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TITLE: Epigenomic Landscape of Primary Prostate Cancer in African American Men

PRINCIPAL INVESTIGATOR: Tamara Lotan

CONTRACTING ORGANIZATION: Johns Hopkins University, Baltimore, MD

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14. ABSTRACT

We hypothesize that differences in the epigenomic landscape may interact with somatic genomic alterations and tumor microenvironment to drive racial disparities in prostate cancer outcomes and that epigenomic alterations may serve as prognostic molecular biomarkers in AA PCa. Here, we propose to conduct the largest study to comprehensively define the epigenomic landscape of PCa arising in AA men with long-term oncologic follow-up and/or tumor somatic sequencing and immune microenvironment characterization. This research will identify unique epigenomic drivers of aggressive biology and adverse PCa outcomes among AA patients, elucidating novel biological underpinnings of this critical health care disparity.

15. SUBJECT TERMS
Prostate cancer, heath disparities, methylation

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1. **INTRODUCTION:**

We hypothesize that differences in the epigenomic landscape may interact with somatic genomic alterations and tumor microenvironment to drive racial disparities in prostate cancer (PCa) outcomes and that epigenomic alterations may serve as prognostic molecular biomarkers in AA PCa. In **Aim 1**, we will identify differentially methylated CpG sites associated with genetic racial ancestry, oncologic outcomes, somatic genomic alterations and immune response and oncologic outcomes in a retrospective Johns Hopkins cohort of matched prostate tumors from 200 AA and 200 WH men at radical prostatectomy. Using the Infinium MethylationEPIC microarray platform to interrogate over 850K methylation sites per sample at single nucleotide resolution, we will identify differentially methylated CpG sites stratified by racial ancestry, clinical-pathologic parameters and oncologic outcomes (recurrence and metastasis) overall and within each group, focusing on the CpGs with concurrent transcriptional changes by completed microarray profiling (Affymetrix 1.0ST arrays). Then, we will integrate tumor methylation profiles with previously assessed tumor somatic genomic alterations and microenvironment immunophenotyping data to identify novel biomarkers of PCa outcome disparities**.** In **Aim 2**, we will validate epigenomic signatures associated with adverse oncologic outcomes in AA patients discovered in Aim 1 using the Baylor College of Medicine (BCM) retrospective cohort of 300 AA tumors at radical prostatectomy with long term follow-up. Race-specific methylation signatures from the JHU cohort will be validated by comparison of the BCM AA samples to historical WH control samples from TCGA (n=300) or the Moffitt Cancer Center (n=120) previously arrayed on Infinium 450K arrays. Finally, in **Aim 3**, we will validate epigenomic signatures associated with pathologic tumor aggression, somatic genomic alterations and immune microenvironment alterations in AA patients using the RESPOND cohort of 500 prospectively collected AA tumors from SEER cancer registry sites around the country. Her, we will perform and analyze whole-genome methylation profiling using the Infinium MethylationEPIC microarray platform to validate a signature of differentially methylated CpG sites associated with pathologic measures of tumor aggression (tumor grade and stage), tumor somatic genomic alterations, tumor immunophenotype and environmental stressors among AA patients.

2. **KEYWORDS:**

Prostate cancer, cancer health disparities, methylation, epigenomic

ACCOMPLISHMENTS:

- **What were the major goals of the project?**

Research-Specific Tasks:

Specific Aim 1: Identify differentially methylated CpG sites associated with genetic racial ancestry, oncologic outcomes, somatic genomic alterations and immune response in a retrospective Johns Hopkins cohort of matched primary PCa from 200 AA and 200 WH men at radical prostatectomy.	**Timeline (Months)**	**% completed**
Major Task 1: Using previously collected data on the Infinium MethylationEPIC microarray platform to interrogate over 850K methylation sites per sample at single nucleotide resolution, we will identify differentially methylated CpG sites stratified by racial ancestry, clinical-pathologic parameters and oncologic outcomes (recurrence and metastasis) overall and within each group		
Subtask 1: Obtain HRPO Approval for study (Hopkins IRB approval is in place already)	1-3	100%
Subtask 2: Integrate tumor methylation profiles with previously assessed tumor somatic genomic alterations, microenvironment	3-24	90%

immunophenotyping data and genetic racial ancestry data to identify novel biomarkers of PCa outcome disparities**.**		
Subtask 3: Validate biomarkers by pyrosequencing/methylation specific PCR	24-36	0%
Specific Aim 2: Validate epigenomic signatures associated with racial ancestry and adverse oncologic outcomes in AA patients using the Baylor College of Medicine (BCM) retrospective cohort of 300 AA tumors at radical prostatectomy with long term follow-up.		
Major Task 2: Perform and analyze whole-genome methylation profiling using the Infinium MethylationEPIC microarray platform on BCM samples		
Subtask 1: Obtain HRPO Approval for study	1-3	100%
Subtask 2: Receive DNAs from BCM and run methylation arrays at NXTDx	6-18	10%
Subtask 3: Validate a signature of differentially methylated CpG sites associated with biochemical recurrence and metastasis among AA patients.	18-36	0%
Subtask 4: Validate a signature of differentially methylated CpG sites associated with racial ancestry by comparison to TCGA and Moffitt Cancer Center WH cohorts	18-36	50%
Specific Aim 3: Validate epigenomic signatures associated with pathologic tumor aggression, genetic racial ancestry, somatic genomic alterations and immune microenvironment alterations in AA patients using the RESPOND cohort of 400 <u>prospectively collected</u> AA tumors		
Major Task 3: Perform and analyze whole-genome methylation profiling using the Infinium MethylationEPIC microarray platform on RESPOND samples	25-36	0%
Subtask 1: Obtain HRPO Approval for studies	1-3	100%
Subtask 2: Receive DNAs from RESPOND and run methylation arrays at NXTDx	6-30	50%
Subtask 3: Validate a signature of differentially methylated CpG sites associated with clinical pathologic risk category among RESPOND AA patients.	30-36	0%
Subtask 4: Integrate methylome in RESPOND cohort with previously assessed tumor somatic genomic subtype, genetic racial ancestry and tumor immonophenotyping	30-36	0%
Milestone(s) Achieved: Validated prognostic signature for recurrence/metastasis in AA PCa	36	

- **What was accomplished under these goals?**

1) Major activities: Most activities during this period continued to be focused on Aim 1: examining the methylation array data in the Johns Hopkins race-matched primary PCa cohort and correlating with somatic genomic data. As a validation step to assess the quality of the methylation data, and to simultaneously integrate with the methylation profiling as proposed, we used the Infinium EPIC array data to derive somatic genomic copy number alteration (CNA) status of 290 samples in the Johns Hopkins cohort and began to explore associations with the germline genetic ancestry data from this cohort. Our cohort was composed of 145 self-identified AA patients and 145 self-identified WH surgically-treated patients with accompanying genetic ancestry estimation via SNP array (Illumina GSAv3). EPIC array-derived somatic copy number data estimated through the *conumee* package on R. We used a comprehensive genome annotation with >80k coding and non-coding regions from FANTOM CAT.

As a quality check, we first compared somatic CNAs identified by targeted sequencing of the same tumors [1] for a panel of 100 cancer driver genes with CNA estimates by *connumee* and found these to be significantly correlated (**Figure 1**). We also observed a significant association between genomic losses of the *PTEN* gene estimated by *connumee* and PTEN protein loss by immunohistochemistry in the 290 samples ($p<0.001$). Similar observations were made for *TP53* gene copy loss by *connumee* and p53 protein nuclear accumulation detected by immunohistochemistry ($p<0.001$). The somatic CNA landscape in AA samples is depicted in **Figure 2**.

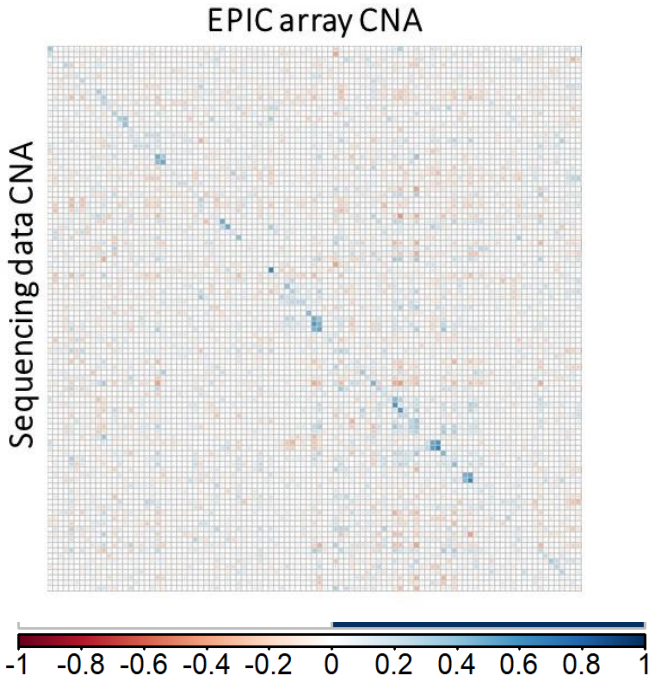

Figure 1: Correlation of copy number estimates for a panel of 100 genes between targeted sequencing and EPIC array estimates across all 290 patients. The Spearman correlation coefficient is coded by color based on key below. The blue diagonal line indicates a significant correlation between the two methods across these 100 genes assayed.

Next, we derived a measure of total somatic CNA known as percent genome altered (PGA) from EPIC array data for our 290 patients using an Excitation-Maximization algorithm to set the CNA cutoffs. PGA derived from the EPIC array was significantly correlated with PGA obtained from targeted sequencing of a subset of AA tumors ($n=119$, $P<0.0001$, $R^2=0.50$) (**Figure 3**). No difference in PGA was found between self-identified AA and WH patients ($P<0.05$), though PGA levels were significantly associated with Gleason Grade groups for both AA ($P<0.0001$) and WH ($P=0.003$). This is the first genome-wide analysis of CNA data from grade-matched AA and WH samples to our knowledge.

We then used SNP arrays to estimate the percent African ancestry in all patients in the cohort. We found an excellent correlation between self-identified race and genetic ancestry: Self-identified WH patients showed a median of 0.001% African (YRI) ancestry compared to self-identified AA patients who showed a median of 78.8% YRI ancestry ($p<0.001$) (**Figure 4**).

We then used these data to perform a genome-wide discovery study of CNAs associated with percent genetic African ancestry (**Figure 5**). We used a comprehensive genome annotation with >80k coding and non-coding regions from FANTOM CAT and implemented a generalized linear model (GLM) to assess which CNAs (estimated via *conumee* from methylation data as described above) in the 290 patient Johns Hopkins cohort were significantly associated with percent African ancestry, adjusting for age, pre-operative PSA, and Gleason GG. As expected, genes around *PTEN*, *TP53* and *ERG* (**Figure 5,** red boxes) show significantly higher relative copy number estimates in patients with higher percent African ancestry (positive

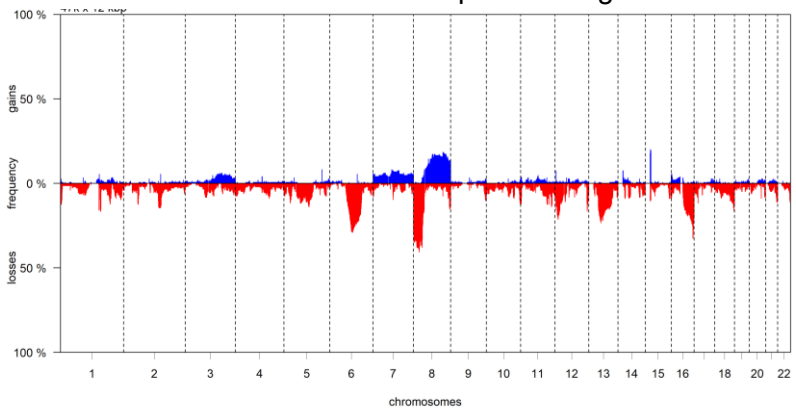

Figure 2. CNA landscape of AA cases in the JHU matched race cohort. The *conumee* pipeline was used to infer the sCNA landscape for AA PCa cases from Infinium MethylationEPIC array data.

coefficients) consistent with lack of deletion in these cases [2,3] and validating the model. In addition, multiple novel regions were identified where copy number correlates with proportion of African ancestry, including a prominent cluster on 6p showing relative copy number gain in patients with higher proportional African ancestry or a cluster around WT1 at 11p13 with relative copy number loss in patients with higher proportional African ancestry (**Figure 5**, black boxes).

In the process of performing a GLM analysis for CNAs that vary by genetic racial ancestry, we serendipitously identified a number of loci where there is germline copy number variation (gCNV) by racial ancestry accompanied by altered expression of immune-related genes. Though we normalized the methylation profiling using germline DNA derived from a mixed group of benign prostate samples (15 AA and 15 W cases), we quickly recognized that a number of the race-related sCNAs we identified were likely actually race-related gCNVs (**Figure 6**). To robustly assess this, we performed a separate *conumee* analysis of copy number using Infinium MethylationEPIC data derived from normal colonic mucosa samples from AA (n=88) or W (n=40) patients (publicly available). Strikingly, we found that 41% of the race-related CNA found to be significant in the GLM were present in the race comparison of benign colonic mucosa, suggesting they were likely race-related gCNV rather than CNA. Intriguingly, these race-related gCNV often involved immune-related genes, as exemplified by a chemokine cluster on 17q12 containing *CCL3L1* and *CCL4L1*. *CCL3L1* is the paralogue to *CCL3*, with 95.8% sequence homology, and these genes encode MIP-1α isoforms, the ligands for CCR5 and CCR1. *CCL4L1* is the paralogue to *CCL4* and together they encode MIP-1β, another ligand for CCR5. *CCL3L1* and *CCL4L1* are predominantly expressed by hematopoietic cells, including B-lymphocytes as well as monocytes upon stimulation and they are potent chemoattractants for monocytes, T-lymphocytes, dendritic cells and NK cells. Copy number at *CCL3L1* may modify risk for a number of autoimmune and infectious diseases [4-6]. Given that the MIP-1α/β signaling axis regulates diverse inflammatory responses

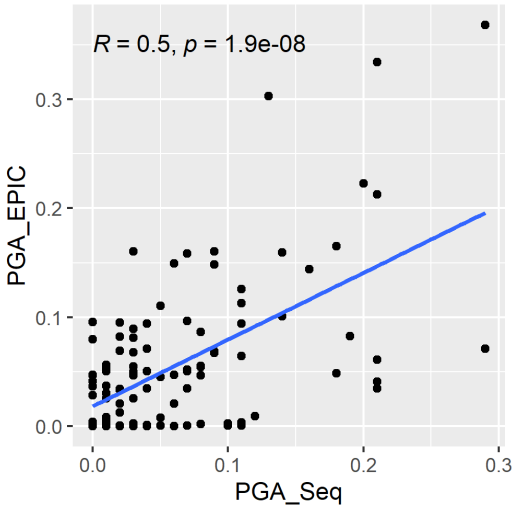

Figure 3: Correlation of PGA estimates between targeted sequencing and EPIC array across 119 AA tumors.

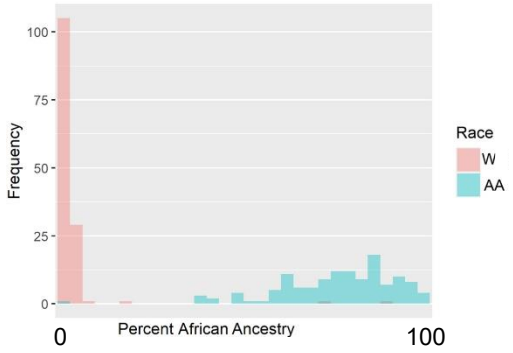

Figure 4: Percent AA ancestry in JHU matched race cohort, stratified by self-identified race.

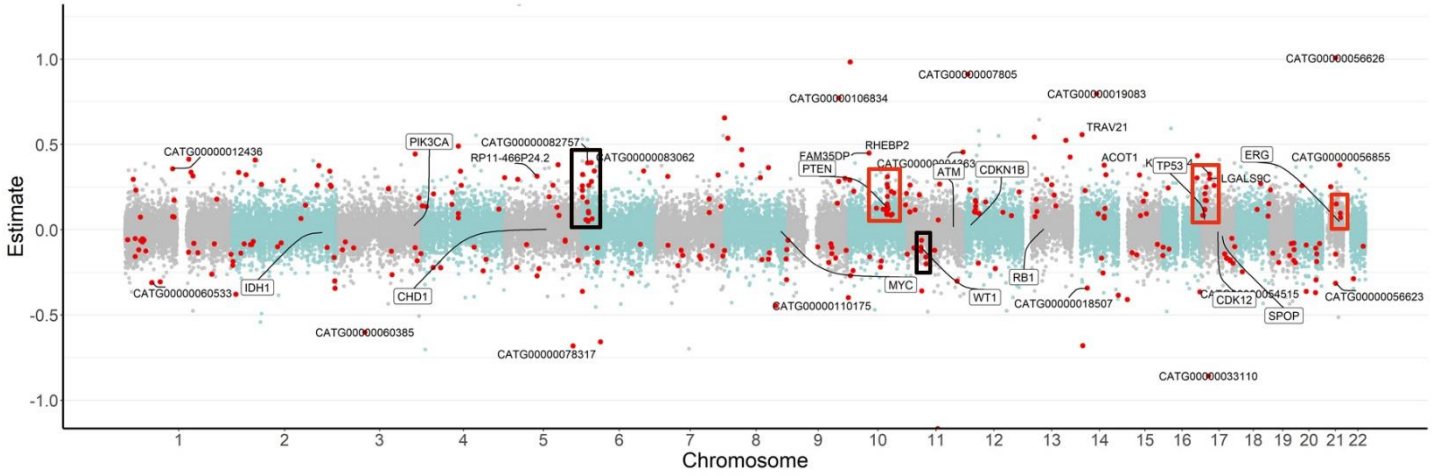

Figure 5. Coefficient estimates for relative gene copy number from generalized linear model (GLM) for percent African ancestry. Red dots represent coefficient estimates for relative copy number of genes with FDR-corrected p-value < 0.001. As expected, genes around *PTEN*, *TP53* and *ERG* (red boxes) show significantly higher relative copy number estimates in patients with higher percent African ancestry (positive coefficients) consistent with lack of deletion in these cases. In addition, multiple novel genes are identified where copy number correlates with proportion of African ancestry, including a prominent cluster on 6p showing relative gain in patients with higher African ancestry or a cluster at 11p13 with relative loss (black boxes). The model was adjusted for age, PSA and Gleason grade group. Germline CNV have been filtered out in this depiction.

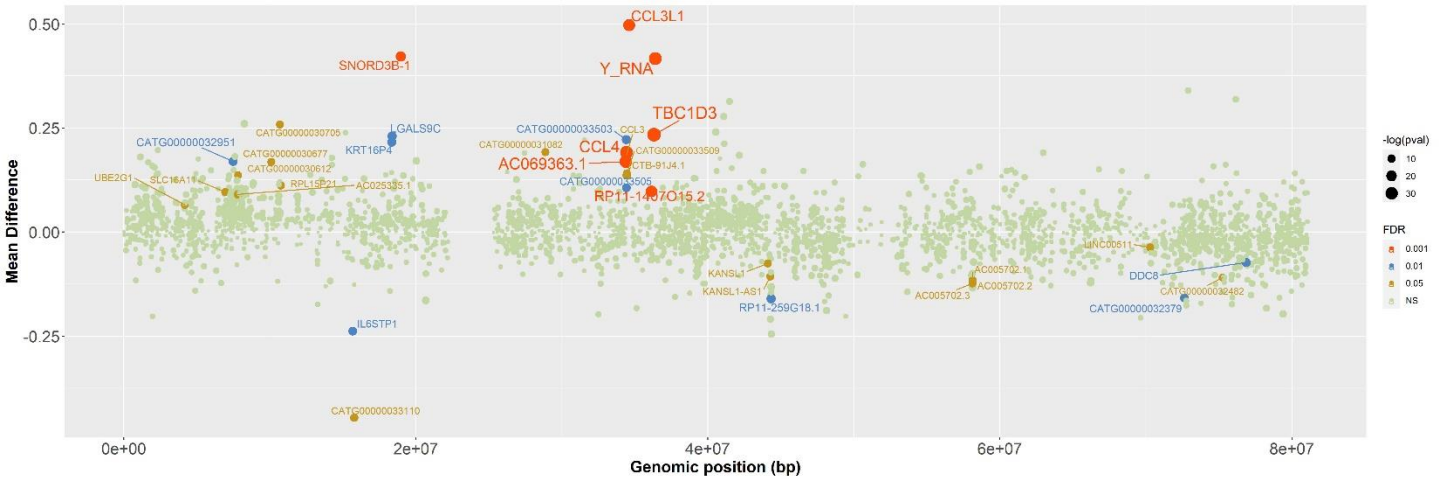

Figure 6: Plot of mean copy number difference between samples from W and AA PCa for genes on Chr17 (inferred from methylation arrays). Each point represents a coding/non-coding gene annotated FANTOM CAT with mean difference in average estimated copy number in PCa samples from AA vs W patients from the matched 200/200 patient JHU cohort. Each point is colored by FDR-corrected p-value. A strong signal for *CCL3L1* and *CCL4* is seen, with increased relative copy number in PCa samples from AA vs W patients. *TBC1D3* is an adjacent gene that has been shown to have ancestry-associated gCNV.

including macrophage function and B-cell-dependent immune responses, it is of particular interest that African patients have, on average, twice as many germline copies of *CCL3L1* as Europeans, and this gCNV is highly correlated with increased gene expression in white blood cells [7]. *CCL4L1*, the paralogue for *CCL4* shows similar race-related gCNV and is adjacent to *CCL3L1*. *Significantly, three independent datasets showed increased expression of CCL3 and CCL4 in AA compared to W PCa samples* [8,9]. However, the extent to which these gCNVs associate with the immune TME or clinical outcomes in PCa has not been examined, thus this is a novel and intriguing observation in our cohort.

Finally, to integrate our CNA data with clinical outcome, we performed multivariable Cox regression models adjusted for age, Gleason Grade Group, and pre-operative PSA levels and found that chromosome 8q gains (including *MYC*, *GRHL2*, and *FZD6*) were significantly associated with biochemical recurrence and metastasis. However, when we stratified the models by self-identified race, only AA tumors showed significant associations with 8q gains and poor outcome. Further clinical, *in silico* and mechanistic validation will be conducted to confirm whether chromosome 8 gains may be a potential biomarker for prostate cancer outcome in AA men.

2) specific objectives: The objectives were to identify differentially methylated CpG sites associated with genetic racial ancestry, oncologic outcomes, somatic genomic alterations and immune response and oncologic outcomes in a retrospective Johns Hopkins cohort of matched prostate tumors from 200 AA and 200 WH men at radical prostatectomy. Here we have focused on discerning somatic CNA (a subset of the somatic genomic alterations) in the cohort.

3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative) Significant results to date include: a) validation of self-identified race using genetic ancestry data in the Johns Hopkins cohort (Figure 4); b) Validation of methylation data using the CNA extracted from the methylation arrays by comparison to CNA data extracted from sequencing (Figures 1 and 3); c) Finding that PGA is not variable by race in grade-matched cohort of AA and W samples (Figure 2); d) Finding of novel genomic gains and losses that vary by percent African ancestry (Figure 5); e) Finding that 8q gains are associated with biochemical recurrence and death in AA patients; 6) Finding of significant regions of gCNV that vary by genetic ancestry where gene expression of these same genes varies in PCa between AA and WH samples. This finding may explain some of the immunobiological differences reported between AA and WH prostate cancer samples.

4) other achievements. More than 400 RESPOND DNAs (Aim 3) have been extracted and pending for methylation array analysis.

- **What opportunities for training and professional development has the project provided?**
  - Nothing to report
- **How were the results disseminated to communities of interest?**

- Nothing to report

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

We are now working on integrating the methylation data with the genetic ancestry and somatic CNA data described above. The methylation analyses will use the identical code that we have just validated for CNA analysis above to examine associations of methylation with genetic ancestry and clinical outcome data in the Johns Hopkins cohort (via GLM and Cox regression models). We expect to have these data complete within the next month or two. We have also received and isolated DNA from more than 400 RESPOND patients, and we will perform methylation profiling on these samples as planned in Year 3.

IMPACT:

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

Once complete, the hope is that the work in this proposal will identify many of the molecular contributors to the disparity in PCa outcomes among AA patients, enabling the rational design of therapies targeted for this population of patients. Given that AA PCa shows fewer mutations and copy number alterations associated with adverse outcomes than seen in non-Latino White PCa (WH), current molecular biomarkers gleaned from studies of WH PCa are clearly inadequate and additional prognostic biomarkers are needed specifically in the AA population. In the short term, an immediate deliverable of this award is a highly validated epigenomic signature of tumor recurrence and metastasis among men with AA PCa.

- **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?**

Understanding the root causes (biological and social) of cancer health disparities will be a key stepping stone in rectifying the longstanding history of racial injustice in our country.

3. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

Dr. Luigi Marchionni has left Johns Hopkins for Cornell University. With CDMRP approval, Dr. Thiago Vidotto (a bioinformatician in Brazil who trained as a postdoctoral fellow at JHU and works under contract) has taken over the bioinformatics analyses. He continues to meet every single week with Dr. Marchionni and Dr. Lotan by Zoom as we works on the project and Dr. Marchionni has been very generous with his time. This remote collaboration has worked seamlessly.

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

The major goal we have not met for the second year is the receipt of Baylor DNAs for methylation analysis which have been delayed due to the COVID pandemic. We have received a total of 30 samples to date from this group and have confirmed that they are high quality and can proceed with the remaining samples. We have agreed to receive tissue for DNA extraction, rather than DNA, in order to facilitate the receipt of the samples and the tissue has yielded high quality DNA in microgram quantities. We will work with the Baylor group on increasing receipt of these samples over the next year and if necessary, we can look for alternative sample sources. The RESPOND

study recruiting has increased dramatically in the past year and if necessary, after consultation with our grants officer, we can potentially profile more of these samples in lieu of the Baylor samples, however the hope is that the Baylor samples will be forthcoming.

- **Changes that had a significant impact on expenditures**

  The COVID19 pandemic resulted in delays as described above that have decreased expenditures on methylation profiling (these were the bulk of the costs in this project). We will catch up rapidly over the next year as we profile more RESPOND cases.

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

  - Nothing to report

- **Significant changes in use or care of human subjects**

  - Nothing to report

- **Significant changes in use or care of vertebrate animals.**

  - Nothing to report

- **Significant changes in use of biohazards and/or select agents**

  - Nothing to report

4. **PRODUCTS:**

- **Publications, conference papers, and presentations**
  An abstract with the above CNA data has been submitted to 14th AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved on October 6-8, 2021. A manuscript is currently in preparation and will be submitted in the next two months.

- **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**
  We have assembled a database of whole genome methylation profiling results for the race-matched Johns Hopkins cohort and now a database of somatic copy number alterations. This database, integrated with somatic mutations as well as clinical outcomes will be made available to public upon publication and provide a valuable resource and the first of its kind in prostate cancer.

5. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name:	*Tamara Lotan*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Lotan supervises all data collection and data analysis on the project*
Funding Support:	*Please see below*

-

Name:	*Luigi Marchioni*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*0*
Contribution to Project:	*Dr. Marchionni supervises bioinformatics data analysis on the project*
Funding Support:	*Please see below*

Name:	*Thiago Vidotto*
Project Role:	*Postdoctoral fellow*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Vidotto performs all of the bioinformatics data analysis on the project*
Funding Support:	*Please see below*

Name:	*Daniela Salles*
Project Role:	*Postdoctoral fellow*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Salles assists with DNA extraction and methylation validation experiments*
Funding Support:	*Please see below*

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  Changes since last report are as follows (see Appendix below):
  National Institutes of Health #R01CA255349 -- active
  CDMRP #W81XWH-20-1-0177 -- active
  CDMRP #W81XWH-20-1-0254—active
  CDMRP # W81XWH-20-1-0843 – active
  Brown Foundation #90091444 -- active
  National Institutes of Health P50CA058236 -- active
  PCF 18CHAL15 --completed
  National Institutes of Health #R01CA200859 --completed
  CDMRP # W81XWH-16-1-0737 --completed
  Fidelity Charitable –90087049 --completed
  CDMRP # W81XWH-19-1-0345 --completed

- **What other organizations were involved as partners?**

  - **Organization Name: Baylor University School of Medicine**
  - **Location of Organization:** *Houston, TX*
    - **Other: Provides PCa samples for analysis**

- **Organization Name: Moffitt Cancer Center**
- **Location of Organization:** *Miami, FL*
    - **Other: Provides methylation data on PCa**

6. **SPECIAL REPORTING REQUIREMENTS**
    - **COLLABORATIVE AWARDS:**
    - **QUAD CHARTS:**
7. **APPENDICES:**

References:

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9. Rayford W, Beksac AT, Alger J, *et al.* Comparative analysis of 1152 African-American and European-American men with prostate cancer identifies distinct genomic and immunological differences. *Commun Biol* 2021; **4**: 670.

OTHER SUPPORT

Lotan, Tamara

Changes since last report are as follows:
National Institutes of Health #R01CA255349 -- active
CDMRP #W81XWH-20-1-0177 -- active
CDMRP #W81XWH-20-1-0254—active
CDMRP # W81XWH-20-1-0843 – active
Brown Foundation #90091444 -- active
National Institutes of Health P50CA058236 -- active
PCF 18CHAL15 --completed
National Institutes of Health #R01CA200859 --completed
CDMRP # W81XWH-16-1-0737 --completed
Fidelity Charitable –90087049 --completed
CDMRP # W81XWH-19-1-0345 --completed

Active Support:

Award ID: 109644168
Title: Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Immunity and Access to Care (RESPOND)
Effort: 1.80 calendar months (10% effort)
Supporting Agency: University of Southern California
Grants Officer: Lillian Rivera
Address of Funding Agency: 2001 Soto Street, SSB-205, Los Angeles, CA 90089-9235
Performance Period: 07/05/2018-06/30/2023
Level of Funding:
Principal Investigator: Chris Haiman (University of Southern California)
Project Goals: The major goal of this project is to assemble a prospective cohort of African-American prostate cancer patients from SEER registries across the country. Dr. Lotan will lead the Pathology Core for this project, processing ~3000 prostate cancer tumor specimens from this cohort.
Specific Aims:

Award: 19CHAS03
Title: The Inflammatory Microenvironment of Aggressive Prostate Cancer in African American Men (Project 4/RESPOND)
Effort: .60 calendar months (5% effort)
Supporting Agency: Prostate Cancer Foundation
Name of Procuring Contracting/Grants Officer:
Address of Funding Agency:
Performance Period: 10/11/2019 – 10/10/2024
Level of Funding:
Principal Investigator: Karen Sfanos
Project Goals: The major goal of this project is to better understand the molecular, immune and genetic components of primary and metastatic prostate cancer aggressiveness in African American men.
Specific Aims: Aim 1: To characterize the immune cell constituents in the prostate tumor microenvironment in tumors from AA men and determine whether specific tumor immune cell profiles are associated with PCa aggressiveness and/or outcomes including recurrence and survival. Aim 2. To examine associations between high-risk immune phenotype, and genetic and non-genetic factors in 500 radical prostatectomy specimens from AA men in the RESPOND cohort. Aim 3. Pilot a portable single-cell RNA sequencing platform to study cellular states in primary prostate cancer and the tumor immune microenvironment in men with prostate cancer.

Award ID: R01CA200858
Title: Molecular and Cellular Mechanisms of Resistance to mTORC1 Inhibition in the Skin
Effort: No effort
Supporting Agency: National Institutes of Health
Grants Officer: Romy Reis
Address of Funding Agency: 9000 Rockville Pike, Bethesda, MD 20892
Performance Period: 02/03/2016-01/31/2021(NCE)
Level of Funding:
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to elucidate the mechanism by which mTORC1 inhibition up-regulates receptor tyrosine kinase signaling and down-regulates cell-cell adhesion in the skin
Specific Aims: Aim 1: Determine how mTORC1 activity modulates net ligand-stimulated EGFR degradation; Aim 2: Establish how mTORC1 loss-of-function suppresses adherens junction maturation; Aim 3: Examine the role of mTORC1 signaling perturbation during skin cancer progression
Award ID: R01CA238284
Title: Genetic and genomic determinants of homologous recombination repair deficiency as treatment selection markers for lethal prostate cancer
Effort: 0.36 calendar months (3% effort)
Supporting Agency: National Cancer Institute
Grants Officer:
Address of Funding Agency: 9000 Rockville Pike, Bethesda, MD 20892
Performance Period: 09/01/2020 – 08/31/2024
Level of Funding:
Principal Investigator: Jun Luo
Project Goals: The major goal of this project is to determine the genetic/genomic drivers of HRD predicting "deep" response to abiraterone and enzalutamide.
Specific Aims: Aim 1. To ascertain the HRD mutations status, both somatic and germline, in three existing advanced/lethal prostate cancer cohorts enriched for HRD using blood-based assays. Aim 2. To determine the association of HRD status defined by blood-based assays with treatment response to first-line AR-directed therapy (abiraterone/enzalutamide) and taxane chemotherapies in mCRPC patients by comparing treatment outcomes of men in these three groups. Aim 3. To determine the expression correlates of HRD status defined by blood-based assays and further ascertained by tissue-based assays, by performing RNA-Seq in surgical specimens from men with lethal prostate PCa with: 1) germline/somatic HRD; 2) somatic-only HRD; and 3) negative HRD.

Award ID: R01CA255349
Title: Stromal senescence in lethal prostate cancer: a novel target for prognosis and therapy
Effort: .24 calendar months (2% effort)
Supporting Agency: National Cancer Institute (NCI)
Grants officer: TBD
Address of Funding Agency: 9000 Rockville Pike, Bethesda, MD 20892
Performance Period: 01/01/2021 – 03/31/2024
Level of Funding:
Principal Investigator: Elizabeth Platz (contact), Alan Meeker
Project Goal: The major goal of this project is to examine senescent stromal fibroblasts in localized and metastatic prostate cancer.
Specific Aims: Aim 1: Evaluate the association between senescent stromal fibroblasts, especially in the presence of stromal inflammation, in prostatectomy tissue and risk of progression to metastatic prostate cancer in men with intermediate and high-risk disease (Cohort 1). **Aim 2:** Evaluate the association between senescent stromal fibroblasts, especially in the presence of stromal inflammation, in prostatectomy tissue and risk of progression to metastasis or rapidly rising PSA in a second, independent cohort of men with intermediate and high-risk disease (Cohort 2). **Aim 3:** Determine whether senescent fibroblasts are present in metastases, and if

so, their heterogeneity across metastatic sites of bone and soft tissues in men who died of castrate-resistant prostate cancer.

Award ID: W81XWH-17-1-0286
Title: Interaction between the Inflammatory Microenvironment and Somatic Genomic Alterations as a Driver of Prostate Cancer Aggressiveness in African American Men
Effort: .12 calendar months (1% effort)
Supporting Agency: Department of the Army
Grants Officer: TBD
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 7/01/2017-06/30/2021 (NCE)
Level of Funding:
Principal Investigator: Karen Sfanos
Project Goals: The major goal of this project is to correlate immune and molecular profiling of African-American and White primary prostate tumors with oncologic outcomes.
Specific Aims: Aim 1: To characterize the immune cell components and degree of inflammation in the prostate tumor microenvironment in tumors from AA and WH men and determine whether specific tumor immune cell profiles are associated with biochemical recurrence after radical prostatectomy in either population. Aim 2: To test whether specific tumor immune profiles are associated with underlying tumor somatic genomic alterations in AA and WH men and determine whether there is an interaction between immune microenvironment and genomic alterations in the association with oncologic outcomes in AA men and in WH men.

Award ID: W81XWH-17-1-0425
Title: Prospective-Retrospective Analysis of PTEN Immunohistochemistry Assay for Prediction of Outcomes in Recurrent and Metastatic Prostate Cancer
Effort: 1.20 calendar months (10% effort)
Supporting Agency: Department of the Army
Grants Officer: Janet Kuhns
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 09/01/2017-08/31/2021(NCE)
Level of Funding:
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to test if PTEN (alone or in combination with ERG) may serve as a prognostic and/or predictive marker for hormonal therapy response in metastatic/recurrent prostate cancer in two large contemporary clinical trials. ECOG 3805 and RTOG 96-0.1
Specific Aims: Aim 1: Test whether PTEN status modifies overall survival benefit associated with treatment in ECOG 3805 (CHAARTED), a phase III trial that demonstrated a benefit for docetaxel chemotherapy at the time of starting androgen deprivation therapy (ADT) for men with high volume metastatic disease. Aim 2: Test whether PTEN status modifies metastasis-free survival benefit associated with treatment in RTOG 96-01, a phase III trial that demonstrated a benefit for AR-targeted therapy with bicalutamide at the time of radiation therapy for non-metastatic PSA recurrence after radical prostatectomy.

Award ID: W81XWH-19-1-0292
Title: Epigenomic Landscape of Primary Prostate Cancer in African-American Men
Effort: 1.20 calendar months (10% effort)
Supporting Agency: DOD PCRP Health Disparity Award
Grants officer: Kimberly Carter
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 06/01/2019 – 05/31/2022
Level of Funding:
Principal Investigator: Tamara Lotan
Project Goal: The major goal of this project is to identify epigenomic markers of lethal prostate cancer in African American men.

Specific Aims: Aim 1: Identify differentially methylated CpG sites associated with genetic racial ancestry, oncologic outcomes, somatic genomic alterations and immune response in a retrospective Johns Hopkins (JHH) cohort of matched primary PCa from 200 AA and 200 WH men at radical prostatectomy Aim 2: Validate epigenomic signatures associated with racial ancestry and adverse oncologic outcomes in AA patients using the Baylor College of Medicine (BCM) retrospective cohort of 300 AA tumors at radical prostatectomy with long term follow-up. Aim 3: Validate epigenomic signatures associated with pathologic tumor aggression, genetic racial ancestry; somatic genomic alterations and immune microenvironment alterations in AA patients using the RESPOND cohort of 400 prospectively collected AA tumors.

Award ID: W81XWH-19-1-0345
Title: Discovery and Functional Analyses of Susceptibility Genes for Lethal Prostate Cancer
Effort: 0.60 calendar months (5% effort)
Supporting Agency: Department of Defense, CDMRP
Grants Officer: TBD
Address of Funding Agency: 1077 Patchel Street, Fort Detrick, MD 21702-5024; 301-619-7782
Performance Period: 07/01/2019 – 06/30/2023
Level of Funding:
Principal Investigator: William Isaacs
Project Goal: The major goal of this project is to ascertain a set of candidate susceptibility genes for aggressive prostate cancer can be used to identify men at risk for aggressive/lethal disease.

Award: W81XWH-19-1-0781
Title: mTORC1 Regulates MiTF Expression and Lysosomal Biogenesis
Effort: .24 calendar months (2% effort)
Supporting Agency: Department of the Army
Name of Procuring Contracting/Grants Officer: Jason D. Kuhns
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 09/01/2019 – 08/31/2021
Level of Funding:
Principal Investigator: Kaushal Asrani
Project Goals: The major goal of this project is to study the regulation of MiT/TFE gene expression and determine whether MiT/TFE over-expression and a concomitant increase in lysosomal biogenesis are key drivers of tumorigenesis following TSC1/2 loss.
Specific Aims: Aim 1: To elucidate the molecular mechanism(s) of MiT/TFE regulation in the context of epidermal *Tsc1* and *Raptor* loss. Aim 2: To study the expression of MiT/TFEs and lysosomal genes in human and murine AML and *TSC1/2*-related RCC and the role of lysosomal biogenesis in renal tumors driven by TSC1/2 loss.

Award ID: W81XWH-19-1-0686
Title: Genetic and genomic determinants of homologous recombination repair deficiency as treatment selection markers for lethal prostate cancer
Effort: 0.60calendar months (5% effort)
Supporting Agency: Department of Defense, CDMRP
Grants Officer:
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702
Performance Period: 09/01/2019 – 08/31/2022
Level of Funding:
Principal Investigator: Jun Luo
Project Goal: The major goal of this project is to determine the genetic/genomic drivers of HRD predicting "deep" response to abiraterone and enzalutamide.
Specific Aims: Aim 1. To ascertain the HRD mutations status, both somatic and germline, in three existing advanced/lethal prostate cancer cohorts enriched for HRD using blood-based assays. Aim 2. To determine the association of HRD status defined by blood-based assays with treatment response to first-line AR-directed

therapy (abiraterone/enzalutamide) and taxane chemotherapies in mCRPC patients by comparing treatment outcomes of men in these three groups. Aim 3. To determine the expression correlates of HRD status defined by blood-based assays and further ascertained by tissue-based assays, by performing RNA-Seq in surgical specimens from men with lethal prostate PCa with: 1) germline/somatic HRD; 2) somatic-only HRD; and 3) negative HRD.

Award ID: W81XWH-20-1-0177
Title: Sequencing Testosterone and Enzalutamide to Prevent Unfavorable Progression (The STEP-UP Trial)
Effort: 0.60 calendar months (5% effort)
Supporting Agency: Department of Defense (DOD)
Grants Officer: TBD
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702
Performance Period: 04/01/2020-03/31/2024
Level of Funding:
Principal Investigator: Sam Denmeade
Project Goals: The major goal of this study is to generate proof-of-concept clinical data that could lead to a fundamental change in the way we administer hormonal therapy for prostate cancer.
Specific Aims: Aim 1. Evaluate the effect of high dose T and enzalutamide on prostate cancer immune microenvironment. Aim 2. Evaluate the effect of high dose T and enzalutamide on prostate cancer immune microenvironment. Aim 3. Evaluate the effects of alternating high dose T and Enza vs. Enza alone on emergence of neuroendocrine/small cell transdifferentiation. Aim 4. To evaluate the effect of rapid cycling of T and enzalutamide on cellular metabolism to identify potentially exploitable therapeutic targets.

Award ID: W81XWH-20-1-0254
Title: Deciphering DDX3-Mitochondrial Axis in Prostate Cancer
Effort: .60 calendar months (5% effort)
Supporting Agency: Department of Defense, CDMRP
Grants officer: Melaine Neagley
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702
Performance Period: 09/01/2020 – 08/31/2023
Level of Funding:
Principal Investigator: Venu Raman
Project Goal: The major goal of this project is to use DDX3 as a molecular determinant of mitochondrial heterogeneity associated with aggressive prostate cancer phenotype in AA men.
Specific Aims: Aim 1: To ascertain DDX3's functions in maintaining mitochondrial integrity and heterogeneity to promote aggressive prostate cancer phenotypes in the African American men.
Aim 2: To determine the effect of targeting the DDX3-mitochondrial axis by RK-33 both *in vitro* and *in vivo* models generated from African American and European American prostate cancer samples.
Aim 3: To compare African American and European American prostate cancer clinical samples for DDX3 expression that can be associated with aggressive cancer phenotypes.

Award ID: W81XWH-20-1-0843
Title: Targeting Lysosomal Biogenesis in Renal Tumors with TSC1/2 Loss
Effort: 1.44 calendar months (12% effort)
Supporting Agency: Department of Defense (DOD)
Grants officer: TBD
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702
Performance Period: 09/01/2020 – 08/31/2022
Level of Funding:
Principal Investigator: Tamara Lotan
Project Goal: The major goal of this project are to test whether lysosomal biogenesis is a potential driver and therapeutic target for renal tumorigenesis in the setting of TSC1 or TSC2 loss.

Specific Aims: Aim 1: Determine whether TSC1/2 loss is sufficient to drive lysosomal biogenesis and function analogous to MiT/TFE gene fusions in renal cell carcinoma. Aim 2: Establish whether MiT/TFE activity or lysosomal function drives tumorigenesis or tumor progression downstream of TSC1/2 loss or SFPQ-TFE3 fusion protein expression.

Award ID: 90091444
Title: Spatially Mapping the Tumor
Effort: .48 calendar months (4% effort)
Supporting Agency: Brown Performance Group
Grants officer:
Address of Funding Agency:
Performance Period: 10/26/2020 – 10/23/2023
Level of Funding:
Principal Investigator: Eugene Shenderov
Project Goal: The major goal of this project is to use Digital Spatial Profiling to examine the immune tumor microenvironment in primary prostate cancer.
Specific Aims:

Award ID: P50CA058236
Title: SPORE in Prostate Cancer
Effort: .24 calendar months (2% effort)
Supporting Agency:
Grants officer:
Address of Funding Agency:
Performance Period: 09/25/2014 – 08/31/2021
Level of Funding:
Principal Investigator: Sam Denmeade
Project Goal: The major goal of this core is to support the tissue banking and tissue-based assay development in the prostate cancer SPORE.
Specific Aims:

Pending Support:
None

Overlap: There is no scientific, budgetary, or commitment overlap

Recently Completed

Award ID: W81XWH-13-1-0271
Title: Molecular Profiling of Intraductal Prostate Carcinoma
Effort: 0.60 calendar months (5% effort)
Supporting Agency: Department of the Army
Grants Officer: Melissa D. Cunningham, Ph.D.
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 10/01/2013-09/30/2016
Level of Funding:
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to ascertain the molecular profile (at DNA and RNA level) of intraductal prostate carcinoma.

Award ID: W81XWH-12-PCRP-TIA
Title: Toward the Practice of Precision Medicine: A Biomarker Validation Coordinating Center
Effort: 1.2 calendar months (10% effort)

Supporting Agency: Department of the Army
Grants Officer: Melissa D. Cunningham, Ph.D.
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 10/01/2013-09/30/2017 (EWOF)
Level of Funding: (JHU)
Principal Investigator: Howard Scher (MSKCC)
Project Goals: The major goal of this project is to develop a number of tissue-based predictive biomarkers for use as integral markers in ongoing clinical trials in prostate cancer.

Award ID:
Title: Molecular and Clinical investigations to reduce the Morbidity of Prostate Cancer
Effort: 0.60 calendar (5% effort)
Supporting Agency: Prostate Cancer Foundation
Grants Officer: Howard R. Soule
Address of Funding Agency: 1250 Fourth Street, Santa Monica, CA 90401, 310-570-4700
Performance Period: 07/01/2013-06/30/2018
Level of Funding:
Principal Investigator: Ted Schaeffer
Project Goals: The major goal of this project is to identify molecular profiles of lethal prostate cancer.

Award ID: W81XWH-15-1-0661
Title: Comprehensive Molecular Profiling of African-American Prostate Cancer to Inform on Prognosis and Disease Biology
Effort: 0.60 calendar months (5% effort)
Supporting Agency: Department of the Army
Grants Officer: Kimberly Carter
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 10/01/2015-9/30/2018
Level of Funding:
Principal Investigator: Scott Tomlins (University of Michigan)
Project Goals: The major goal of this project is to identify the somatic genomic alterations and expression signatures associated with lethal prostate cancer in African-Americans.

Award ID: R01CA211695
Title: Regulation of Metastatic Development of Heritable Variants in the Tumor Microenvironment
Effort: 0.36 calendar months (3% effort)
Supporting Agency: National Cancer Institute
Grants Officer: Romy Reis
Address of Funding Agency: 9000 Rockville Pike, Bethesda, MD 20892
Performance Period: 09/01/2017 – 08/31/2022
Level of Funding:
Principal Investigator: Paula Hurley
Project Goals: Our goals are 1) to determine the contribution of ASPN to local tumor growth and metastatic development in autochthonous animal models, and to delineate the 2) cellular and 3) molecular based mechanisms by which ASPN D14 promotes and ASPN D13 restricts tumor progression and metastatic-invasion of prostate cancer.
***Role on project completed. - 09/01/2017 – 06/23/2019**

Award ID: RSG-17-160-01-CSM
Title: The Function of SPARC1 in Tumor Suppression
Effort: 0.36 calendar months (3% effort)
Supporting Agency: American Cancer Society
Grants Officer: Charles Saxe

Address of Funding Agency: 250 Williams St., Atlanta, GA 30303-1002
Performance Period: 01/01/2018 – 12/31/2021
Level of Funding:
Principal Investigator: Paula Hurley
Project Goal: Our long-term goal is to understand how SPARCL1 restricts tumor and metastatic progression.
***Role on project completed. - 01/01/2018 – 06/23/2019**

Award ID: 18CHAL15
Title: Dissecting the prostate cancer diaspora
Effort: 0.48 calendar months (4% effort)
Supporting Agency: Prostate Cancer Foundation (Challenge Award)
Grants Officer: Audrey Gardner
Address of Funding Agency: 1250 Fourth Street, Santa Monica, CA 90401, 310-570-4700
Performance Period: 02/08/2019-02/07/2022
Level of Funding:
Principal Investigator: Kenneth Pienta
Project Goal: The major goal of this project is to utilize a combination of PSMA-PET scans to identify early metastatic disease and leukapheresis to collect and genotype / phenotype CTCs to answer three fundamental questions related to the prostate cancer diaspora at the time of B.
***Role on project completed. - 02/08/2019 – 01/30/2020**

Award ID: R01CA200859
Title: Hardwiring Mechanism into Predicting Cancer Phenotypes by Computational Learning
Effort: 0.30 calendar months (2.5% effort)
Supporting Agency: National Cancer Institute
Grants Officer: Rebecca Brightful
Address of Funding Agency: 9000 Rockville Pike, Bethesda, MD 20892, 301-631-3011
Performance Period: 04/05/2016 – 03/31/2021
Level of Funding:
Principal Investigator: Luigi Marchionni
Project Goals: The major goal of this project is to develop an analytical framework to embed mechanistic constraints derived from network biology into the statistical learning process.
Specific Aims: (Aim 1) gene expression regulatory networks, (Aim 2) cell signaling activity, and (Aim 3) metabolism to classify breast and prostate cancer.
***Role on project completed. - 04/05/2016 – 08/31/2020**

Award ID: W81XWH-16-1-0737
Title: Developing a PTEN-ERG Signature to Improve Molecular Risk Stratification in Prostate Cancer
Effort: .12 calendar months (1% effort)
Supporting Agency: Department of the Army
Grants Officer: Kimberly Carter
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 09/30/2016 – 09/29/2020
Level of Funding:
Principle Investigator: Tamara Lotan
Project Goals: The major goal of this project is to develop a gene expression signature for PTEN loss in prostate cancer, stratified by ERG status.
Specific Aims: Aim 1: Validate association of PTEN and ETS status with risk of lethal PCa. Aim 2: Leverage multi-dimensional public domain data to discover genomic features and signaling pathways associated with PTEN loss in ERG-positive and ERG-negative PCa. Aim 3: Discover and validate gene regulatory and expression signatures associated with PTEN loss on genetically homogeneous ERG-positive and ERG-negative backgrounds.

Award ID: 90087049
Title: Validation of a mutational signature in oligometastatic prostate cancer treated with metastasis directed therapy
Effort: 0.24 calendar months (2% effort)
Supporting Agency: Fidelity Charitable
Grants Officer:
Address of Funding Agency:
Performance Period: 03/01/2020-02/28/2021
Level of Funding:
Principal Investigator: (**MPI:** Paller, Channing; Tran, Phuoc (Contact))
Project Goals: The major goal of this project is to validate a new mutational signature in men with oligometastic prostate cancer who have been treated with SABR
Specific Aims:

Award ID: W81XWH-19-1-0345
Title: Discovery and Functional Analyses of Susceptibility Genes for Lethal Prostate Cancer
Effort: 0.60 calendar months (5% effort)
Supporting Agency: Department of Defense, CDMRP
Grants Officer: TBD
Address of Funding Agency: 1077 Patchel Street, Fort Detrick, MD 21702-5024; 301-619-7782
Performance Period: 07/01/2019 – 06/30/2023
Level of Funding:
Principal Investigator: William Isaacs
Project Goal: The major goal of this project is to ascertain a set of candidate susceptibility genes for aggressive prostate cancer can be used to identify men at risk for aggressive/lethal disease.