Figure 1. OncoPlex*HRD*. We added over 3,000 SNP probes to the UW-OncoPlex backbone for even tiling across the genome to measure %LOH as a surrogate of HRD. The assay workflows and bioinformatics pipelines have been modified to accommodate paired tumor-normal testing.

carefully selected common SNPs designed to tile evenly across the genome to serve as a backbone for genomic LOH profiling. LOH is detected using the R package Sequenza, which performs probabilistic analysis of sample pairs through estimation of tumor cellularity and ploidy to calculate copy number variation and variant allele frequency in the paired tumor sample to determine overall genomic % LOH (PMID:25319062) (**Figure 1**).

OncoPlexHRD Prostate Cancer Validation: To date, we have performed validation analyses for OncoPlex*HRD* on a collection of 111 prostate cancer tumor-normal tissue sample pairs according to the following categories: 49 primary prostate cancer samples, 4 LN metastasis samples, 13 distant metastasis samples, 25 ctDNA samples from men with mCRPC, and 20 LuCaP PDX prostate cancer samples. Samples with insufficient quantity or very low tumor cellularity were dropped from analysis (n=16).

The breakdown of samples according to HRR gene mutation is given in **Table 1 and 2** and **Figure 2** below. Although not strictly defined at HRR genes, we including *CDK12* and *CHD1* in these analyses as they have been shown to interact in important ways with HRR genes. Samples tested with identified mutations in HR genes had significantly higher % LOH (AVG: 14%, SD: 8%, t-test two-tailed p=0.0004263) than samples lacking HR mutations (AVG: 8%, SD: 5%) (**Table 2**).

Because TP53 mutation is associated with increased chromosome instability and has been suggested to raise overall LOH scores independent of HRD status in other cancer types, we analyzed the LOH score according to TP53 mutation status (**Table 3**). We observed a slightly higher overall average LOH score (12%) in *TP53* mutant cancer compared to TP53 wild type (10%), but this was not statistically significant (t-test, two tailed, p=0.24).

Exploration of multi-modal HRD detection strategies for OncoPlexHRD: The hallmarks of HRD include increased genomic LOH, as well as SNV substitution signatures (COSMIC signature 3), indels at regions of microhomology, and characteristic rearrangement signatures (PMID:28288110). Due to limitations of a targeted panel approach, we are focusing on quantitative LOH as the primary measure of HRD for the clinical assay, but we will also explore incorporating COSMIC signature 3, and indel signatures. Our paired normal approach will results in "clean" calls for both SNVs and indels, facilitating incorporation of this data even though it will be sparse in comparison to a whole exome or genome approach.

Our results to date are already very close to establishing an optimal prostate-specific LOH% threshold for positivity. Following the data-lock we will establish this threshold empirically based on Receiver Operator Curve (ROC) analysis and define an indeterminate LOH% range. Within- and between run reproducibility will be performed across at least 3 runs for 20 sample pairs. Lower limit of detection will be established by mixing studies using a low-positive and high-positive HRD tumor.

HRR Gene	Ave. LOH Score	SD LOH Score
ATM (n=8)	0.12	0.05
BAP1 (n=1)	0.08	NA
BRCA1 (n=2)	0.19	0.06
BRCA2 (n=12)	0.15	0.07
BRIP1 (n=1)	0.11	NA
CDK12 (n=5)	0.07	0.03
CHD1 (n=6)	0.12	0.07
CHEK2 (n=3)	0.15	0.12
FANCA (n=2)	0.08	0.01
FANCD2 (n=1)	0.17	0.00
PALB2 (n=4)	0.10	0.03
RAD51B (n=1)	0.25	NA
None (n=49)	0.09	0.06
QC failure (n=16)	NA	NA

Table 1. Average LOH score by OncoPlex*HRD* in prostate cancer cases according to HRR gene mutation

HRR Gene Mutation	Average LOH score	SD LOH Score
Present	0.14	0.08
Absent	0.08	0.05
t-test, two tailed	p= 0.000426	

Table 2. Overall Average LOH score by OncoPlex HRD in prostate cancer cases with or without HRR gene mutations.

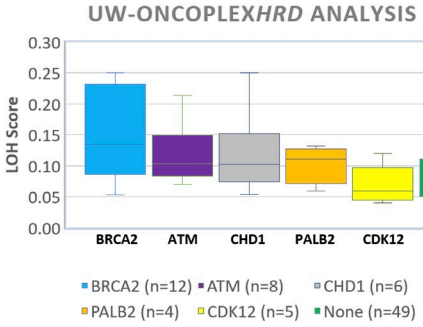


Figure 2. OncoPlexHRD results according to underling HRR gene mutation. Excluded from this box boxplot graph are cases with fewer than 4 samples (CHEK2 n=3, BRCA1 n=2, FANCA n=2, BRIP1 n=1, BAP1 n=1, RAD51B n=1, FANCD2 n=2).

TP53 Mutation	Average LOH score	SD LOH Score
Absent	0.10	0.06
Present	0.12	0.08
t-test, two tailed	p= 0.24	

Table 3. LOH Score according *TP53* mutation status

AIM 2. Identify specific combinations of DNA repair gene and metabolic parameters that confer functional homology directed DNA repair deficiency.

Progress to Date: The major activities for this aim focused on identifying or developing model systems with variation in the expression/function of genes/pathways involved in HR DNA repair and metabolic functions that plausibly influence HR gene expression and/or pathway activity.

Development of assays for defining functional HRD. To assess the potential clinical use of mutation signatures – specifically COSMIC SVS mutation signature 3 (CSig3) and the composite metric of genomic alterations associated with HRD (iHRD) classification in treatment selection, we carried out functional studies to compare responses based on a core HR gene (HRG) mutation (HRGmut), CSig3 activity and iHRD status. Using whole exome sequencing (WES) we annotated a panel of 20 PC patient derived xenograft (PDX) lines according to alterations in the core HRGs: HRG-BAL, n=1; HRG-MML, n=7; and HRG-MAL or wild type, n=12. Two lines were CSig(+), and 9 classified as iHRD(+) (**Figure 3a**). Of the 9 iHRD(+) tumors, 1 was explained by *BRCA2* bi-allelic loss, 2 were HRG-MML, 3 were HRG-MAL, whereas 3 had no genomic alteration in any core HRG. Two iHRD(+) PDX lines were CSig3(+) and of the iHRD(-) tumors, none were CSig3(+).

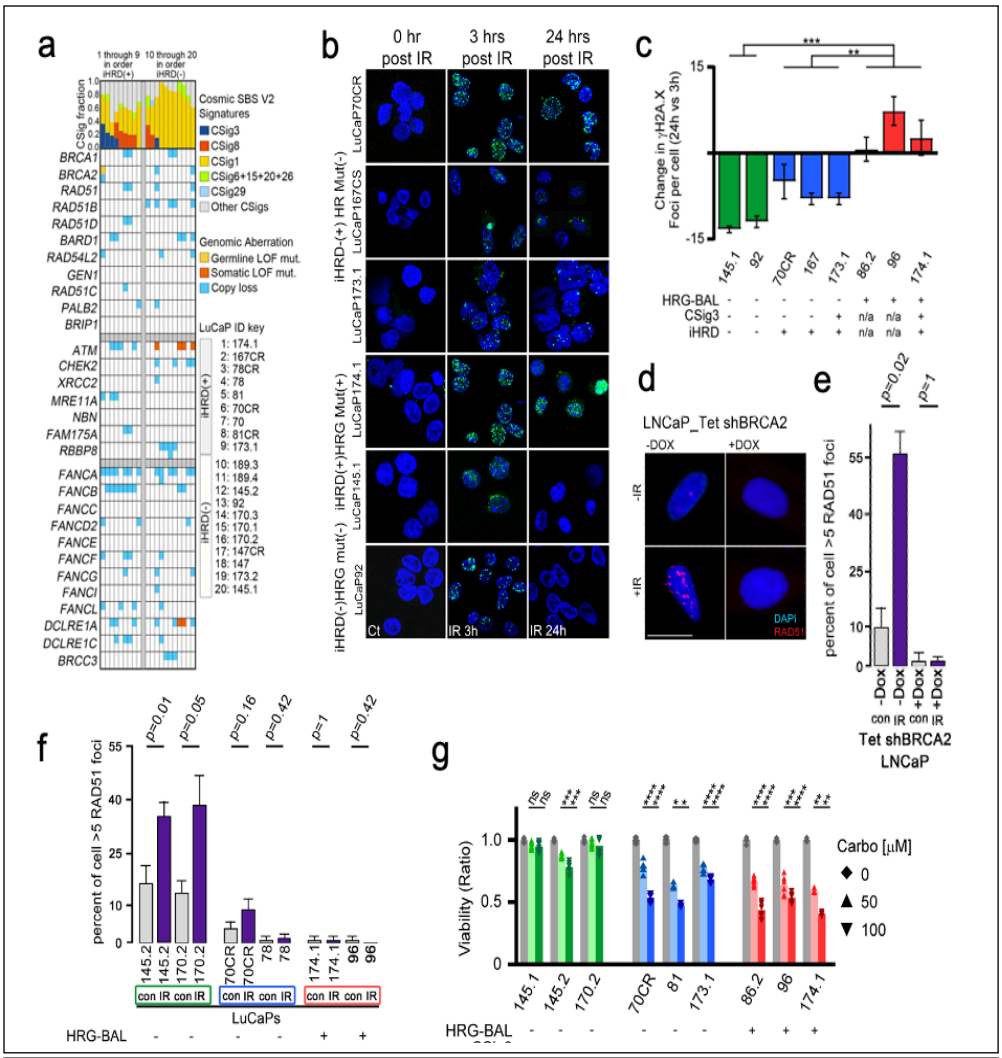


Figure 3. Evaluation of HRR gene mutation, CSig3 and iHRD classification with responses to DNA damaging therapeutics.
(a) Distribution of Cosmic single base substitution mutational signatures (CSigs) across prostate cancer patient derived xenograft (PDX) lines. The class of Cosmic mutation signatures are color coded and tumors are ordered in decreasing frequency of Cosmic signature 3 fraction(CSig3).
(b,c) Confocal immunostaining and quantitation of γH2AX foci in short term cultures of the indicated PDX line 3hr and 24hr after exposure to 6Gy IR or sham treatment (Ct). Foci counts for each time point are the mean ± SD of 3 replicate experiments. Intergroup comparison in change foci counts 3 frequency per cell was performed by a Welch's t-test. (P-Value ** < 0.01; *** < 0.001)
(d,e) Immunofluorescence microscopy quantitation of RAD51 foci in LNCaP_Tet_shBRCA2 with or without DOX and with or without ionizing radiation (IR); (d) representative images of cells with and without designated treatments; (e) percentage of 50 cells counted with >5 RAD51 foci/cell. Each measurement represents the mean +/- SD of 3 independent measurements. Significance was determined by Fisher's exact test. Magnification bar = 10 μM.
(f) Quantitation of RAD51 immunofluorescence staining in short-term cultures of LuCaP PDX lines exposed to IR or sham treatment. The percentage of 50 cells counted with >5 RAD51 foci/cell is plotted with each measurement representing the mean +/- SD of 3 independent measurements. Significance was determined by Fisher's exact test.
(g) Cell viability assessments of LuCaP PDX lines grown *in vitro* and measured 72 hr after treatment with vehicle, 50 μM or 100 μM carboplatin. Each measurement = mean +/- SD of 3 replicate experiments. Comparison of cell viability was performed using paired t-tests with Bonferroni corrections. (P-Value * ≤ 0.05; ** < 0.01; *** < 0.001; **** < 0.0001, ns: nonsignificant).

We were able to establish several of the PDX lines as short-term *in vitro* cultures and used these to assess the function of DNA repair competency by exposing them to y-irradiation (IR) and measuring DNA double-strand breaks by quantitating y-

H2AX foci by immunofluorescence staining. Three hours after radiation all lines had significantly greater numbers of yH2AX foci compared to baseline, and there were no significant differences based on genotype, CSig3, or iHRD status (**Figure 3b**). However, 24 hours after IR, 2 lines, LuCaP92 and LuCaP145.1, classified as HRGmut(-);CSig3(-);iHRD(-), had completely resolved these foci to levels equivalent to baseline (**Figure 3b,c**). Two HRGmut(+) lines, LuCaP96 and LuCaP86.2 where CSig3 and iHRD status could not be determined due to lack of germline control to ascertain mutation signatures, and one line, LuCaP174.1 classified as HRGmut(+) CSig3(+);iHRD(+), had persistently elevated yH2AX foci counts at 24 hr equal to or greater than foci counts at 3 hr. Three lines lacked genomic alterations in core HR or Fanconi pathway genes, but classified as iHRD(+): two of these lines, LuCaP173.1, and LuCaP167 had reduced yH2AX foci by 24hr, though they remained significantly higher than baseline levels ($p<0.01$) and higher than iHRD(-) lines, while foci numbers in the HRGmut(-);CSig3(-);iHRD(+) LuCaP70CR cells were the highest of all lines at 3hr and remained substantially elevated at 24hr ($p<0.001$)(**Figure 3c**).

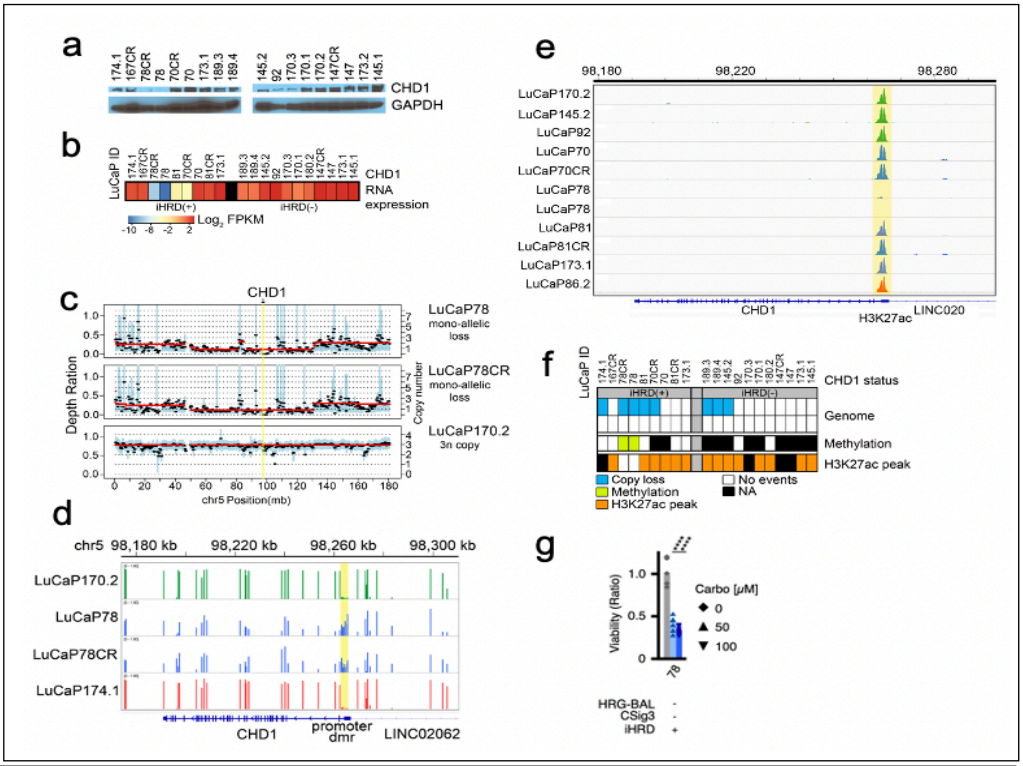


Figure 4. A *de novo* model of *CHD1* loss demonstrates functional HR repair deficiency
(a) Western blot showing CHD1 protein expression across 20 LuCaP prostate cancer PDX lines.
(b) Heatmap showing median centered CHD1 mRNA expression across 20 LuCaP PDX lines determined by RNAseq. The heat map scale represents the log2 transformed CHD1 RNAseq read counts as FPKM.
(c) Copy number profile of *CHD1* in 3 representative LuCaP PDX lines determined by whole exome sequencing. LuCaP78 and LuCaP78CR exhibit monoallelic copy number loss of CHD1
(d) *CHD1* genomic methylation status determined by EPIC methylation arrays. Shown are the IGV tracks indicating promoter hypermethylation at the upstream promoter of *CHD1* in LuCaP78 and LuCaP78CR PDX lines. A comparison of normalized beta values across probes for 12 CPG loci in the putative *CHD1* promoter region was done using a 2-sided independent sample t-test ($p= 2.17x10^{-10}$).
(e) IGV track showing the H3K27ac mark at the *CHD1* 5' promoter locus demonstrating loss of the H3K27ac peak in the upstream promoter of LuCaP78 and LuCaP78CR PDX lines.
(f) Heatmap showing *CHD1* genomic status across 20 LuCaP PDX lines. LuCaP78 and LuCaP78 CR have *CHD1* mono-allelic copy-loss paired with *CHD1* promoter hypermethylation and loss of H3K27ac.
(g) Cell viability assessments of LuCaP78 PDX lines grown *in vitro* and measured 72 hours after treatment with vehicle, 50 μM or 100 μM carboplatin. Measurement represents the mean +/- SD of 8 replicate experiments. Comparison of cell viability was performed using 2-sided paired t-tests. (P-Value: **** < 0.0001, ns: nonsignificant).

In the setting of intact HR repair, the detection of RAD51 foci by immunofluorescence microscopy following DNA damage serves as functional readout of HRR proficiency(38, 39). We next assayed RAD51 foci formation following IR exposure in PDX cell line models classified as iHRD(+) or iHRD(-). As a control, we engineered LNCaP cells to express a doxycycline (DOX)-inducible shRNA targeting BRCA2. Following IR, the number of control shBRCA2 cells with RAD51 foci increased from a baseline of 10% to 55% ($p=0.02$) whereas the number of DOX-treated shBRCA2 cells with RAD51 foci did not change significantly ($p=1$) (**Figure 3d,e**). In short-term cultures of LuCaP PDX lines, RAD51 foci were induced significantly by IR treatment in both lines classified as CSig3(-) and iHRD(-), but not in either of the CSig3(-)/iHRD(+) LuCaP70CR and LuCaP 78 lines, or in the HRG-BAL LuCaP174.1 and LuCaP96 lines (**Figure 3f**).

Tumor cells with incompetent HRR exhibit enhanced sensitivity to DNA crosslinking agents such as platinum chemotherapy. We quantitated the viability of the LuCaP cells *in vitro* following 72 hours of exposure

to either 50 µM or 100 µM carboplatin. The 3 HRGmut(-);CSig3(-);iHRD(-) lines, LuCaP145.1, LuCaP145.2 and LuCaP170.2, were largely resistant to both carboplatin concentrations while the HRGmut(+) lines, LuCaP86.2, LuCaP96, and LuCaP174.1 showed substantial dose-dependent reductions in viability (**Figure 3g**). Notably carboplatin treatment significantly reduced the viability of each of the three PDX lines classified as iHRD(+) but lacking biallelic mutations in HRGs: LuCaP70CR, LuCaP81 and LuCaP173.1 (**Figure 3g**) (PMID:34877933).

Identification of CHD1 as a HR repair gene in prostate cancer. In the analyses of mPCs a substantial fraction of tumors without biallelic loss of a gene classically associated with HR repair classified as CSig3(+) or iHRD(+), and this group included tumors with biallelic *CHD1* loss or low CHD1 expression. To determine if *CHD1* loss could underlie CSig3 or iHRD classification of any of the PDX models, we measured CHD1 protein by immunoblot and identified two iHRD(+) lines, LuCaP78 and LuCaP78CR that lacked CHD1 protein and also CHD1 transcripts (**Figure 4a,b**). Both lines, originating from the same patient, had monoallelic loss of *CHD1* determined by whole exome sequencing (**Figure 4c**). We next sought to determine if the remaining allele was silenced by methylation using whole genome bisulfite sequencing and found a region of hypermethylation located in the 5'UTR of *CHD1* (**Figure 4d**) which was accompanied by loss of H3K27 acetylation marks ascertained through a recent study of genome-wide H3K37ac in these PDX lines (**Figure 4e**). We confirmed the hypermethylation status of *CHD1* in the LuCaP78 and LuCaP78CR PDX lines using a targeted methylation PCR assay and concluded that *CDH1* is lost in these tumors by a combination of monoallelic genomic loss combined with epigenetic silencing of the remaining allele (**Figure 4f**). Notably, following IR treatment, the LuCaP78 PDX cells failed to form RAD51 foci (**Figure 4f**), indicating functional HR repair deficiency as reflected by iHRD(+) classification, and these cells were sensitive to carboplatin treatment with significant reductions in cell viability with both 50 µM and 100 µM concentrations (**Figure 4g**).

Identification of androgens/testosterone as a metabolic modulator of HRD. We determined that a subset of PCs with monoallelic loss of an HRG exhibit features of HRD. These finding suggested that other cellular mechanisms may contribute to HRD in the proper context. Metabolic variation such as the generation or elimination of aldehydes is one potential pathway that has the potential to modulate the expression or activity of HR repair. We also recently determined that high levels of androgens – supraphysiological androgens (**SPA**) - can repress the expression of HR genes and consequently induce DNA damage. Notably, these effects vary by tumor genotype with PCs harboring complete or monoallelic HRG loss exhibiting greater responses (**Figure 5**).

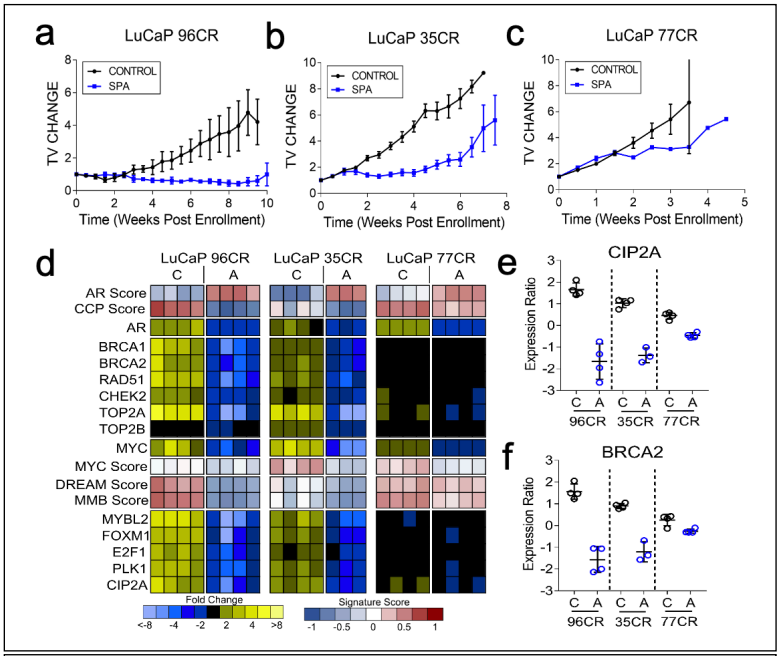


Figure 5. In vivo assessments of DNA repair gene expression following SPA treatment. (a-c) PDX lines exhibit variable responses to SPA.(d) Downregulated expression of key genes involved in HR in PDX tumors treated in vivo with SPA. (e,f) Quantitation of BRCA2 and CIP2A from replicate PDX tumors with or without SPA treatment.

AIM 3. Identify pharmacological agents that promote HDR deficiency (HRD) and that enhance the effects of genotoxic drugs and PARPi.

Overall Strategy: The objectives for this Aim are to: (i) identify drug combinations that will act synergistically to eradicate all tumor cells that are HRD; and (ii) take advantage of 'conditional haploinsufficiency' to induce a full 'BRCAness' phenotype in tumors with partial attenuation of repair capacity. We utilize a well-characterized panel of PDX lines and engineered models (e.g. cell lines) to develop support for advancing promising combinations into the clinic.

Supraphysiological androgens and selective androgen receptor mediators repress HR and promote

responses to HR-directed therapy: The AR positively regulates a spectrum of DNA repair genes, and repressing AR retards DNA repair and promotes radiation-induced cytotoxicity. However, we found expression of DNA repair genes (e.g. *BRCA2*, *ATM*, others) in CRPC is *inversely* related to AR activity suggesting the AR, when hyperactivated, also represses DNA repair. Prior studies found SPA induces DNA damage via stabilization of AR re-licensing on origins of DNA replication, resulting in apoptosis or arrest in early S phase. However we determined that SPA-induced DNA damage occurs within hours, a time-course incompatible with re-licensing effects (**Figure 6**). Moreover, the extent of DNA damage was increased with AR overexpression (green bars) and ligand levels (**Figure 6**). SPA suppressed growth and induced senescence and apoptosis (**Figure 6**). *These results are compatible with a mechanism of growth repression via transcription-associated AR-programmed DNA breaks.* Further, although we confirmed that a spectrum of genes encoding DNA damage/repair proteins are down-regulated with AR inhibition, *SPA exposure repressed these genes to a significantly greater extent*. HR genes were substantially repressed by SPA, indicating SPA may synergize with PARPi or DNA damaging therapeutics.

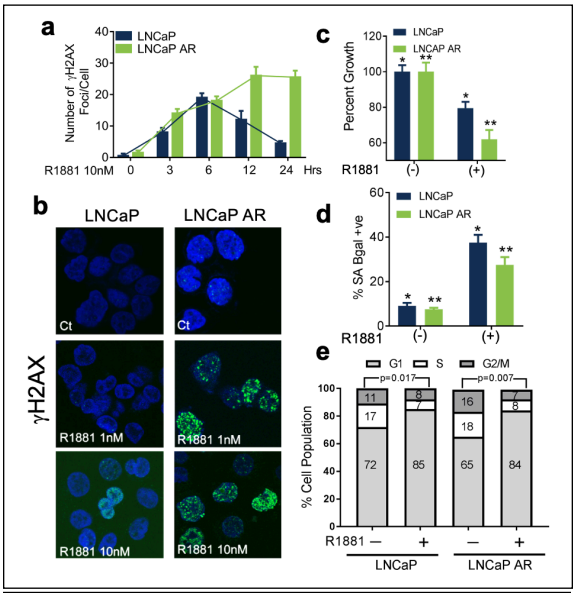


Figure 6. SPA induces DNA damage. DNA damage was assessed by yH2AX staining of tumor cells (a,b). SPA suppressed growth (c), increased senescence (d) and arrested cell cycle (e). SPA induced damage and growth repression was enhanced by AR overexpression (LNCaP-AR).

We further determined: (i) SPA-induced DNA damage was increased in cells with higher AR levels; (ii) SPA-induced DNA damage was enhanced in cells with *BRCA2* loss; (iii) Co-administration of PARPi (Olaparib) and SPA further increased DNA damage and induced apoptosis and senescence (**Figure 7**). These results suggest that AR amplification and HR gene aberrations may serve as biomarkers predictive of enhanced SPA clinical responses and that SPA may induce anti-tumor effects preferentially in tumors with (i) AR amplification and/or (ii) HR deficiency – either complete or partial.

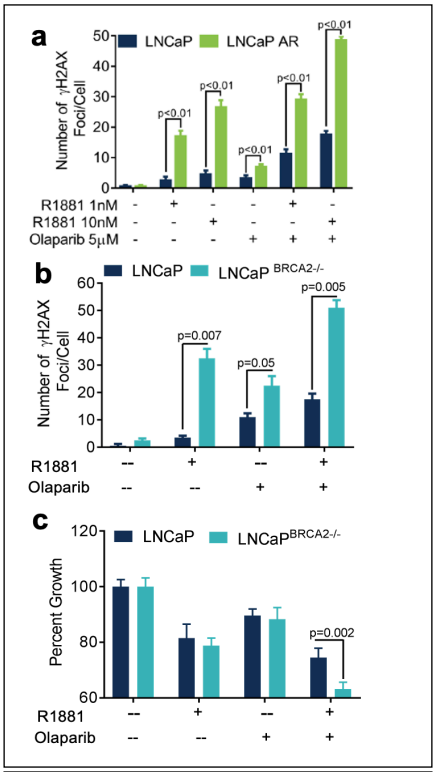


Figure 7. Anti-tumor effects of supraphysiological androgen (SPA) (a) Enhanced DNA damage in the context of AR amplification; (b) Enhanced DNA damage in the context of BRCA2 loss; (c) Enhanced PC growth inhibition in the context of SPA and the PARPi

4) Other Achievements

None to report

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

The project has supported the training and professional development of Dr. Tony Chu (external support), a post-doctoral fellow, and Lisa Ang, a staff scientist who managed the PDX studies. The project supported the career development of Ilsa Coleman, a bioinformatics specialist who received a Masters degree in bioinformatics for work related to this proposal. The project provided professional development for Dr. Nelson, who delivered several seminars relating to DNA repair and prostate cancer (see below in 6.Products).

How were the results disseminated to communities of interest?

The study results have primarily been disseminated through peer-reviewed publications. The results have also been presented at scientific meetings through oral presentations (see below in 6.Products).

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

(1) Next Steps for Analytical Validation of OncoPlexHRD: In the coming year we will continue to evaluate the performance of the modified OncoPlex*HRD* sequencing panel in accordance with metrics defined for the validation of laboratory developed clinical tests, specifically, confirmation of basic performance metrics defined by the Clinical and Laboratory Standards Institute (sensitivity, analytic specificity, within and between run reproducibility/precision, limit of detection/limit of quantitation, analytic measurement range).

We will lock the analysis to evaluate the analytic sensitivity and specificity will be performed by 1) comparison to samples with HRD gene mutation status (*BRCA1, BRCA1, PALB2, RAD51B, RAD51C, RAD51D*) established by a clinically-validated method (UW-OncoPlex or BROCA, available to the Pritchard group), and 2) comparison to FMI LOH HRD score (n=10). We will reflex samples with upper quartile LOH% but without detected HRD gene mutations to whole genome sequencing in collaboration with Navonil de Sarkar for iHRD full analysis.

In year 2 and 3 we will next evaluate OncoPlexHRD using prostate cancer samples from prospective clinical trials of PARPi and PLAT for which we can obtain access to biological specimens and treatment outcomes. We have already obtained biospecimens from the ABCD clinical trial of platinum chemotherapy in men with metastatic prostate cancer and underling HRR gene mutations. This trial has completed and outcomes are available. Testing by OncoPlexHRD is underway and results will be available in the 2nd year of this award. We will also focus on obtaining samples from the PLATIPARP, and POPCAP/VA Olaparib clinical trials. We will follow REMARK biomarker criteria guidelines (PMC3362085). We will establish the clinical validity of OncoPlexHRD by ROC analysis for clinical trial populations based on the pre-determined primary endpoints of PARPi/PLAT responsiveness. We will perform Kaplan Meyer analysis for each trial using OncoPlexHRD vs. mutation-only analysis, with particular attention on HRD+ cases without detected HR gene mutations.

(2) Next steps for identifying combinations of DNA repair gene and metabolic parameters that confer functional homology directed DNA repair deficiency. We will continue to follow the work plan and develop isogenic models with heterozygous alterations in key genes involved in HR repair and identify combinations that confer HRD. A particular area of emphasis will involve the transcriptional kinase CDK12 – which may regulate the expression of several HR genes. We will also focus on metabolic pathways with the potential to produce products that either produce genotoxic events or impair the activity of HR repair mechanisms.

(3) Next steps for identifying pharmacological agents that promote HDR deficiency (HRD) and that enhance the effects of genotoxic drugs and PARPi. We will continue to follow the work plan and screen specific drugs and drug combinations that induce HRD – including synthetic androgens and SARMs. We will also evaluate drugs that alter metabolic pathways to produce products that alter HR repair, and that consequently have the capability to induce 'BRCAness'. We anticipate that such agents would produce synthetic lethality with genotoxic drugs and PARPi.

4. IMPACT

What was the impact on the development of the principle disciplines of the project?

(1) We have developed a new assay, termed OncoplexHRD, that represents a read-out of functional HDR-D. This assay is suitable for tissue based analyses or circulating tumor DNA (ctDNA);

(2) We developed a composite assays for functional HDR-D that incorporates mutation signatures – termed iHRD, and demonstrated strong associations with responses to platinum chemotherapy and PARPi;

(3) We determined that inherited mutations in DNA repair genes are rare in men with low risk prostate cancer;

(4) We determined that TP53 is an inherited prostate cancer predisposition gene, and that TP53 can influence metrics usually associated with HDR-D such as LOH scores;

(5) We determined that aggressive prostate cancers with BRCA2 loss exhibiting neuroendocrine features respond to PARPi, concordant with typical adenocarcinomas with HDR-D;

(6) We confirmed that HR gene mutations ascertained in analyses of primary prostate cancers are generally concordant with events identified in metastatic biopsies or ctDNA – confirming that primary tumors can serve as a relevant source for ascertaining HDR-D status and allocating appropriate treatment;

(7) We identified a pattern of structural DNA alterations that associate with HDR-D, adding an additional parameter for clinical testing for determining HDR-D in patients.

What was the impact on other disciplines?
Nothing to report

What was the impact on technology transfer?
Nothing to report

What was the impact on society beyond science and technology?
Nothing to report

5. CHANGES/PROBLEMS:
Changes in approach and reasons for change: Nothing to report.
Actual or anticipated problems or delays and actions or plans to resolve them: Nothing to report.

6. PRODUCTS:

Publications, conference papers, and presentations

Publications.
De Sarkar N, Dasgupta S, Chatterjee P, Coleman I, Ha G, Ang LS, Kohlbrenner EA, Frank SB, Nunez TA, Salipante SJ, Corey E, Morrissey C, Van Allen E, Schweizer MT, Haffner MC, Patel R, Hanratty B, Lucas JM, Dumpit RF, Pritchard CC, Montgomery RB, Nelson PS. Genomic attributes of homology-directed DNA repair deficiency in metastatic prostate cancer. JCI Insight; 6:2021; 23:e152789.
Acknowledgement of federal support (yes).

Brady L, Newcomb LF, Zhu K, Zheng Y, Boyer H, Sarkar N, McKenney JK, Brooks JD, Carroll PR, Dash A, Ellis WJ, Filson CP, Gleave ME, Liss MA, Martin F, Morgan TM, Thompson IM, Wagner AA, Pritchard CC, Lin DW, Nelson PS. Germline mutations in penetrant cancer predisposition genes are rare in men with prostate cancer selecting active surveillance. Cancer Med. 2022; 10.1002/cam4.4778. PMID: 35467778.
Acknowledgement of federal support (yes).

Maxwell KN, Cheng HH, Powers J, Gulati R, Ledet EM, Morrison C, Le A, Hausler R, Stopfer J, Hyman S, Kohlmann W, Naumer A, Vagher J, Greenberg SE, Naylor L, Laurino M, Konnick EQ, Shirts BH, AlDubayan SH, Van Allen EM, Nguyen B, Vijai J, Abida W, Carlo MI, Dubard-Gault M, Lee DJ, Maese LD, Mandelker D, Montgomery B, Morris MJ, Nicolosi P, Nussbaum RL, Schwartz LE, Stadler Z, Garber JE, Offit K, Schiffman JD, Nelson PS, Sartor O, Walsh MF, and Pritchard CC. Inherited *TP53* Variants and Risk of Prostate Cancer. Eur Urol. 81:2022; 243-250.
Acknowledgement of federal support (yes).

Patel RA, Coleman I, Roudier MP, Konnick EQ, Hanratty B, Dumpit R, Lucas JM, Ang LS, Low JY, Tretiakova MS, Ha G, Lee JK, True LD, De Marzo AM, Nelson PS, Morrissey C, Pritchard CC, Haffner MC. Comprehensive assessment of anaplastic lymphoma kinase in localized and metastatic prostate cancer reveals targetable alterations. Cancer Res Commun. 2:2022; 277-285.
Acknowledgement of federal support (yes).

Symonds L, Konnick E, Vakar-Lopez F, Cheng HH, Schweizer MT, Nelson PS, Pritchard CC, Montgomery B. *BRCA2* Alterations in Neuroendocrine/Small-Cell Carcinoma Prostate Cancer: A Case Series. JCO Precis Oncol. 2022; doi: 10.1200/PO.22.00091. PMID: 35834759.
Acknowledgement of federal support (yes).

Schweizer MT, Sivakumar S, Tukachinsky H, Coleman I, De Sarkar N, Yu EY, Konnick EQ, Nelson PS, Pritchard CC, Montgomery B. Concordance of DNA Repair Gene Mutations in Paired Primary Prostate Cancer Samples and Metastatic Tissue or Cell-Free DNA. JAMA Oncology; 7:2021; 1-5.
Acknowledgement of federal support (yes).

Zhou M, Ko M, Hoge AC, Luu K, Liu Y, Russell ML, Hannon WW, Zhang Z, Carrot-Zhang J, Beroukhim R, Van Allen EM, Choudhury AD, Nelson PS, Freedman ML, Taplin ME, Meyerson M, Viswanathan SR, Ha G. Patterns of structural variation define prostate cancer across disease states. JCI Insight. 2022 Sep 8;7(17):e161370. PMID: 35943799.
Acknowledgement of federal support (yes).

Presentations.
Peter Nelson: Cancer Therapy Resistance: Mechanisms, Challenges, and Opportunities. David Gandara Lectureship,
UC Davis Cancer Center. Davis, CA 10/2021

Peter Nelson: Cancer Therapy Resistance: Anticipating and Targeting New Species Evolving Through Treatment
Pressures. Sylvester Cancer Center, University of Miami. Miami, FL 12/2021

Peter Nelson: The genotypic and phenotypic heterogeneity of metastatic neuroendocrine prostate cancer. Forbeck
Symposium on Neuroendocrine Cancers. Asilomar, CA 3/2022.

Website(s) or other Internet site(s)
Nothing to Report.

Technologies or techniques
Nothing to report.
Inventions, patent applications, and/or licenses
Nothing to Report

Other Products
Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	**Peter S. Nelson, MD**
Project Role:	Principal Investigator
Nearest person month worked:	2
Contribution to Project:	Dr. Nelson provided oversight and direction for the entire project. His research effort was primarily devoted toward: (i) assisting Dr. Pritchard with biospecimen acquisition for OncoPlexHRD evaluation; (ii) interpreting results of OncoPlexHRD in the context of clinical outcomes to PARPi and PLAT; (iii) managing trainees and staff conducting the preclinical in vitro and in vivo studies of HDR deficiency; (iv) designing and interpreting experiments; (v) analyzing data; (vi) disseminating research findings through scientific presentations and manuscripts; (vii) managing the fiscal and regulatory components of the project. Dr. Nelson also works closely with collaborator Drs. Haffner and Etzioni.
Funding Support:	P50 CA097186, P01 CA163227, R01 CA234715, PC200262 (this award), PC200608, R01 CA266452, Institutional Support

Name:	**Ruth D. Etzioni, PhD**

Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to Project: Dr. Etzioni assisted in designing statistically-powered experiments and will analyze the results of molecular profiling data and pharmacological studies using preclinical models and with analyses performed on biospecimens evaluating PARPi and PLAT responses in the context of OncoPlexHRD biomarker status.
Funding Support: UH3 CA218909, P50 CA097186, U01 CA253915, PC200262 (this award), U24 CA086368, 75D30122C13505, R35 CA274442

Name: **Michael Haffner, MD, PhD**
Project Role: Other Significant Contributor
Nearest person month worked: No effort
Contribution to Project: Dr. Haffner has provided his expertise as a urologic pathologist who provides pathology review for the clinical samples.
Funding Support: PC190137, R01 CA234715-01A1, PC200608, PC200334, PC210181, PC210387, Doris Duke Foundation, V Foundation, Brotman Baty Institute

Name: **Ilsa Coleman**
Project Role: Research Scientist
Nearest person month worked: 1
Contribution to Project: Ms. Coleman assisted with experiments and procedures that involve preparing libraries for NextGen sequencing and primarily focus on analyzing sequencing data including gene expression levels (RNAseq), single cell RNAseq, pathway analyses, mutation assessments and CNV analysis. She also provided biostatistical support and worked closely with Dr. Etzioni.
Funding Support: P01 CA163227; P50 CA097186; R01 CA234715; R01 CA266452; R01 CA249528

Name: **Jared Lucas**
Project Role: Staff Scientist
Nearest person month worked: 1
Contribution to Project: Dr. Lucas provided expertise in cell culture and modifications to cell lines/model systems. He also assisted with measurements of gene expression in the preclinical models.
Funding Support: PC200262 (this award); P50 CA097186; R01 CA234715

Name: **Lisa Ang, PhD**
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Dr. Ang provided expertise in the acquisition and maintenance of prostate cancer xenografts.
Funding Support: PC200262 (this award); P01 Balk 224273, R01 Nelson 225577

Name: **Ruth Dumpit**
Project Role: Research Technician
Nearest person month worked: 1
Contribution to Project: Ms. Dumpit purified nucleic acids from tumors, assisted with

	confirmatory assays of molecular abberations in human metastases, isolated ctDNA and performed IHC assays.
Funding Support:	P01 CA163227; P50 CA097186; PC171001; PC170503; PC180550; PCF 19CHAS02; Institutional funds.

Name:	**Marc Villanueva Martinez**
Project Role:	Laboratory Assistant
Nearest person month worked:	6
Contribution to Project:	Mr. Martinez assisted with cell cultures and DNA/RNA/protein purifications.
Funding Support:	PC200262 (this award)

Name:	**Talina Asis Nunez**
Project Role:	Research Technician
Nearest person month worked:	2
Contribution to Project:	Ms. Nunez provided expertise in the acquisition and maintenance of prostate cancer xenografts
Funding Support:	PC200262 (this award)

Name:	**Yong Tao**
Project Role:	Post-Doctoral Fellow
Nearest person month worked:	4
Contribution to Project:	Dr. Tao provided expertise in cell culture and modifications to cell lines/model systems. He also assisted with measurements of gene expression in the preclinical models and measurements of DNA damage.
Funding Support:	PC200262 (this award)

Name:	**Reza Alizadeh Ghodsi**
Project Role:	Post-Doctoral Fellow
Nearest person month worked:	2
Contribution to Project:	Dr. Ghodsi provided expertise in measurements of gene expression by qRTPCR and immunoblotting in the preclinical models.
Funding Support:	PC200262 (this award)

Name:	**Tony Lok Heng Chu**
Project Role:	Post-Doctoral Fellow
Nearest person month worked:	1
Contribution to Project:	Dr. Chu provided expertise in cell culture and modifications to cell lines/model systems. He also assisted with the generation of DNA repair gene mutations and measurements of gene expression in the preclinical models.
Funding Support:	PC200262 (this 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?

Please find Previous/Current/Pending Support attached for Dr. Peter Nelson and Ruth Etzioni.

What other organizations were involved as partners?

There is one other organization involved with this project, University of Washington, Award #W81XWH-21-1-0264-P1

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:
This is a collaborative award between Dr. Peter Nelson at the Fred Hutchinson Cancer Center and Dr. Colin Pritchard at the University of Washington. Dr. Pritchard will submit the same overall SOW and research results that reflect the research outcomes in Y1 for this collaborative award.

QUAD CHART: Attached

9. APPENDICES:
None

DEFINING AND MODULATING BRCAness TO IMPROVE THE PRECISION OF PROSTATE CANCER THERAPY

PC200262

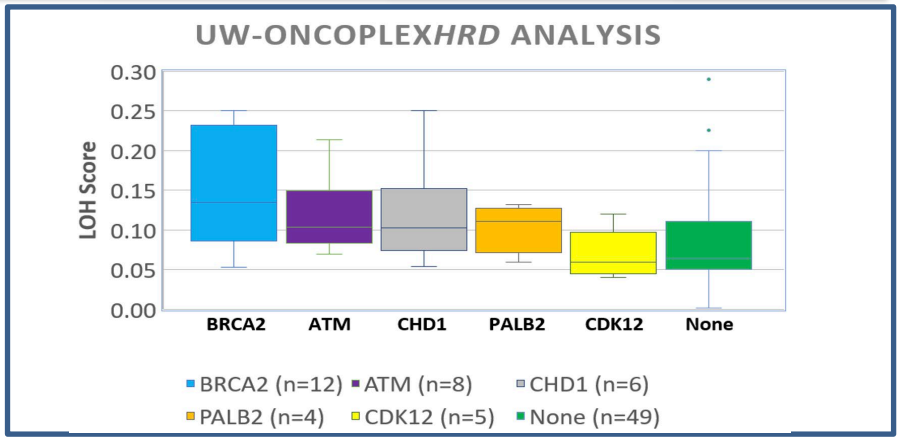
PI: Peter S. Nelson, MD **Org: Fred Hutchinson Cancer Center** **Award Amount:** $1,125,843

Study/Product Aim(s)

AIM 1. Develop and test clinical grade assays that define prostate cancers with functional homology directed DNA repair deficiency to improve sensitivity and specificity relative to HR gene mutations.
AIM 2. Identify specific combinations of DNA repair gene and metabolic parameters that confer functional homology directed DNA repair deficiency.
AIM 3. Identify pharmacological agents that promote HDR deficiency (HRD) and that enhance the effects of genotoxic drugs and PARPi

Approach

The research strategy for this proposal involves the development and testing of a clinical grade assay for defining tumors with DNA repair defects; the use of preclinical model systems to identify molecular mechanisms contributing to HRD; and the assessment of therapeutic strategies that exploit HRD.



Accomplishment: OncoPlexHRD results according to underling HRR gene mutation. Excluded from this box boxplot graph are cases with fewer than 4 samples (CHEK2 n=3, BRCA1 n=2, FANCA n=2, BRIP1 n=1, BAP1 n=1, RAD51B n=1, FANCD2 n=2).

Timeline and Cost

	Project Year		
Activities	**1**	**2**	**3**
Develop + Validate Oncoplex HRD			
Identify HR pathways in prostate ca			
Identify drugs targeting HR			
Publications and Final Report			
Estimated Budget	**$373,331**	**$370,096**	**$382,416**

Updated: (08/01/2021-07/31/2022)

Goals/Milestones

CY21 Goals – System demonstration
☑ Develop a prototype HRD assay (OncoplexHRD)
☑ Identify molecular contributors to HRD in prostate cancers
CY22 Goals – System validation
-Validate OncoplexHRD on clinical samples in ongoing studies
-Identify molecular and drug combinations that exploit HRD
CY23 Goals – Production readiness
-Validate molecular combinations that confer HRD including metabolic pathways and variation in metabolic products
-Validate drugs and drug combinations that exploit HRD

Comments/Challenges/Issues/Concerns

- None

Budget Expenditure to Date (07/31/2022)
Projected Expenditure: $373,331
Actual Expenditure: $464,225

PC200262: Defining and Modulating BRCAness to Improve the Precision of Prostate Cancer Therapy

PI: Peter S. Nelson; Fred Hutchinson Cancer Center; WA

Budget: $1,125,843

Topic Area: Prostate Cancer Research Program

Mechanism: TSA

Award Status: 8/1/2021 – 7/31/2024

Study Goals:

Purpose: This proposal is focused on exploiting a specific subtype of metastatic CRPC, termed *Homology Directed DNA Repair Deficient* (HDR-D) prostate cancer (PC) to enhance treatment outcomes, reduce morbidity and improve survival. HDR-D represents at least 20% of metastatic PC and is most commonly identified through the genomic analysis of biopsies from metastatic tumors and identifying mutations in *BRCA1*, *BRCA2* and related genes.

Scope: This proposal is designed to address two challenges: First, to improve the accuracy of detecting PCs with functional HDR-D for appropriate treatment allocation. It is clear from prospective studies that simply evaluating the mutation status of HDR-associated genes lacks precision for predicting treatment responses: a high percentage (>50%) of biomarker 'positive' patients fail to respond. Second, to increase the number of men with PC that could benefit from therapeutics targeting HDR-D by promoting 'conditional haploinsufficiency' converting HDR-competent tumors to a 'BRCAness' phenotype.

Specific Aims:

SPECIFIC AIM 1. Develop and test clinical grade assays that define prostate cancers with functional homology directed DNA repair deficiency to improve sensitivity and specificity relative to HR gene mutations.

SPECIFIC AIM 2. Identify specific combinations of DNA repair gene and metabolic parameters that confer functional homology directed DNA repair deficiency.

SPECIFIC AIM 3. Identify pharmacological agents that promote HDR deficiency (HRD) and that enhance the effects of genotoxic drugs and PARPi

Key Accomplishments and Outcomes:

Publications: De Sarkar N et al JCI Insight; 6:2021; 23:e152789; Brady L et al Cancer Med. 2022; PMID: 35467778; Maxwell KN et al Eur Urol. 81:2022; 243-250. Patel RA et al Cancer Res Commun; Symonds L et al JCO Precis Oncol. PMID: 35834759. Schweizer MT et al JAMA Oncology; Zhou M et al JCI Insight. 2022 Sep 8;7(17):e161370. PMID: 35943799.

Patents: None.

Funding Obtained: None.

PREVIOUS / CURRENT / PENDING SUPPORT – NELSON, PETER S.

PREVIOUS SUPPORT

Title: *Resistance to Cancer Therapeutics Through Microenvironment Damage Responses*
Grant #: R01 CA165573
Time Commitments: 5% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Nicholas Mitrano
9609 Medical Center Drive
Room 2W348
Rockville, MD 20850
Performance Period: 03/01/2012 - 01/31/2018
Level of funding (direct costs):
Brief description of the project's goals:
To evaluate the concept that conventional cancer therapeutics modify the tumor microenvironment to enhance resistance to subsequent treatments, consequently promoting adverse cancer phenotypes.
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine the ability of specific paracrine-acting DNA-damage Secretory Program (DDSP) proteins (e.g. SPINK1) to modulate adverse tumor cell behaviors (e.g. therapy resistance) and determine the mechanism(s) by which they do so.
Aim 2: Determine the intracellular signal transduction programs that differentially modulate subsets of effector proteins comprising DDSP.
Aim 3: Determine the consistency of the DDSP across different tumor types and establish the temporal and cell type-specific variability of damage response programs.

Title: *Androgen Receptor Action in Castration Resistant Prostate Cancer*
Core A: Administrative / Clinical / Biostatistics Core
Grant #: P01 CA163227
Time Commitments: 5% effort
Supporting Agency: Beth Israel Deaconess Medical Center – NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Linda M.S. Fritze
330 Brookline Avenue
BR264
Boston, MA 02215-5491
Performance Period: 05/24/2013 - 04/30/2018
Level of funding (direct costs):
Brief description of the project's goals:
Support is limited to Dr. Nelson's effort.
Overlap with proposed research: None
List of specific aims: Not applicable.
inter-SPORE interactions.

Title: *Pacific Northwest Prostate Cancer SPORE*
Core A: Leadership and Administration

Grant #: P50 CA097186
Time Commitments: 7.6% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Renee Carruthers
9000 Rockville Pike
Bethesda, MD 20892
Performance Period: 09/17/2013 - 08/31/2018
Level of funding: (Core A)
Brief description of the project's goals:
The Leadership and Administrative Core (LAC) will serve to integrate and enhance the research conducted by the SPORE projects and cores, as well as the Career Development faculty and investigators supported through the Developmental Research Program, through the application of general administrative support and the facilitation of communication and data dissemination.
Overlap with proposed research: None
List of specific aims:
Aim 1: To provide oversight of all SPORE-activities involving the independent research projects, the Career Development Program (CDP), the Developmental Research Program (DRP), the shared resource cores, and the parent institutions.
Aim 2: To provide the organizational structure, based on a group of interacting committees, for supporting and evaluating the key objectives of the PNW SPORE.
Aim 3: To organize and coordinate forums for interactions of the Executive Committee, Internal Advisory Board, and External Advisory Board.
Aim 4: To provide efficient and effective fiscal management of **Grant** funds.
Aim 5: To communicate and consult with the NCI Project Officer(s) and staff in the preparation of required progress reports, publications lists, and regulatory documents.
Aim 6: To develop and maintain virtual mechanisms that efficiently facilitates multi-institutional intra- and inter-SPORE interactions.

Title: *Pacific Northwest Prostate Cancer SPORE*
Project 4: Clinical Development of Therapeutic Strategies Targeting Damage Responses in the Prostate Tumor Microenvironment
Grant #: P50 CA097186
Time Commitments: 7.6% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Renee Carruthers
9000 Rockville Pike
Bethesda, MD 20892
Performance Period: 09/17/2013 - 08/31/2018
Level of funding: (Project 4)
Brief description of the project's goals:
To determine whether inhibiting components of the microenvironment-derived DNA damage secretory program will enhance the responses of prostate tumors to commonly used genotoxic cancer treatments.
Overlap with proposed research: None
List of specific aims:
Aim 1: To evaluate the effects of inhibiting key regulators and effectors of the microenvironment DNA Damage Secretory Program on therapy responses in preclinical models of prostate cancer.
Aim 2: To conduct a Phase l-II trial evaluating the clinical effect of inhibiting master regulators and specific effectors of the DNA Damage Secretory Program in augmenting genotoxic chemotherapy in men with metastatic CRPC.

Title: *Developing PDX Models of Prostate Cancer for Use in Evaluating Novel Therapeutic Approaches*
Grant #: P50 CA097186-14S1
Time Commitments: 3.8% Effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Crystal Wolfrey
Office of **Grant**s Administration, NCI
9609 Medical Center Drive, Room #2W472
Bethesda, MD 20892
Performance Period: 09/01/2016 - 08/31/2018
Level of funding (direct costs):
Brief description of the project's goals:
This proposal is designed to address a major limitation in the development of effective therapeutics for advanced PC by generating PDX models representing the diverse genotypes and phenotypes found across the spectrum of advanced prostate cancer.
Overlap with proposed research: None
List of specific aims:
Aim 1: Develop and characterize new prostate cancer PDX models that can be used to test cancer therapies, including drug combinations and NCI-IND agents.
Aim 2: Test existing PDX models of prostate carcinoma against NCI-IND agents and agent combinations for tumor response, to integrate and analyze PDX molecular characteristics against response to therapeutic regimens, and to collaborate with NCI-funded investigators in the study of mechanisms of drug sensitivity and resistance.

Title: *Minimally-Invasive Assessments of Prostate Cancer Molecular Heterogeneity to Direct Precision Therapy*
Grant #: W81XWH-15-1-0430
Time Commitments: 7.6% Effort
Supporting Agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
Joshua D. McKean
USAMRAA
820 Chandler Street
Ft. Detrick, MD 21702
Performance Period: 09/01/2015 - 08/31/2018
Level of funding (direct costs):
Brief description of the project's goals:
This application focuses on the developing an accurate and minimally-invasive approach for evaluating the molecular composition of metastatic castration resistant prostate cancer (mCRPC).
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine the molecular identity and genomic diversity across the spectrum of metastasis found within individual men with CRPC. This aim will take advantage of a robust tissue acquisition necropsy (TAN) program where multiple metastasis are acquired from each patient.
Aim 2: Determine the genomic and gene expression states of individual circulating tumor cells (CTCs) acquired from the same men that will undergo a TAN procedure.
Aim 3: Compare the molecular alterations present in original untreated primary tumors with those alterations found in metastatic tumors and CTCs to assess how well an archival sample represents the spectrum of actionable targets found in metastatic prostate cancer.

Title: *Development of Precision Immunotherapy for Advanced Prostate Cancer*
Grant #: W81XWH-15-1-0562
Time Commitments: 7.6% effort
Supporting Agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
Joshua D. McKean
USAMRAA
820 Chandler Street
Ft. Detrick, MD 21702
Performance Period: 09/30/2015 - 09/29/2018
Level of funding (direct costs):
Brief description of the project's goals:
Long-term goal is to propel integration of the precision immunotherapy enabled by nanoparticle-mediated reprogramming T cells into the standard-of-care for the treatment of metastatic prostate cancer.
Overlap with proposed research: None
List of specific aims:
Aim 1: Establish that engineering T cells to express CARs recognizing multiple tumor subtypes improves their anticancer activity.
Aim 2: Measure the ability of injectable DNA nanocarriers to program CAR expression by host T cells.
Aim 3: Determine how some prostate cancer subtypes resist CAR-based T cell therapy, and identify novel targets expressed by them.

Title: *Non-Invasive Biomarkers for Diagnosing Clinically Significant Prostate Cancer*
Grant #: R01 CA181605
Time Commitments: 7.6% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Renee Carruthers
9000 Rockville Pike
Bethesda, MD 20892
Performance Period: 01/01/2014 - 12/31/2018
Level of funding (direct costs):
Brief description of the project's goals:
The goal of this proposal is to exploit distinct prostate cancer associated RNAs using quantitative urine assays and a multi-institutional longitudinal cohort of men managed by active surveillance with attendant biospecimens, pathological, and clinical data.
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine if PCA3 and TMPRSS2:ERG mRNA concentrations in urine associate with the presence or development of clinically-significant prostate cancer using longitudinal repeat assessment in men on Active Surveillance.
Aim 2: Evaluate a panel of long non-coding RNAs in tissue and urine for the detection of significant prostate cancer in men on Active Surveillance.
Aim 3: Define and evaluate a panel of Gleason Pattern-associated RNAs in tissue and urine for the detection of significant prostate cancer in men on Active Surveillance.

Title: *Androgen Receptor Action in Castration Resistant Prostate Cancer*
Project 1: Steroid Metabolism in Castration Resistant Prostate Cancer

Grant #: P01 CA163227
Time Commitments: 3.8% effort
Supporting Agency: Beth Israel Deaconess Medical Center – NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Linda M.S. Fritze
330 Brookline Avenue
BR264
Boston, MA 02215-5491
Performance Period: 05/24/2013 - 02/11/2019
Level of funding (direct costs):
Brief description of the project's goals:
To determine whether identification and subsequent inhibition of key ligand-generating mechanisms would reduce AR signaling, with potential substantially improved responses, reduced morbidity, and prolonged survival.
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine the contribution of steroid biosynthetic enzymes to the generation of intratumoral androgens and consequent tumor cell survival in CRPC.
Aim 2: Determine the mechanism(s) underlying the coordinate regulation of androgen biosynthetic enzymes and activation of the AR gene expression program in prostate cancers following androgen suppression.
Aim 3: Determine the therapeutic effectiveness of progressive inhibition of androgen metabolism and identify resistance mechanisms to metabolism-directed therapy in CRPC.

Title: *Determining and Exploiting Mechanisms of AR-Mediated Suppression of Cell Proliferation and Survival*
Grant #: R01 CA233863
Time Commitments: 10% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Crystal Wolfrey, 240-276-6277, wolfrey@mail.nih.gov
Performance Period: 09/01/2018 - 02/11/2023
Level of funding:
Brief description of the project's goals:
The objectives of the current proposal are to define the molecular pathway(s) by which SPA represses PC growth and activates senescence/apoptotic programs, and to identify the genomic and epigenomic cellular states that rewire the AR cistrome to respond to – or resist – high androgen concentrations.
Overlap with proposed research: There was significant overlap with the currently-funded (renewed) P01. Thus, this award was relinquished prior to acceptance of the P01 (CA163227-06A1).
List of specific aims:
Aim 1: Determine the primary mechanism(s) by which SPA represses CRPC.
Aim 2: Define the AR cistrome in prostate cancers reprogrammed by SPA and identify cooperating genes and pathways that are essential or suppressive of SPA effects.
Aim 3: Identify drug combinations that synergize with SPA to repress tumor growth and optimize the effects of AR agonism based on a mechanistic understanding of SPA-mediated growth arrest.

Title: *Selective Androgen Receptor Modulators for the Treatment of Prostate Cancer*
Grant #: R21 CA230138
Time Commitments: 10% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Terri Jarosik, 301-443-3858, tjarosik@mail.nih.gov

Performance Period: 07/11/2018 – 06/30/2020
Level of funding:
Brief description of the project's goals:
This proposal will evaluate the feasibility of using small molecule replacements for testosterone in the treatment of prostate cancer.
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine effects of non-steroidal AR agonists on AR activity in prostate cancer cells.
Aim 2: Determine whether non-steroidal AR agonists recapitulate the physiological and molecular changes associated with exposure to supraphysiological testosterone (SPT).
Aim 3: Determine anti-tumor efficacy of AR agonists and explore dynamic dosing strategies.

Title: *Targeting the Mechanisms Driving Double-Negative Basal-Like Prostate Cancer*
Grant #: W81XWH-17-1-0415
Time Commitments: 7.6% effort
Supporting Agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
Joshua McKean, 301-619-4046, Joshua.d.mckean3.civ@mail.mil
Performance Period: 08/01/2017 – 07/31/2020
Level of funding:
Brief description of the project's goals:
The objective of this proposal is to address the fundamental lack of knowledge concerning the biology underlying therapy-related DNPC in order to understand the key molecular mechanisms responsible for their genesis, behavior and response to treatment.
Overlap with proposed research: None
List of specific aims:
Aim 1: Identify survival and growth programs operative in DNPC though deep molecular profiling of metastatic tumors and PDX models.
Aim 2: Utilize engineered cell lines and PDX models to determine which specific molecular alterations observed in the human DNPC tumors cause AR-bypass and promote a DNPC phenotype.
Aim 3: Evaluate pharmacological agents targeting DNPC driver pathways that emerge following AR ablation to confirm anti-tumor effects and support further clinical evaluation.

Title: *Evaluating DNA Damage and DNA Repair Capacity as Biomarkers of Non-Indolent Prostate Cancer*
Grant #: PC171001
Time Commitments: 7.5% effort
Supporting Agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
DOD/CDMRP, help@ebrap.org; 301-682-5507
Performance Period: 08/01/2018 - 07/31/2021
Level of funding:
Brief description of the project's goals:
This proposal will test the hypothesis that subtypes of prostate cancer – defined by mutational processes and DNA repair deficiency – associate strongly with adverse prostate cancer characteristics including extra-prostatic spread, biochemical recurrence, and metastasis. We further hypothesize that these molecular characteristics can assist in further stratifying patients for less intensive or no further active monitoring or conversely, for immediate curative therapy.
Overlap with proposed research: None
List of specific aims:

Aim 1: Determine if DNA repair signatures and metrics of DNA damage associate with adverse reclassification and adverse pathology in men on active surveillance.
Aim 2: Determine if genomic signatures of DNA mutational processes associate with prostate cancer characteristics indicative of non-indolent behavior.
Aim 3: Determine if specific defects in specific genes involved in DNA repair are predictive of adverse prostate cancer outcomes.
**This project was previously listed as CURRENT*

Title: *The MSKCC-UW/Fred Hutch Prostate Cancer Drug Resistance and Sensitivity Center*
Grant #: U54 CA224079-S1
Time Commitments: 1% effort
Supporting Agency: MSKCC - NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Vincent Madonia, madoniav@mskcc.org
Performance Period: 12/1/2020 – 08/31/2021
Level of funding: (total costs)
Brief description of the project's goals:
In this supplement, the role of translational control in the context of resistance to AR pathway-directed therapeu-tics will be evaluated.
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine how alterations in mRNA translation initiation promote resistance to AR pathway directed therapies.
Aim 2: Delineate the translational gene networks that promote resistance to AR signaling inhibitors.
**This project was previously listed as CURRENT*

Title: *Therapeutic Strategies to Target Treatment-Resistant Merkel Cell Carcinoma (MCC) and Neuroendocrine Prostate Cancer (NEPC)*
Grant #: 19CHAL02
Time Commitments: 1% effort
Supporting Agency: Prostate Cancer Foundation
Name and address of the funding agency's procuring Contracting/Grants Officer:
Audrey Gardner, 1250 4th Street, Santa Monica, CA 90401 (audrey.gardner@pcf.org)
Performance Period: 01/01/2019 – 8/14/2021
Level of funding: /year (total costs)
Brief description of the project's goals:
This Challenge Award is designed to integrate the underlying biology of MCC and NEPC to identify or ex-pose tumor vulnerabilities to target the substantial number of treatment resistant MCCs and NEPC that contribute to high mortality rates for these aggressive cancers.
Overlap with proposed research: None
List of specific aims:
Aim 1: Identify mechanisms contributing to the resistance of MCC and NEPC to conventional and immune-based therapeutics.
Aim 2: Evaluate strategies to augment immune-based therapy of MCC and NEPC.
Aim 3: Identify combinations of therapeutics targeting lineage and survival pathways in MCC and NEPC that can be rapidly advanced to clinical trials.
**This project was previously listed as CURRENT*

Title: *Eradicating Metastatic Prostate Cancer through the Systematic Identification of Synergistic Drug Combinations*
Grant #: PC170431
Time Commitments: 1% effort
Supporting Agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
DOD/CDMRP, help@ebrap.org;
Performance Period: 08/01/2018 – 12/31/2021
Level of funding: Total Costs for the Award Period (Nelson Program only)
Brief description of the project's goals:
We will test the hypothesis that specific combinations of therapeutics can rapidly and completely eradicate subtypes of mPC, and that patient-derived xenografts (PDX) representing the diversity of molecular 'driver' aberrations found in human CRPC can be used to rapidly and systematically identify these potent drug combinations.
Overlap with proposed research: None
List of specific aims:
Aim 1: Conduct a systematic assessment of combination pharmacological therapy to eradicate CRPC using panels of PDX models that reflect the diversity of molecular aberrations found in mCRPC.
Aim 2: Identify molecular features (genotype/phenotype) of PDX responders to drug combination(s).
Aim 3: Establish an International consortium for evaluating and validating novel therapeutic combinations capable of eradicating CRPC.
**This project was previously listed as CURRENT*

Title: *Targeting the Subtype of Metastatic Prostate Cancer Deficient in DNA Repair Capacity*
Grant #: PC170503
Time Commitments: 1% effort
Supporting Agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
DOD/CDMRP, help@ebrap.org;
Performance Period: 08/15/2018 – 11/30/2021
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
This proposal will address the challenge of effectively treating mPC by exploiting specific tumor vulnerabilities conferred by defects in HR DNA repair.
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine if germ-line and somatic aberrations in homologous recombination DNA repair pathways associate with responses to FDA-approved therapeutics in men with mCRPC.
Aim 2: Develop minimally-invasive biomarkers capable of distinguishing patients for therapeutics targeting homologous recombination DNA repair pathways and ascertaining resistance mechanisms.
Aim 3: Identify rational drug combinations that exploit DNA repair vulnerabilities to eradicate prostate cancers with homologous recombination repair deficiency.
**This project was previously listed as CURRENT*

Title: *2021 cfDNA Award*
Grant #: No **Grant #**
Time Commitments: 0% effort
Supporting Agency: Brotman Baty Institute – University of Washington
Name and address of the funding agency's procuring Contracting/Grants Officer:
Nola Klemfuss, klemfuss@uw.edu

Performance Period: 03/01/2021 – 02/28/2022
Level of funding: No Funding (award in-kind)
Brief description of the project's goals:
We hypothesize a low pass whole-genome (LP_WGS) sequence data do is a substantial representation of high depth whole genome sequencing in retaining nucleosome and transcription factor binding genomic signatures. LP_WGS data can be reliably utilized in classifying epigenetic/phenotypic subtypes of prostate cancer. (DNPC, Amphicrine, NEPC and ARPC).
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine whether ctDNA inserts aligning to actively transcribing genes are consistently different than the inserts aligning to non-transcribing or repressed genes.
**This project was previously listed as CURRENT*

Title: *The MSKCC-UW/Fred Hutch Prostate Cancer Drug Resistance and Sensitivity Center*
Project 3: Defining the Appropriate Context for Targeting Kinase Signaling in Combination with Androgen Receptor Blockade to Enhance Therapeutic Response in Metastatic Prostate Cancer
Grant #: U54 CA224079
Time Commitments: 5% effort
Supporting Agency: MSKCC – NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
William Zurich
zuricihiw@mskc.org

MSKCC
633 3rd Avenue, 3rd Floor
NYC, NY 10017
Performance Period: 09/30/2017 – 08/31/2022
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
Our proposal aims to: 1) define biomarkers of intrinsic sensitivity and resistance to inform appropriate patient selection for combination therapy; 2) define the mechanisms of acquired resistance; 3) devise therapeutic strategies to overcome resistance; 4) optimize AR pathway targeting in the setting of PI3K pathway inhibition to maximize tumor response; and 5) explore the therapeutic role of FGFR in a novel subset of AR negative prostate cancers.
Overlap with proposed research: None
List of specific aims:
Aim 1: Identifying metastasis suppressors within skeletal muscle.
Aim 2: Reverse engineering growth resistance using rare tumor cells that successfully colonize skeletal muscle.
Aim 3: Delivering skeletal muscle derived factors to prevent colonization of metastasis prone organs.
**This project was previously listed as CURRENT*

Title: *Therapeutic Targeting of Neuroendocrine Prostate Cancer*
Grant #: PC170350P1
Time Commitments: 1% Y1; 0% effort Y2 (administrative effort only as subaward PI)
Supporting Agency: UW – DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
Kelly Sales, , ksales@seattlecca.org
Performance Period: 09/01/2020 – 08/31/2022
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:

Dr. Nelson's lab at the Fred Hutch Cancer Research Center (Fred Hutch) will provide bioinformatics expertise for the RNA-Seq data in Years 2 and 3 of the project. RNA will be isolated from patient-derived xenografts (PDX; n=75). Once the raw array data are acquired, Ms. Ilsa Coleman will use bioinformatic tools working with Drs. Lam and Morrissey to compare and assess treatment response and resistance to therapy in the PDX lines.
Overlap with proposed research: None
List of specific aims:
Not applicable – subaward.
**This project was previously listed as CURRENT*

Title: *3D Light-Sheet Microscopy: Identification and Molecular Characterization of Prostate Carcinoma with De Novo Resistant to Total Androgen Ablative Therapy*
Grant #: PC180686 / W81XWH-19-1-0589
Time Commitments: 1% effort
Supporting Agency: UW – DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
Mirelle Aziz, Program Operations Specialist, maziz@uw.edu
Performance Period: 08/15/2020 – 08/14/2022
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
Dr. Nelson will coordinate the RNA sequencing work to be performed by the Fred Hutch Genomics Core and participate in data analysis and interpretation. Additionally, he will oversee the work of Ms. Ilsa Coleman, Research Scientist, who will be designing and carrying out the activities outlined in all Aims 2 and 3 of the project.
Overlap with proposed research: None
List of specific aims:
Aim 1: To demonstrate improved sensitivity of OTLS-guided 3D microdissection, we will compare sequencing results using 3D microdissection versus slide-based methods.
Aim 2: To define the molecular landscape of PC response to neoadjuvant total AAT, we will sequence 3D microdissected residual carcinoma regions from RP specimens.
Aim 3: To better understand PC pathogenesis in response to neoadjuvant total AAT, we will sequence carcinoma regions from pre-treatment biopsies and post-treatment lymph node metastases.
**This project was previously listed as CURRENT*

CURRENT SUPPORT

Title: *Cancer Center Support Grant*
Grant #: P30 CA015704
Time Commitments: 5% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Michael A. Marino, PhD
9609 Medical Center Drive
Room 2W204
Rockville, MD 20850
Performance Period: 01/01/1997 - 12/31/2024
Level of funding (direct costs): Total Costs for the Award Period (Nelson Program only) **Brief description of the project's goals**:

The Cancer Center Support Grant provides funding for the infrastructure, shared resources, and other activities which promote interdisciplinary cancer research conducted within the Fred Hutchinson/University of Washington Cancer Consortium. Dr. Nelson's support is limited to his charged effort.
Overlap with proposed research: None
List of specific aims: Not applicable

Title: *Pacific Northwest Prostate Cancer SPORE*
Core A: Leadership and Administration
Grant #: P50 CA097186-21
Time Commitments: 10% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Renee Carruthers
9000 Rockville Pike
Bethesda, MD 20892
Performance Period: 09/01/2018 - 08/31/2023
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
The Leadership and Administrative Core (LAC) will serve to integrate and enhance the research conducted by the Pacific Northwest Prostate SPORE Projects and Cores – as well as the faculty supported through both the career Enhancement and Developmental Research Programs – through the application of general administrative support and the facilitation of communication and data dissemination.
Overlap with proposed research: None
List of specific aims:
Aim 1: To provide the organizational structure, based on a group of interacting committees, for supporting and evaluating the key objectives of the PNW SPORE.
Aim 2: To provide oversight of all SPORE activities involving the independent research projects, the Career Enhancement Program (CEP), the Developmental Research Program (DRP), the shared resource cores, and the parent institutions.
Aim 3: To organize and coordinate forums for interactions of the Executive Committee, Internal Advisory Board, and External Advisory Board.
Aim 4: To provide efficient and effective fiscal management of SPORE **Grant** funds.
Aim 5: To communicate and consult with the NCI Project Officer(s) and staff in the preparation of required progress reports, publications lists, and regulatory documents.
Aim 6: To develop and maintain virtual mechanisms that efficiently facilitate multi-institutional, intra- and inter-SPORE interactions.

Title: *Pacific Northwest Prostate Cancer SPORE*
Project 4: Clinical Development of Therapeutic Strategies Targeting DNA Damage Repair
Grant #: P50 CA097186-21
Time Commitments: 10% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Renee Carruthers
9000 Rockville Pike
Bethesda, MD 20892
Performance Period: 09/01/2018 - 08/31/2023
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:

Our studies will optimize SPT-based therapy, elucidate the mechanisms underlying responses to SPT, develop novel combinatorial SPT-based treatment strategies, and identify predictive biomarkers for response/resistance to SPT-based therapies.
Overlap with proposed research: None
List of specific aims:
Aim 1: Conduct in vitro and in vivo testing of combinatorial SPT-strategies to inhibit CRPC progression and evaluate mechanism of action.
Aim 2: Conduct a clinical trial to test alternative dosing schedules of SPT-based therapy and a trial to test combinatorial SPT-based therapy.
Aim 3: Identify mechanisms of SPT action, sensitivity and resistance, and biomarkers of responses.

Title: *Androgen Receptor Action in Castration Resistant Prostate Cancer*
Project 1: Determining and Exploiting Mechanisms of AR-Mediated Suppression of Cell Proliferation & Survival
Grant #: P01 CA163227-07
Time Commitments: 12.5% effort
Supporting Agency: Beth Israel Deaconess Medical Center – NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Renee Carruthers
9000 Rockville Pike
Bethesda, MD 20892
Performance Period: 02/12/2019 - 01/31/2024
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
The objective of this project is to identify mechanisms contributing to the activation and activity of androgen metabolic enzymes in castration resistant prostate cancer.
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine the primary mechanism(s) by which SPA represses CRPC.
Aim 2: Define the AR cistrome in prostate cancers reprogrammed by SPA and identify cooperating genes and pathways that are essential or suppressive of SPA effects.
Aim 3: Identify drug combinations that synergize with SPA to repress tumor growth and optimize the effects of AR agonism based on a mechanistic understanding of SPA-mediated growth arrest.

Title: *Defining and Targeting Lineage Transition Programs Operative in AR Pathway Independent Prostate Cancer*
Grant #: R01 CA234715-03
Time Commitments: 15% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Jason Gill, gilljas@mail.nih.gov
Performance Period: 08/15/2020 - 04/30/2025
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
We will test the hypothesis that AR Pathway-Independent Prostate Cancers (APIPC) activate – and are dependent upon – a limited set of specific survival and growth regulatory pathways that are regulated via de-repressed feedback loops and/or genetic/epigenetic alterations.
Overlap with proposed research: None
List of specific aims:
Aim 1: Target prostate cancer vulnerabilities exposed by resistance to AR-directed therapy.

Aim 2: Determine alterations in the prostate cancer epigenome resulting from AR pathway signaling inhibition that regulate druggable signaling programs driving survival and growth.
Aim 3: Develop co-targeting strategies directed toward permissive epigenomic regulators and deterministic features associated with prostate cancer cell lineage.

Title: *Defining and Modulating BRCAness to Improve the Precision of Prostate Cancer Therapy*
Grant #: PC200262
Time Commitments: 12.5% Y1, 10% Y2-3
Supporting Agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
Joshua D. McKean, joshua.d.mckean3.civ@mail.mil
Performance Period: 08/01/2021 – 07/31/2024
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
This proposal is designed to address two challenges: First, improve the accuracy of detecting prostate cancers with HDR defects for appropriate treatment allocation. Second, to increase the number of men with metastatic prostate cancer that could benefit from therapeutics that target DNA repair deficiency be converting partially sensitive tumors into fully-sensitive tumors; that is, generating a 'BRCAness'phenotype.
Overlap with proposed research: None
List of specific aims:
Aim 1: Develop and test clinical grade assays that define prostate cancers with functional homology directed DNA repair deficiency to improve sensitivity and specificity relative to HR gene mutations.
Aim 2: Identify specific combinations of DNA repair gene and metabolic parameters that confer functional homology directed DNA repair deficiency.
Aim 3: Identify pharmacological agents that promote HRR-D and that enhance the effects of genotoxic drugs and PARPi.
[THIS AWARD]

Title: *Defining and Targeting the DNA Hypomethylation Phenotype in Advanced Prostate Cancer*
Grant #: PC200608 / W81XWH-21-1-0229
Time Commitments: 1% effort
Supporting Agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
Joshua McKean, **Grant**s Officer, joshua.d.mckean3.civ@mail.mil
Performance Period: 07/01/2021 – 06/30/2024
Level of funding: Total Costs for the Award Period, Nelson Lab)
Brief description of the project's goals:
Dr. Nelson will contribute next generation sequencing data of LuCaP patient derived xenografts and rapid autopsy samples. He will also share novel cell line models derived from LuCaP xenografts with Dr. Haffner. In addition, he will provide guidance as the project evolves and will meet with Dr. Haffner on a quarterly basis to discuss the results, assess progress and provide assistance when needed.
Overlap with proposed research: None
List of specific aims:
Aim 1: Establish the prevalence, clinical associations and patterns of DNA hypomethylation in PC.
Aim 2: Determine the biological consequences of global DNA hypomethylation in PC.
Aim 3: Define tumor cell intrinsic targetable vulnerabilities in DHMPC.
**This project has been added to Dr. Nelson's OS*

Title: *Targeting Vulnerabilities Exposed by Cancer Treatment-Induced Lineage Plasticity*

Grant #: R01 CA266452-01
Time Commitments: 15% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Jacquelyn Saval, savalj@mail.nih.gov,
Performance Period: 07/01/2022 – 06/30/2027
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
Dr. Nelson will provide oversight and direction for the research plan which involves defining mechanisms driving treatment-associated lineage switching and developing therapeutic strategies that can be rapidly translated for clinical evaluation. Dr. Nelson will also supervise the PDX studies, bioinformatics analyses and interactions with clinical colleagues involving access to novel therapeutics and clinical trial designs that exploit findings from the planned preclinical work.
Overlap with proposed research: None
List of specific aims:
Aim 1: Identify the key determinants and permissive factors that promote a lineage switch from conventional ARdriven.
prostate cancer to new phenotypes following AR-directed treatment.
Aim 2: Determine if modulating factors that drive or permit lineage specification can prevent, delay, or reverse resistance to AR pathway inhibition.
Aim 3: Determine if co-targeting characteristics of re-directed lineages that emerge in the context of lineage switching will prolong responses to AR pathway inhibition.
**This project was previously listed as PENDING is now CURRENT*

PENDING SUPPORT

Title: *A Prostate Cancer Dependency Map to Identify Tumor Subtype-Specific Vulnerabilities*
Grant #: R21 CA277368-01 (currently in JIT status)
Time Commitments: 10% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
To Be Determined
Performance Period: 12/01/2022 – 11/30/2024
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
Dr. Nelson will provide oversight and direction for the research plan which involves defining mechanisms driving treatment-associated lineage switching and developing therapeutic strategies that can be rapidly translated for clinical evaluation. Dr. Nelson will also supervise the PDX studies, bioinformatics analyses and interactions with clinical colleagues involving access to novel therapeutics and clinical trial designs that exploit findings from the planned preclinical work.
Overlap with proposed research: None
List of specific aims:
Aim 1: Conduct genome-wide loss-of-function genetic screens in novel and existing models of mPC to develop a PC dependency map.
Aim 2: Conduct in vitro drug screens of approved agents and those in developmental pipelines in new and existing models of mPC and integrate responses with PC dependency map data.
Aim 3: Validate synthetic lethal/collateral lethal responses observed in the cell line screens using in vivo patient derived xenograft (PDX) models to confirm responses and support clinical advancement. _

Title: *Pacific Northwest Prostate Cancer SPORE*
Core A: Leadership and Administration
Grant #: P50 CA097186-22
Time Commitments: 10% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Renee Carruthers
9000 Rockville Pike
Bethesda, MD 20892
Performance Period: 09/01/2023 - 08/31/2028
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
The Leadership and Administrative Core (LAC) will serve to integrate and enhance the research conducted by the Pacific Northwest Prostate SPORE Projects and Cores – as well as the Career Enhancement faculty, and investigators supported through the Developmental Research Programs – through the application of general administrative support and the facilitation of communication and data dissemination.
Overlap with proposed research: None
List of specific aims:
Aim 1: To provide the organizational structure, based on a group of interacting committees and working groups, for supporting and evaluating the key objectives of the PNW SPORE, which are to:

- Conduct innovative and high-impact translational science;
- Provide opportunities for the development of novel early phase ideas or hypotheses;
- Provide opportunities for career development in prostate cancer translational research;
- Engage patient advocates in the promotion of prostate cancer research and treatment; and,
- Educate scientists, clinicians, and the lay public.

Aim 2: To provide oversight of all SPORE activities involving the independent research projects, the Career Enhancement Program (CEP), the Developmental Research Program (DRP), the shared resource cores, and the four parent institutions: Fred Hutchinson Cancer Center (FHCC), the University of Washington (UW) (and affiliated Veterans Affairs Puget Sound Health Care System (VAPSHCS)), the Oregon Health and Sciences University (OHSU), and the University of British Columbia / Prostate Centre at Vancouver General Hospital (UBC/VGH).
Aim 3: To organize and coordinate forums for interactions of the Executive Committee, Internal Advisory Board, and External Advisory Board.
Aim 4: To provide efficient and effective fiscal management of **Grant** funds, including **Grant** disbursements, record-keeping, and coordination of equipment and supply purchasing; and to provide rigorous record-keeping for and compliance with governmental, NIH, NCI, and institutional regulations and requirements, including Radiation Safety, Animal Care, and Protection of Human Subjects.
Aim 5: To communicate and consult with the NCI Project Officer(s) and staff in the preparation of required progress reports, publications lists, and regulatory documents.
Aim 6: To develop and maintain virtual mechanisms that facilitate efficient multi-institutional intra- and inter-SPORE interactions. These include the maintenance of a PNW Prostate Cancer SPORE website, and the organization of on-site and video 'face-to-face' meetings across the institutions of the SPORE investigators.

Title: *Pacific Northwest Prostate Cancer SPORE*
Project 4: Clinical Development of Therapeutic Strategies Targeting DNA Damage Repair
Grant #: P50 CA097186-22
Time Commitments: 10% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Renee Carruthers
9000 Rockville Pike

Bethesda, MD 20892
Performance Period: 09/01/2023 - 08/31/2028
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
In this proposal, our objective is to integrate and leverage two key aspects of PC biology: AR activity and DNA damage/repair. Integrating AR signaling and HR repair has important treatment ramifications as a substantial body of preclinical and clinical work indicates that HR deficiency (HRd) result in vulnerabilities to at least two drug classes: platinum (PLAT) chemotherapy and PARP inhibitors (PARPi).
Overlap with proposed research: None
List of specific aims:
Aim 1: Conduct a Phase 2 clinical trial combining genotoxic therapeutics and supraphysiological androgen (SPA) in patients with mCRPC to determine response rates, identify resistance mechanisms, and establish biomarkers that associate with clinical responses.
Aim 2: Identify the mechanism(s) by which therapeutics overdriving AR activity induce DNA damage, regulate DNA repair processes, and enhance genotoxic chemotherapy.
Aim 3: Identify therapeutic drug combinations and dosing/administration strategies that optimize the therapeutic window resulting from AR expression and activity in mCRPC.

Title: *Combinatorial ADC Therapy to Overcome Mechanisms Driving Acquired Prostate Cancer Treatment Resistance*
Grant #: PC220577 / W81XWH-22-PCRP-TSA
Time Commitments: 10% effort
Supporting Agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
To Be Determined
Performance Period: 04/01/2023 – 03/31/2026
Level of funding: Total Costs for the Award Period
Brief description of the project's goals:
The overall objective is to demonstrate that combinations of different antibodies carrying different (complementary) drugs can effectively eliminate complex treatment resistant prostate cancers, with minimal side-effects on the host. A second objective is to identify optimal combinations of targets in men with advanced prostate cancer – and use these targets to design the optimal ADC combinations.
Overlap with proposed research: None
List of specific aims:
Aim 1: Exploit the specificity of ADC therapy for eradicating metastatic prostate cancers of specific phenotypes using a gated drug delivery strategy to maximize the therapeutic window.
Aim 2: To determine the effectiveness of combinatorial antibody drug conjugate (ADC) therapy in eradicating metastatic prostate cancers comprised of heterogeneous phenotypes.
Aim 3: To determine response and resistance mechanisms operative in vivo to ADC therapeutics

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Title: *Evaluating Prostate Cancer Phenotype and Genotype Classification from Circulating Tumor DNA as Biomarkers for Predicting Treatment Outcomes*
Grant #: R01 CA280056-01
Time Commitments: 10% effort
Supporting Agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
To Be Determined
Performance Period: 4/01/2023 – 3/31/2028
Level of funding:Total Costs for the Award Period

Brief description of the project's goals: The overall objective is to test the hypothesis that nucleosome profiling of ctDNA can be used to classify mixed CRPC phenotypes by capturing intra-tumor or inter-tumor phenotype heterogeneity within mCPRC patients. The aims will also test the hypothesis that ctDNA nucleosome profiling can be used to predict treatment outcomes for patients receiving standard and new targeted therapies.
Overlap with proposed research: None
List of specific aims:
Aim 1: Develop ctDNA classifiers that distinguish prostate cancer phenotypes.
Aim 2: Evaluate ctDNA classifiers for assessing phenotype heterogeneity in men with mCRPC.
Aim 3: Determine the utility of ctDNA for predicting prostate cancer treatment outcomes.

OVERLAP
There exists neither scientific nor budgetary overlap. Should pending application be funded, effort will not exceed 100%.

POSITIONS AND SCIENTIFIC APPOINTMENTS RELEVANT TO THIS PROPOSAL
None

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge.

Signature: Peter S. Nelson, MD Digitally signed by Peter S. Nelson, MD Date: 2022.12.08 20:50:32 -08'00'

Date: 12/8/2022

PREVIOUS, CURRENT AND PENDING SUPPORT – ETZIONI, RUTH D.

PREVIOUS SUPPORT

Title: *Modeling to Minimize Detection Bias in Cancer Risk Prediction Studies*
Grant #: R01CA242735
Time commitments: 15% effort
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Jacquelyn Saval, Grants Management Specialist, savalj@mail.nih.gov,
Performance Period: 09/19/19 – 08/31/22
Level of funding (direct costs):
Brief description of the project's goals:
This application will develop methods that will help people understand how common risk factors like family history and breast density affect their risk of getting cancer rather than their risk of getting a cancer diagnosis.
Overlap with proposed research: None
List of specific aims:
Aim 1: Develop and validate a cancer modeling method for assessing and reducing detection bias in risk prediction studies based on screened populations.
Aim 2: Apply the method developed in Aim 1 to assess and remediate any detection bias in published associations between breast density and breast cancer risk.
Aim 3: Develop, test, and deploy an online user interface that will permit investigators conducting cancer risk prediction studies in screened populations to assess their susceptibility to detection bias.
Aim 4: Assess the impact of detection bias on harm-benefit tradeoffs of candidate prostate cancer screening policies as a proof of concept for the translation of detection bias to the policy setting.
**This project was previously listed as CURRENT*

Title: *Defining and Targeting Lineage Transition Programs Operative in AR Pathway Independent Prostate Cancer*
Grant #: R01 CA234715-01A1
Time commitments: 5% effort
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Jason Gill, gilljas@mail.nih.gov
Performance Period: 08/15/2020 – 04/30/2025 (effort ended 4/30/22)
Level of funding:
Brief description of the project's goals:
We will test the hypothesis that AR Pathway-Independent Prostate Cancers (APIPC) activate – and are dependent upon – a limited set of specific survival and growth regulatory pathways that are regulated via de-repressed feedback loops and/or genetic/epigenetic alterations.
Overlap with proposed research: None
List of specific aims:
Aim 1: Target prostate cancer vulnerabilities exposed by resistance to AR-directed therapy.
Aim 2: Determine alterations in the prostate cancer epigenome resulting from AR pathway signaling inhibition that regulate druggable signaling programs driving survival and growth.
Aim 3: Develop co-targeting strategies directed toward permissive epigenomic regulators and deterministic features associated with prostate cancer cell lineage.
**This project was previously listed as CURRENT*

Title: *Modeling to Improve Prostate Cancer Outcomes Across Diverse Populations*
Grant #: 5U01CA199338
Time commitments: 4%
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Ashley Salo
BG 9609 RM 2W554, 9609 Medical Center Dr., Rockville, MD 20850
Performance Period: 09/01/15 – 08/31/21
Level of funding:
Brief description of the project's goals:
This work will advance the evidence necessary to make informed decisions about screening and treatment for prostate cancer. The objective of this research is to examine efficiency gains of screening only high-risk individuals, benefits of avoiding or delaying treatment for low-risk cancers, and feasible approaches for reducing racial disparities.
Overlap with proposed research: None
List of specific aims:
Aim 1. Identify active surveillance strategies that minimize patient burden without increasing risks of progression to non-curable disease or death. *Area 9: Cancer-specific opportunities.*
Aim 2. Develop stratified approaches to prostate cancer screening that target high-risk men based on poly-genic risk and baseline PSA at age 45. *Area 1: Exploring the evolving potential of stratification.*
Aim 3. Model secondary treatment strategies, their impact on primary treatment decisions, and implications for population prostate cancer control. *Area 3: Understanding screening and treatment in real-world settings and determining routes to optimize the process.*
Aim 4. Determine whether racial disparities in prostate cancer mortality can be reduced by using stratified screening and treatment strategies. *Area 8: Suggesting routes to reduce health disparities.*
Aim 5. Modularize models to evaluate cancer control programs in non-US populations, including low-resource countries, and collaborate with investigators in the UK and the Caribbean to develop policies that are tailored to their populations and resources. *Area 2: State, local, and international cancer control planning.*
Aim 6. Develop online calculators to support patient-physician decisions and policy-maker deliberations about PSA screening and treatment for localized prostate cancer. *Area 4: Assisting in the development of decision support tools.*
**This project was previously listed as CURRENT*

Title: *Partnership for the Advancement of Cancer Research: NMSU-FHCRC (2 of 2)*
Pilot Project 1: Risk of cancer versus risk of cancer diagnosis? Accounting for diagnostic bias in predictions of breast cancer risk by race/ethnicity and breast density
Grant #: U54CA132381
Time commitments: 10% effort
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Carol Perry, perryc@mail.nih.gov
Performance Period: 09/01/18 - 08/31/21
Level of funding:
Brief description of the project's goals:
The overall goal of this collaboration between New Mexico State University (NMSU), a minority-serving institution, and the Fred Hutchinson Cancer Research Center (FHCRC), a comprehensive cancer center, is to expand our current regional cancer program to increase knowledge and attention to cancer-related health disparities among disadvantaged populations. The pilot project aims to investigate the impact of racial/ethnic disparities in screening and biopsy utilization on risk factor-breast cancer associations in the risk prediction

setting, using simulation modeling techniques.
Overlap with proposed research: None
List of specific aims: (for the pilot project)
1. Investigate how patterns of screening and biopsy referral vary by categories of race/ethnicity and breast density.
2. Develop and calibrate a model of breast cancer natural history to BCSC screen- and interval-detected cancer incidence by race/ethnicity and breast density.
3. Determine how the dependence of breast cancer risk on race/ethnicity and breast density would change if screening and biopsy utilization were similar across risk groups.

**This project was previously listed as CURRENT*

Title: *Targeting the Subtype of Metastatic Prostate Cancer Deficient in DNA Repair Capacity*
Grant #: PC170503
Time commitments: 3% effort
Supporting agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
DOD/CDMRP, help@ebrap.org;
Performance Period: 08/01/18 - 07/31/21
Level of funding:
Brief description of the project's goals:
This proposal will address the challenge of effectively treating mPC by exploiting specific tumor vulnerabilities conferred by defects in HR DNA repair.
Overlap with proposed research: None
List of specific aims:
Aim 1: Determine if germline and somatic aberrations in homologous recombination DNA repair pathways associate with responses to FDA-approved therapeutics in men with mCRPC.
Aim 2: Develop minimally invasive biomarkers capable of distinguishing patients for therapeutics targeting homologous recombination DNA repair pathways and ascertaining resistance mechanisms.
Aim 3: Identify rational drug combinations that exploit DNA repair vulnerabilities to eradicate prostate cancers with homologous recombination repair deficiency.

**This project was previously listed as CURRENT*

Title: *Eradicating Metastatic Prostate Cancer through the Systematic Identification of Synergistic Drug Combinations*
Grant #: PC170431
Time commitments: 5% effort
Supporting agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
DOD/CDMRP, help@ebrap.org;
Performance Period: 08/01/18 - 07/31/21
Level of funding:
Brief description of the project's goals:
We will test the hypothesis that specific combinations of therapeutics can rapidly and completely eradicate subtypes of mPC, and that patient-derived xenografts (PDX) representing the diversity of molecular 'driver' aberrations found in human CRPC can be used to rapidly and systematically identify these potent drug combinations.
Overlap with proposed research: None
List of specific aims:

Aim 1: Conduct a systematic assessment of combination pharmacological therapy to eradicate CRPC using panels of PDX models that reflect the diversity of molecular aberrations found in mCRPC.
Aim 2: Identify molecular features (genotype/phenotype) of PDX responders to drug combination(s).
Aim 3: Establish an International consortium for evaluating and validating novel therapeutic combinations capable of eradicating CRPC.
**This project was previously listed as CURRENT*

Title: *Estimation and Communication of Overdiagnosis in Cancer Screening*
Grant #: 1R01CA192402
Time commitments: 10%
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Justin Birken
BG 9609 RM 2W454, 9609 Medical Center Dr., Rockville, MD 20850
Performance Period: 05/01/15 – 10/30/20
Level of funding:
Brief description of the project's goals:
The objective of this work is to advance knowledge about how to estimate and disseminate information about overdiagnosis associated with cancer screening so as to inform screening policy development and patient decision making.
Overlap with proposed research: None
List of specific aims:
Aim 1: Investigate reliability of the two major approaches for estimating overdiagnosis in a simulated population where the true extent of overdiagnosis is known.
Aim 2: Estimate personalized (by age, comorbidity, tumor grade and stage) frequencies of overdiagnosis among breast and prostate cancers detected by screening in the US.
Aim 3: Develop online calculators to provide estimates of overdiagnosis for use by policy makers and clinicians.

Title: *Targeting the Mechanisms Driving Double-Negative Basal-Like Prostate Cancer*
Grant #: PC160622P1
Time commitments: 5%
Supporting agency: DOD/CRMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
Joshua D. McKean 820 Chandler Street Ft. Detrick, MD 21702
Performance Period: 08/01/17 – 07/31/20
Level of funding:
Brief description of the project's goals:
We hypothesize that DNPC is driven by a limited number of molecular programs that promote survival and proliferation, a subset of which subsume the role of AR in conventional AR-driven PC. Identifying these programs will provide key therapeutic targets capable of suppressing tumor progression.
Overlap with proposed research: None
List of specific aims:
Aim 1: Identify survival and growth programs operative in DNPC though deep molecular profiling of metastatic tumors and PDX models.
Aim 2: Utilize engineered cell lines and PDX models to determine which specific molecular alterations observed in the human DNPC tumors cause AR-bypass and promote a DNPC phenotype.
Aim 3: Evaluate pharmacological agents targeting DNPC driver pathways that emerge following AR ablation to confirm anti-tumor effects and support further clinical evaluation.

Title: *PALS: Prostate Cancer Active Lifestyle Study*
Grant #: R01CA184075
Time commitments: 5%
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Justin Birken
BG 9609 RM 2W454, 9609 Medical Center Dr., Rockville, MD 20850
Performance Period: 06/01/15 – 05/31/20
Level of funding:
Brief description of the project's goals:
We propose a randomized study of a lifestyle intervention of diet and exercise aimed at improving glucose regulation through weight loss in overweight and obese men with prostate cancer. Considering the non-cancer health benefits of maintaining a healthy weight, where even small losses in body weight lead to a decreased risk of cardiovascular disease and diabetes mellitus, weight loss in men with prostate cancer offers a potential opportunity to improve both overall and disease-specific survival.
Overlap with proposed research: None
List of specific aims:
Aim 1: To test whether the DPP lifestyle intervention (vs. control) improves serum fasting glucose.
Aim 2: To test whether the DPP lifestyle intervention (vs. control) improves serum biomarkers of glucose regulation (insulin, C-peptide, insulin-like growth factor-1 (IGF-1), IGF binding protein 3 (IGF-BP3) and adiponectin).
Aim 3: To test whether the DPP lifestyle intervention decreases the levels of insulin receptor or insulin-like growth factor-1 receptor (IGF-1R) in PCa tissue epithelium on follow-up prostate biopsy.
Aim 4: To test whether PCa patients randomized to the DPP lifestyle intervention sustain the lifestyle changes for at least 6 months after the end of the intervention period.

Title: *PROMISS – Prostate Modeling to Identify Surveillance Strategies*
Grant #: R01CA183570
Time commitments: 30%
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Justin Birken
BG 9609 RM 2W454, 9609 Medical Center Dr., Rockville, MD 20850
Performance Period: 09/01/13 – 08/31/19
Level of funding:
Brief description of the project's goals:
This project aims to improve our understanding of active surveillance, an approach to managing newly diagnosed low-risk prostate cancers that monitors disease closely and only treats tumors that appear to be progressing. We will analyze data from several active surveillance studies to assess how likely it is that their disease will progress and become incurable. We will use this information to develop tools for patient decision making so that patients with low-risk prostate cancer con confidently choose less invasive options for managing their disease, thereby reducing overtreatment and the economic burden of cancer while increasing patient satisfaction.
Overlap with proposed research: If the pending project is funded, creating an excessive commitment of effort, Dr. Etzioni's effort on R01 CA183570 will be reduced to 3.0 calendar months (from 3.6 calendar months) for April and May to ensure that at no time will effort exceed a total of 12 person months.
List of specific aims:
Aim 1: Model prostate cancer progression in the absence of treatment using two different modeling approaches and data sources.
Aim 2: Extend the models in Aim 1 to project treatment morbidity and quality-adjusted life expectancy and use

the extended models to project these and other relevant outcomes under different AS approaches.
Aim 3: Develop, test, and release a web-based interface based on the models in Aims 1 and 2 to support clinical decision-making about appropriate AS approaches based on patient age and health status, clinical and pathologic history, and personal preferences.

CURRENT SUPPORT

Title: *ReCAPSE: Recurrence from Claims And PROs for SEER Enhancement*
Grant #: UH3 CA218909
Time commitments: 2% effort
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Jacquelyn Saval, Grants Management Specialist, NATIONAL CANCER INSTITUTE, savalj@mail.nih.gov,
Performance Period: 09/25/2017– 06/30/2023
Level of funding (direct costs):
Brief description of the project's goals:
The proposed work will establish whether widely available medical claims data combined with patient self-report constitute a promising avenue towards determining whether the critical endpoint of cancer recurrence can be added to population-based cancer registries.
Overlap with proposed research: None
List of specific aims:
Working in collaboration with the Kentucky Cancer Registry (KCR), our Specific Aims for the UH3 phase are:

1. Deploy the tool developed in the UG3 phase to identify recurrent cases in the KCR and validate the performance of the tool against gold standard recurrence status from the electronic health record in a sample of recurrent and non-recurrent cases treated at the University of Kentucky
2. Develop an interactive user interface to produce summary statistics, data quality indicators, and graphical displays of recurrence frequencies based on the tool accounting for missing data patterns.

Title: *Pacific Northwest Prostate Cancer SPORE, Core C: Biostatistics Core*
Grant #: P50 CA097186
Time commitments: 10% effort
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Renee Carruthers
9000 Rockville Pike, Bethesda, MD 20892
Performance Period: 09/01/2018 - 08/31/2023
Level of funding:
Brief description of the project's goals:
The Biostatistics Core will provide essential data and analytics support to investigators on the Pacific Northwest Prostate Cancer SPORE. This Core will link study design, data collection, measurement, and analysis to validly address the critical hypotheses and questions of the Program.
Overlap with proposed research: None
List of specific aims:
Aim 1: Study Design: Define study hypotheses, study populations and experimental parameters to answer the research questions of interest, reduce systematic bias and ensure a high likelihood of detection of biologically meaningful effects.
Aim 2: Analysis and Interpretation: Identify and implement state-of-the-art quantitative methods to address the

scientific questions of interest and provide valid statistical inferences about the evidence supporting the various study hypotheses. Provide necessary bioinformatics expertise for study interpretation.
Aim 3: Dataset Creation and Curation: This Aim will use bioinformatics and data science routines to transform raw data into analytic data files and will provide a platform for data storage and investigator access.

Title: *Modeling Precision Interventions for Prostate Cancer Control*
Grant #: U01 CA253915
Time commitments: 10% effort
Supporting agency: NIH/NCI
Name and address of the funding agency's procuring Contracting/Grants Officer:
Alania Foster, alania.foster@mail.nih.gov
Performance Period: 09/10/2020 – 08/31/2025
Level of funding (direct costs):
Brief description of the project's goals:
In this application, we will evaluate personalizing patient care, including screening high-risk men more frequently, using biomarkers and imaging tests to select patients for biopsy, using patient and cancer features to determine when and which kinds of treatment to offer, and practical approaches for reducing racial disparities.
Overlap with proposed research: None
List of specific aims:
Aim 1: Precision early detection, including risk-stratified screening and biopsy using genetic tests, novel biomarkers, and imaging technology. Develop models to evaluate the impact of screening policies that (a) increase diagnostic intensity in high-risk population strata; (b) adapt screening intervals to individual PSA and biopsy histories; (c) personalize biopsy decisions based on novel biomarkers and/or imaging.
Aim 2. Precision active surveillance, including adaptive biopsy intervals and imaging technology. Ex-tend existing models to (a) explore personalized biopsy intervals based on PSA histories and novel biomarkers; (b) model MRI as a substitute for biopsy.
Aim 3: Precision treatment, including type and timing of initial and salvage therapies. Develop natural history models of events after diagnosis (recurrence, metastasis, death) including (a) estimating risks of metastasis and prostate cancer death and how they are altered by salvage treatments; (b) quantifying the impact of precision salvage therapies compared to non-precision approaches.
Aim 4: Targeting screening, biopsy, and treatment policies to reduce racial disparities. We will project the mortality reduction and harm-benefit tradeoffs in black men of (a) screening earlier and more frequently; (b) lowering the threshold for prostate biopsy; (c) in-creasing the utilization of primary curative therapies.
Aim 5: Prioritizing screening and treatment interventions in international settings. This aim will project the reduction in prostate cancer mortality under country-specific screening and treatment strategies while modifying the underlying risk of disease and stage-specific survival to match observed disease incidence and mortality in international populations.

Title: *Defining and Modulating BRCAness to Improve the Precision of Prostate Cancer Therapy*
Grant #: PC200262
Time commitments: 3% effort
Supporting agency: DOD/CDMRP
Name and address of the funding agency's procuring Contracting/Grants Officer:
DOD/CDMRP, help@ebrap.org;
Performance Period: 03/01/2021 – 02/29/2024
Level of funding:
Brief description of the project's goals:
Improve the accuracy of detecting prostate cancers with HDR defects for appropriate treatment allocation and increase the number of men with metastatic prostate cancer that could benefit from therapeutics that target DNA

repair deficiency be converting partially sensitive tumors into fully sensitive tumors; that is, generating a 'BRCAness' phenotype
Overlap with proposed research: None
List of specific aims:
[THIS AWARD]

Title: *The Early Detection Research Network: Data Management and Coordination Center*
Grant #: U24 CA086368
Time commitments: 15% effort
Supporting agency: NIH
Name and address of the funding agency's procuring Contracting/Grants Officer:
Jacquelyn Saval, Grants Management Specialist, NATIONAL CANCER INSTITUTE, savalj@mail.nih.gov,
Performance Period: 08/15/2022 – 03/31/2027
Level of funding:
Brief description of the project's goals:
Provide comprehensive data management and coordination for biomarker discovery and validation. **Overlap with proposed research:** None
List of specific aims:

A. Network Coordination and Outreach (Aim 1)
B. Data Science, Data Management and Study Protocol Development (Aim 2)
C. Validation Study Infrastructure Services (Aim 3)
D. Management of Core Funds (Aim 4)
**This is project has been added to Dr. Etzioni's OS*

Title: *Modeling the Outcomes of Reclassifying low-grade Prostate Cancer as Non-Cancer*
Grant #: 75D30122C13505
Time commitments: 5% effort
Supporting agency: CDC
Name and address of the funding agency's procuring Contracting/Grants Officer:
CDC, Office of Acquisition Services
2900 Woodcock Blvd, MS TCU-4, Atlanta, GA 30341-4004
Performance Period: 09/01/2022 – 08/31/2023
Level of funding:
Brief description of the project's goals:
This work aims to quantify the likely benefit-harm tradeoffs of renaming G6 cancer as non-cancer. We will adapt and extend two existing models of prostate cancer progression to project the outcomes of two scenarios: (1) current management practices involving active treatment or active surveillance for newly diagnosed G6 cancers and (2) new management practices that would not classify G6 as cancer but rather returns these men to screening with tailored criteria for future interventions. We will compare disease-specific progression events and mortality between scenarios as well as frequencies of biopsy and active treatment. Our primary results will consist of the number of lives saved, biopsies performed, and treatment received overall and per G6 cancer diagnosed under Scenario (1) relative to Scenario (2). Since there are different ways to manage G6 cancer in both scenarios, we will produce a paired results for each management approach.
Overlap with proposed research: None
List of specific aims:
N/A
**This is project has been added to Dr. Etzioni's OS*

Title: *Modeling and analytics for cancer diagnostics: traversing the data-evidence divide*
Grant #: R35 CA274442
Time commitments: 50% effort
Supporting agency: NIH
Name and address of the funding agency's procuring Contracting/Grants Officer:
Jacquelyn Saval, Grants Management Specialist, NATIONAL CANCER INSTITUTE, savalj@mail.nih.gov,
Performance Period: 08/01/2022 – 06/30/2029
Level of funding:
Brief description of the project's goals:
We are witnessing explosive growth in new tests that can help detect cancer, predict whether it is likely to spread, and decide which treatments have the best chance of being effective. There are so many new tests that they cannot always be studied properly to make sure they actually improve patients' lives. This research program aims to carefully combine all the available data to learn which new tests we should be recommending to the public.
Overlap with proposed research: None
List of specific aims:
N/A
**This is project has been added to Dr. Etzioni's OS*

PENDING SUPPORT

Title: *Generating Research Opportunities Within Statistics at Fred Hutch (GROWS@FredHutch)*
Grant #: R25 CA272187
Time commitments: 2% effort
Supporting agency: NIH
Name and address of the funding agency's procuring Contracting/Grants Officer: TBD
Performance Period: 04/01/2023 – 03/31/2028
Level of funding:
Brief description of the project's goals:
GROWS@FredHutch (Generating Research Opportunities Within Statistics at Fred Hutch) is a summer mentored research program for undergraduates who identify as underrepresented minorities, and will include an engaging and supportive mentored research experience along with career development, community building, and social/emotional support activities to encourage students to (1) gain skills and confidence in cancer statistics and data science and (2) feel a sense of belonging and rightful place in the statistics and cancer research communities.
Overlap with proposed research: None
List of specific aims:
N/A

OVERLAP
There exists neither scientific nor budgetary overlap. Should the pending application be funded, effort will not exceed 100%.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge.

Signature: Ruth D. Etzioni, PhD Digitally signed by Ruth D. Etzioni, PhD Date: 2022.12.08 19:17:52 -08'00'

Date: 12/8/2022