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TITLE: Comprehensive Molecular Profiling of African-American Prostate Cancer to Inform on Prognosis and Disease Biology

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CONTRACTING ORGANIZATION: University of Michigan
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Regents of the University of
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3003 S. State Street
Ann Arbor, MI 48109

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Epidemiological studies consistently show worse prostate cancer (PCa) incidence and mortality rates in African American (AA) vs. white/Caucasian (CA) men. Although the etiology is likely multi-factorial, increasing evidence supports biologic contributors and AA PCa may arise through distinct pathways and harbor unique molecular alterations. We hypothesized that comprehensive molecular analysis of a carefully annotated AA PCa cohort (including anatomical annotation) will inform on the applicability of PCa prognostic signatures and identify novel drivers of aggressive disease in AA patients, thereby impacting the clinical management of AA patients and improving our understanding of the molecular events that underlie racial disparities in PCa behavior. Herein, using a large well annotated cohort of AA PCa, we are assessing the performance of prognostic gene expression signatures, and characterizing known and novel gene fusions, mutations and copy number alterations to develop novel prognostic signatures and assess the validity of commercially available signatures in AA men.

15. SUBJECT TERMS

African American, prognostic signatures, anterior prostate cancer, molecular signatures, prostatectomy

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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INTRODUCTION:
Epidemiological studies consistently show worse prostate cancer (PCa) incidence and mortality rates in African American (AA) vs. white/Caucasian (CA) men. Although the etiology is likely multi-factorial, increasing evidence supports biologic contributors. Our previous work and others show that that even after adjustment for socioeconomic factors, AA men show elevated risks of poor outcome. Likewise, we have shown that PCa in AA men has a unique zonal distribution within the prostate. Hence, AA PCa may arise through distinct pathways and harbor unique molecular alterations, however this possibility has not been well explored. High throughput technologies have enabled extraordinary insight into the PCa transcriptome/genome, including molecular subtypes driven by recurrent gene fusions; however such studies have been performed nearly exclusively in predominantly CA cohorts. Importantly, prognostic gene expression based tests for PCa have recently been developed, and are being aggressively marketed to patients, despite little validation in AA men. We hypothesized that comprehensive molecular analysis of a carefully annotated AA PCa cohort (including anatomical annotation) will inform on the applicability of PCa prognostic signatures and identify novel drivers of aggressive disease in AA patients, thereby impacting the clinical management of AA patients and improving our understanding of the molecular events that underlie racial disparities in PCa behavior. Herein we will assess the performance of PCa prognostic gene expression signatures and well as characterize known and novel PCA gene fusions, mutations and copy number alterations in AA men to develop novel prognostic signatures and assess the validity of commercially available signatures in AA men.

KEYWORDS:
African American, prognostic signatures, anterior prostate cancer, molecular signatures, prostatectomy

ACCOMPLISHMENTS:
What were the major goals of the project?:

SPECIFIC AIMS
1) Perform comprehensive expression profiling of PCa in AA men to assess the performance of PCa prognostic gene expression signatures.
2) Characterize known and novel PCa gene fusions in AA men.
3) Characterize known and novel PCa mutations and CNAs in AA men to develop an integrated prognostic signature.
.

What was accomplished under these goals?
To accomplish these aims, we developed a collaboration between Drs. Tomlins (PI; University of Michigan [UM]), Dr. Edward Schaffer (Qualifying Co-PI, Johns Hopkins Medical Institute [JHU]; moved to Northwestern University [NU] during the project period), Dr. Tamara Lotan (JHU) and Dr. Luigi Marchionni (JHU). Our proposed statement of work included work at both UM and JHU and progress is reported (in italics) according to the submitted statement of work

1. IRB Approval

a. Local IRB/IACUC Approval (months 1-2)
b. HRPO/ACURO Approval (months 2-3)

Both UM and JHU have received local IRB and HRPO approval. MTAs are in place between UM, JHU and GenomeDX for transferring material (no MTA with NU is needed).

Overall, these tasks are 100% complete.

1. Specific Aim 1: Assess the performance of prostate cancer (PCa) prognostic gene expression signatures in African American (AA) men
    a. Retrospectively identify prostatectomy cases from AA men (n=192) from institutional database. (months 2-9)
    b. Histopathological review of prostatectomy cases to identify tumor foci and evaluate anatomic location. (months 3-12)
    c. Histological processing of a representative formalin fixed paraffin embedded (FFPE) block from each case. (months 3-12)
    d. Macrodissection of FFPE sections to enrich for tumor content as needed (months 3-12).
    e. Transfer of FFPE tissue to UMMS for DNA/RNA isolation and next generation sequencing. (months 3-12)
    f. Isolate DNA/RNA from FFPE tissues. (months 3-12)
    g. Affymetrix profiling of RNA by GenomeDX to generate Decipher, Prolaris and Oncotype DX scores, identify known gene fusions through outlier analysis and nominate gene fusions (months 13-18)
    h. Evaluation of Decipher, Prolaris and Oncotype DX scores for predicting upgrading, high stage and margin status in AA men stratified by NCCN risk group. (months 18-20)

After local IRB and HRPO approval, a retrospective search was performed through the JMHI prostate cancer tissue bank. 192 AA PCa cases were identified. Dr. Lotan reviewed all cases, identified tumor foci and noted anatomical locations, and punched tissue cores from the FFPE block for each case. All cases were transferred to UM and were subjected to co-isolation of DNA and RNA in the Tomlins laboratory. DNA and RNA were quantified using the Qubit fluorometer, with an average of 818ng DNA and 988ng RNA isolated per sample. Over 95% of samples showed acceptable RNA and DNA quantity, and insufficient cases have been replaced. RNA was transferred to GenomeDX after significant delay due to finalization of workplan alignment and prioritization of clinical profiling at GenomeDX. Affymetrix profiling of RNA is now ongoing and estimated to be complete within 3 months.

Overall, tasks a-f are 100% complete. Tasks g and h are 50% complete.

2. Specific Aim 2: Characterize known and novel PCa gene fusions in AA men.
    a. Targeted capture RNA NGS of cases (n=96) with novel candidate gene fusions. (months 18-24)
    b. Exome capture RNA NGS of cases (n=36) without candidate gene fusions. (months 18-24)

c. Targeted multiplexed PCR based next generation sequencing of RNA from AA cases (n=192) to confirm GenomeDX expression signatures and predicted gene fusions. (months 24-30)
d. Compare known and novel gene fusion frequencies between AA and Caucasian (CA) men, NCCN risk groups of AA men, and anatomical tumor location. (months 30-36)

Tasks a-d have been delayed due to delays in RNA profiling in Aim 1 Tasks g & h. All tasks can begin and rapidly completed upon completion of Aim 1.

3. Specific Aim 3: Characterize known and novel somatic PCa mutations in AA men.
    a. Targeted multiplexed PCR based next generation sequencing of DNA from AA cases (n=192) to identify somatic copy number alterations, point mutations and indels. (months 13-18)

Task a is 90% completed. High quality DNA libraries have been generated for all 192 patients using a novel targeted DNA sequencing panel developed for this study and sequencing is complete for half of the overall cohort with the other half to be completed within a month. Of note, this panel, which includes 3,127 amplicons targeting 312,920 bases in 140 genes, enables assessment of both global copy number alterations (informed by assessment of LOH through targeting common SNPs) and oncogenic and tumor suppressive mutations. After finalization of sequencing and inclusion of RNA data, this dataset will be formally locked for final analysis. Across the cohort, we achieved an average of >3,500,000 mapped reads, >1,000x coverage and >90% uniformity.

    b. Compare somatic alteration frequency between NCCN risk groups and anatomical tumor location.(months 18-20)

Task b is 75% completed. The anatomic assessment will be formally completed with integration of RNA analysis from Aim 1.Preliminary assessment of rates of recurrent somatic mutation alteration frequency across NCCN risk groups is shown in ***Table 1****. Results will be finalized once the dataset (RNA and RNA) is finalized and locked for formal analysis.*

Gene	NCCN Risk Group	
	Intermediate	High
SPOP	16.4%	20.7%
TP53	3.0%	3.4%
PTEN	0.0%	3.4%
CTNNB1	0.0%	0.0%
BRAF	6.0%	0.0%
IDH1	1.5%	0.0%
HRAS	3.0%	0.0%
MED12	1.5%	0.0%
FOXA1	11.9%	20.7%
NKX3-1	0.0%	0.0%
ERF	0.0%	0.0%

TABLE 1. Somatic mutation frequencies in prostate cancer driver genes observed in this cohort stratified by NCCN Risk Group. Passenger mutations have been excluded.

c. Compare somatic alteration frequency between profiled AA cases and external CA cohorts. (months 18-20)

Task c is 90% completed. Preliminary assessment of rates of recurrent somatic mutation alteration frequency between this AA cohort and AA and CA patients from the TCGA cohort is shown in ***Table 2****. Results will be finalized once the dataset (RNA and RNA) is finalized and locked for formal analysis.*

Gene	TCGA		This cohort
	CA	AA	AA
SPOP	8.1%	20.9%	13.5%
TP53	8.1%	0.0%	3.1%
PTEN	2.2%	0.0%	1.0%
CTNNB1	2.2%	0.0%	0.0%
BRAF	0.4%	7.0%	4.2%
IDH1	0.7%	2.3%	1.0%
HRAS	1.1%	0.0%	2.1%
MED12	1.1%	0.0%	1.0%
FOXA1	0.7%	0.0%	14.6%
NKX3-1	0.0%	0.0%	0.0%
ERF	0.4%	0.0%	0.0%

TABLE 2. Somatic mutation frequencies in prostate cancer driver genes observed in the TCGA cohort (stratified by CA and AA status) and this cohort. Passenger mutations have been excluded.

d. Determine whether the inclusion of gene fusions or somatic events improves the performance of the gene expression classifiers from Aim 1. (months 20-34)

Task d is 0% completed and will require integration of DNA and RNA data.

e. Prepare manuscript on study. (months) 34-36

Task e is 0% completed and will require integration of DNA and RNA data.

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 have achieved our year 1 goals and the DNA component of our year 2 goals (months 13-24) and have generated the largest cohort of DNA and RNA from anatomically annotated AA PCa. The RNA microarray profiling component was significantly delayed due to workplan prioritization with our commercial partner, however profiling is ongoing. During the next year, we will complete RNA microarray and targeted RNAseq profiling and integrate results with the completed DNA sequencing.

IMPACT:
What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report

What was the impact on other disciplines?
Nothing to Report

What was the impact on technology transfer?
Nothing to Report

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

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
RNA microarray profiling with our commercial partner was delayed, however profiling is now ongoing and should not significantly delay completion of the overall proposal. Importantly, the

targeted RNAseq panel is fully designed and can be run without updating based on RNA profiling if needed.

Changes that had a significant impact on expenditures
Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to Report

PRODUCTS:
Publications, conference papers, and presentations
Nothing to Report

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

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Scott Tomlins
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Tomlins has led all aspects of the study as the PI, including coordinating the project with JHU (and NU) investigators.
Funding Support:	

Name:	Edward Schaeffer
Project Role:	Qualifying Co-PI
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Schaeffer led the identification of cases from JHU and interaction with GenomeDX to advance the microarray profiling.
Funding Support:	

Name:	Tamara Lotan
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Lotan led the histologic review and anatomic localization assessment.
Funding Support:	
Name:	Luigi Marchionni
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Marchionni has led the integration of clinicopathologic information from reviewed samples into a study specific database.
Funding Support:	

Name:	Albert Liu
Project Role:	Technician
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person	7

month worked:	
Contribution to Project:	Mr. Liu led the DNA profiling in the Tomlins lab.
Funding Support:	

- **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 see the Appendix for updated Other Support documents for Drs. Tomlins, Schaeffer, Lotan and Marchionni. New and Ended support is indicated for each investigator.

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

Johns Hopkins University
353 Garland Hall
3400 North Charles Street
Baltimore, MD 21218-2688
Partnering PI and Co-Investigators (Drs. Schaeffer, Lotan and Marchionni)

Northwestern University
Tarry Building Room 16-703
300 E. Superior
Chicago, IL 60611-3010
Partnering PI (Dr. Schaeffer moved institutions during the year 1 project period)

SPECIAL REPORTING REQUIREMENTS

Collaborative Awards:
N/A

Quad Charts:
N/A

APPENDICES (see next page):
Updated Other Support for Dr. Tomlins
Updated Other Support for Dr. Schaeffer
Updated Other Support for Dr. Lotan
Updated Other Support for Dr. Marchionni

PREVIOUS, CURRENT, AND PENDING SUPPORT

TOMLINS, SCOTT

ACTIVE

5 P50 CA069568-15 (PI: Chinnaiyan) 09/01/14 - 08/31/19 12.5%
NIH $193,476/yr

SPORE in Prostate Cancer

Overview: This application consists of four multidisciplinary projects: Project 1: A Precision Medicine Approach to Elucidate Mechanisms of Progression and Resistance to Therapy in Advanced PCa; Project 2: Mechanisms of Sensitivity and Resistance to Cabozantinib in CRPC; Project 3: Development of Novel BET Bromodomain Inhibitors for the Treatment of Advanced PCa; Project 4: Development of IncRNAs as PCa Biomarkers in Urine. These projects are complemented by ongoing, successful Career Development and Developmental Research Programs.

Role: Co-Leader of Project 2

Contact Information at funding agency: Andrew Hruszkewycz, 301-496-8528, hruszkea@mail.nih.gov

R01CA183857 (PI: Tomlins) 04/3/14 - 02/28/19 21%
NIH $207,500/yr

Exploiting drivers of androgen receptor signaling negative prostate cancer for precision medicine

Goal(s): Identify novel potential drivers of AR- prostate cancer through sequencing xenografts and tissue samples. Qualify novel drivers of AR- prostate cancer through in vitro models. Develop novel treatment strategies for AR- and AR+ prostate cancer through in vivo models.

Specific Aims: 1) Identify novel potential drivers of AR- prostate cancer. 2) Qualify novel drivers of AR- prostate cancer through *in vitro* models. 3) Develop novel treatment strategies for AR- and AR+ prostate cancer through *in vivo* models exploiting AR- drivers.

Contact information at Funding Agency: Morrow, Charles, 301-451-4467, morrowcs@csr.nih.gov

R01 CA181605 (PI: Nelson) 01/01/14 - 12/31/18 10%
NIH $80,000/yr

Non Invasive Biomarkers for Diagnosing Clinically Significant Prostate Cancer

Goal(s): Test the hypothesis that biomarkers indicative of adverse prostate cancer behavior—Gleason grade, tumor volume and detrimental molecular alterations—can be reproducibly detected in the urine of men with prostate cancer; Determine whether initial sampling of a panel of urine biomarkers and the repeated assessment of a urine biomarker panel over time will associate with the presence of significant versus insignificant cancer in the prostate, and thus can be used in informing decisions for continuing surveillance or proceeding with definitive treatment.

Specific Aims: 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 assessments in men on Active Surveillance; 2) Evaluate a panel of long non-coding RNAs (lncRNAs) in tissue and urine for the detection of significant prostate cancer in men on Active Surveillance; 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.

Role: Co-Investigator

Contact information at Funding Agency: Alexander Moreno, amoreno@fhcrc.org

R01 DK106618 (PI: Rainey and Tomlins) 03/01/16-02/28/20 10%
NIH $299,867/yr

Adrenal Origins of Aldosterone Excess
Goals(s): This proposal will test the hypotheses that most adults have neoplastic cells bearing "first hit" somatic mutations that cause renin-independent aldosterone production. Primary aldosteronism and hypertension result from additional "multi-hit" mutations that increase cell proliferation, tumor development and pathologic levels of aldosterone. We will test the hypotheses that APCC are dysplastic cells bearing somatic gene mutations that activate aldosterone production and that APA have the same mutations seen in APCC, but exhibit additional mutations that cause cell proliferation and tumor development.
Specific Aims: 1) Define the somatic mutations found in normal adrenals that exhibit adrenal aldosterone-producing cell clusters (APCC). 2) Define the somatic gene mutations present in aldosterone-producing adenomas (APA).
Contact Information at Funding Agency: Saul N Malozowski Email: malozowskis@extra.niddk.nih.gov, Phone: (301) 451-4683

PC141474 (PI: Tomlins) 09/30/15-09/29/18 10%
DOD $169,574/yr
Comprehensive Molecular Profiling of African-American Prostate Cancer to Inform on Prognosis and Disease Biology
Goal(s): Perform comprehensive expression profiling of prostate cancer (PCa) in AA men to assess the performance of PCa prognostic gene expression signatures and characterize known and novel gene fusions, mutations and copy number alterations.
Specific Aims: 1) Perform comprehensive expression profiling of PCa in AA men to assess the performance of PCa prognostic gene expression signatures. 2) Characterize known and novel PCa gene fusions in AA men. 3) Characterize known and novel PCa mutations and CNAs in AA men to develop an integrated prognostic signature.
Contact Information at funding agency: Tom Winter, thomas.s.winter2.civ@mail.mil, (240) 357-1590.

R01 CA196619 (PI: Cho) 05/01/16-04/30/19 2.5%
NIH $304,358/yr
Credentialing Ovarian Cancer Models in the Context of the Dualistic Pathway Paradigm
Goal(s): Enhance the applicability of mouse models for translational research using novel genetically engineered mouse models (GEMMs). We have developed a new GEMM that employs the Ovgp1 promoter to direct expression of Tamoxifen (TAM)-inducible Cre recombinase in the fallopian tube epithelium (FTE). Ovgp1-iCreERT2 mice that also carry floxed alleles of tumor suppressor genes that are characteristically inactivated in ovarian endometrioid carcinoma (OEC, prototypical Type I tumor) and high grade serous ovarian carcinomas (HGSC, prototypical Type II tumor) can be induced to form tumors in the FTE following treatment with TAM, or tumors arising in the ovarian surface epithelium (OSE) following ovarian bursal injection of adenovirus expressing Cre.
Specific Aims: 1) To credential GEMMs of ovarian cancer (OvCa) arising from FTE- transformation as superior to those arising from OSE-transformation in terms of their morphological and molecular similarity to their human OvCa counterparts; and 2) To test a new tool strain for early detection of oviductal HGSCs based on cervical-vaginal lavage (murine Pap test).
Role: Co-Investigator
Contact Information at funding agency: Mariam Eljanne, Email: eljannem@mail.nih.gov, Phone: 301-443-3612

U01CA214170 (PI:Chinnaiyan and Tomlins) 09/01/16-08/31/21 10%
NIH $370,065/yr
Discovery and qualification of transcriptomic biomarkers for the early detection of aggressive prostate cancer

Goal(s): Nominate and develop transcriptomic biomarkers as predictors of aggressive prostate cancer both at and prior to diagnosis.
Specific Aims: 1) Identify and develop assays to study novel aggressive prostate cancer-associated transcriptomic alterations from our MiTranscriptome analysis. 2) Characterize transcripts from Aim 1 as tissue based aggressive prostate cancer biomarkers using individual in situ hybridization assays and a multiplexed next generation sequencing (NGS). 3) Characterize transcripts from Aim 1 as non-invasive, urine-based aggressive prostate cancer early detection biomarkers through collaboration with our industry partner and multiplexed NGS.
Contact information at Funding Agency: Sudhir Srivastava, 240-276-7028, ss1a@nih.gov

PENDING

(PI Rubin) 04/01/17-03/31/22 5%
NIH $97,336/yr
Towards Understanding the Genomic Heterogeneity of Metastatic Prostate Cancer (SPORE Project)
Goal(s): As part of the Weill Cornell Medical College S.P.O.R.E., this project aims to assess a large cohort of paired primary ADT-naïve and metastatic CRPC specimens to understand and exploit the molecular mediators of PCa progression to inform on optimal clinical pathologic practice, identify biomarkers, and inform on disease biology.
Specific Aims: 1). Collect and histologically characterize original primary ADT-naïve specimens from patients enrolled in the CRPC 500 trial. 2). Determine the molecular landscape of multiple tumor foci from the original ADT-naïve CRPC 500 specimens through DNA and RNA sequencing. 3). Identify molecular mediators of PCa progression and track the progressing clone through an integrative molecular profiling analysis of paired primary ADT-naïve and CRPC specimens
Role: Project Co-Leader (Co-Investigator)
Contact information at Funding Agency: Seran Lee-Johnson, sel2016@med.cornell.edu, (646) 962-6998

PC151032 (PI: Cooney) 09/30/18-09/29/19 3%
DOD $26,743/yr
Characterizing the Genetic Landscape of Prostate Cancer in Young African American Men
Goals(s): The underlying hypothesis of this proposal is that African American men with early-onset prostate cancer are more likely to harbor germline variants that increase the risk of developing clinically significant prostate cancer, as well as novel driving somatic alterations. In this proposal, NGS approaches will be used to analyze germline DNA from 750 African American men with clinically significant prostate cancer diagnosed before age 60 years of age focusing on genes already known to be mutated in the germline or tumor of men with prostate cancer or other cancers as well as genes in functional pathways of interest (i.e. hormone biosynthesis and signaling and DNA damage repair).
Specific Aims: 1) Collect germline DNA from 750 young African-American men diagnosed with clinically significant prostate cancer. 2) Perform germline sequencing of candidate genes on the cohort to identify to identify deleterious variance. 3) Perform targeted next generation sequencing on tumor samples from the subset of the men with germline DNA mutations.
Role: Co-Investigator
Christine LaSalle, christine.lasalle@hsc.utah.edu, (801) 585-2734

RO1 (Wei) 8/1/2017-7/31/2019 5%
NIH $628,831/yr
Clinical utility of multiplex biomarkers for high grade prostate cancer: A cost effective followup study expanding upon the existing EDRN prostate cancer reference set.

Goals: The specific aims include: 1) To expand the existing EDRN's unique pre-diagnostic reference set with RNA sequencing of pre-biopsy urine; 2) To optimize the risk prediction for high grade prostate cancer within 5 years of initial prostate biopsy. This aim will focus only on those who were initially biopsied in the PCA3 cohort.
Role: Co-Investigator

RO1 (El Naqa, Piert) 2/1/2018-1/31/2023 5%
NIH $490,890/yr
AN INTEGRATIVE HYBRID IMAGING RADIOMICS AND MOLECULAR BIOMARKERS FRAMEWORK FOR PREDICTING SIGNIFICANT PRIMARY PROSTATE CANCER
Goals: Our goal is to develop a personalized non-invasive diagnostic test to distinguish indolent from aggressive prostate cancer. The study will determine how a new promising PET tracers could be employed to improve prostate risk stratification by combining radiomics features from PET/MR with known laboratory biomarker tests.
Role: Co-Investigator

ENDED WITHIN THE LAST 5 YEARS

Award No. N/A (PI: Knudsen) 10/15/12 – 10/15/14 2%
Movember-Prostate Cancer Foundation $250,000/yr
Challenge Award
Interrogating DNA Repair Defects to Improve Management of Advanced Prostate Cancer
Goal(s): The overall goal of this proposal is to identify therapeutic strategies to target DNA damage response pathway alterations in patients with advanced prostate cancer.
Specific Aims: 1) To identify and comprehensively determine the frequency of aberrations in DNA damage response pathways at different stages of prostate carcinogenesis; 2) To determine the clinical relevance of these DNA repair defects; 3) To evaluate the functional and biological consequences of these DNA repair defects and identify novel therapeutic strategies that will benefit patients suffering from such cancers.
Role: Co-Investigator
Contact Information at funding agency: Audrey Gardner, PCF Applications (applications@pcf.org)

Award No. N/A (PI: Knudsen/Feng/Tomlins) 12/01/13 - 11/30/15 2.5%
Prostate Cancer Foundation $200,000/yr
Targeting DNA Repair Alterations To Improve Treatment for Advanced Prostate Cancer
Goal(s): Comprehensively interrogate DNA repair alterations in both AR-positive and AR-negative CRPC to develop novel biomarkers and therapeutic strategies with the goal of improving outcomes for patients with these aggressive diseases
Specific Aims: 1) Determine the molecular and cellular consequence of tumor-associated DNAPK dysregulation; 2) Assess the impact of targeting DNAPK and the DDR on tumor progression & therapeutic response; 3) Targeting AR-mediated DNA repair through the requisite cofactor USP22; 4) Profiling DNA repair alterations in AR-negative, late stage disease.
Role: Co-PI
Contact Information at funding agency: Audrey Gardner, PCF Applications (applications@pcf.org)

Award No. N/A (Dream team leader: Chinnaiyan) 08/01/12 – 07/31/15 2.5%
AACR Stand up to Cancer and $808,511/yr
Prostate Cancer Foundation Dream Team
Precision Therapy of Advanced Prostate Cancer
Goal(s): The overall goal of this proposal is to catalyze the interaction of a multi-disciplinary team of investigators, with a track record of accomplishments in prostate cancer research, to work together on the challenging problem of metastatic castration resistant prostate cancer (CRPC).

Specific Aim(s): 1) Establish a multi-institutional infrastructure incorporating 5 leading prostate cancer clinical sites, 2 sequencing and computational analysis sites, linked with appropriate sample and data coordination; 2) Establish a prospective cohort of 500 patients (the "CRPC 500") utilizing the multi-institutional infrastructure to support the clinical use of integrative prostate cancer sequencing, analysis, and clinical trial decision making; 3) Conduct parallel, preclinical *in vivo* functional studies of resistance biomarkers and of SU2C-PCF sponsored combination therapies; 4) Identify molecular determinants of abiraterone sensitivity and acquired resistance in patients; 5) Conduct clinical trials of novel combinations targeting AR and/or the PTEN pathway, based on existing preclinical data and an understanding of resistance mechanisms; 6) Identify molecular determinants of sensitivity and acquired resistance to PARP inhibitors in patients.
Role: Co-Investigator
Contact Information at funding agency: Frederic Biemar, (frederic.biemar@aacr.org), (215) 446-7261

PC120464 (PI: Cooney) 09/30/13 - 09/29/16 12%
Department of Defense $125,060/yr
High throughput sequencing of germline and tumor from men with early-onset, metastatic prostate cancer
Goal(s): To perform next generation sequencing on germline DNA, prostate cancer, and normal prostate tissue on samples from men with early-onset, clinically significant disease.
Specific Aims: 1. To identify and clinically characterize a set of 20 men who present with Stage 4 (Tx N1 and/or M1) prostate cancer at an early age defined as at or before age 60, and 2. To interrogate the germline exome and tumor exome/transcriptome from 20 men with early-onset Stage 4 prostate cancer to identify novel molecular alterations that may contribute to the early-onset, aggressive prostate cancer.
Role: Co-Investigator
Contact Information at Funding Agency: Kathy E. Robinson, Grants Officer, Us Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick Md 21702-5014

PC121111 (PI: Scher, H.) 10/01/13 – 09/30/16 2%
Department of Defense $300,000/yr
Toward the Practice of Precision Medicine: A Biomarker Validation Coordinating Center
Goals(s): Establish Multicenter Validation of Biomarker Assays for Clinical Management of Prostate Cancer and validate TMPRSS2:ERG assays; Validate the utility of the TMPRSS2:ERG TMA assay for the non-invasive detection of clinically significant prostate cancer in urine; Validate the ERG rearrangement FISH assay on tissues and determine the prevalence of ERG rearrangements in isolated precursor and diagnostically challenging lesions
Specific Aims: 1) To cross-validate an initial set of assays for biomarkers corresponding to the AR and PI3K/PTEN axes ready for near-term filing with the FDA for use in prospective integral biomarker-driven trials in prostate cancer; 2) To use the centralized infrastructure of the Assay Validation Coordinating Center to cross-validate additional assays for biomarkers identified via established and emerging discovery platforms (i.e., NCI Prostate Cancer SPOREs, PCF, SU2C, and TCGA) for use in prospective integral biomarker-driven trials in prostate cancer.
Role: Co-Investigator
Contact Information at Funding Agency: Kathy E. Robinson, Grants Officer, Us Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick Md 21702-5014

UM1HG006508 (PI: Chinnaiyan) 07/19/13 – 06/30/17 2%
National Institutes of Health $1,312,107/yr
Exploring Precision Cancer Medicine for Sarcoma and Rare Cancers
Goal(s): The overall goal of this project is to bring together expertise at the University of Michigan including clinical oncology, cancer genetics, genomic science/bioinformatics, clinical pathology, social and behavioral sciences, and bioethics in order to implement clinical cancer sequencing of patients with

sarcomas and other rare cancers to enable the detection of clinically significant molecular lesions (point mutations, insertions/deletions, gene fusions and rearrangements, outlier expressed genes, and amplifications/deletions).
Specific Aims: Project 1: Clinical Genomic Study, 1) Accrue 500 patients with advanced or refractory rare cancer for participation in an integrated approach to Clinical Genomics; 2) Interpret results through a multi-disciplinary Sequencing Tumor Board and disclose results to patients and their physicians; 3) Measure the influence of sequence results provided to patients; 4) Determine the frequency of clinically significant germline mutations in patients undergoing comprehensive tumor sequence analysis.
Project 2: Sequencing, Analysis, and Interpretation of Sequencing Data; 1) Process and track specimens and ensure quality control; 2) Sequence tumor and germline biospecimens; 3) Analyze sequencing data to identify clinically significant variants; 4) Interpret and translate sequence variants into clinical oncology setting; 5) Assess and evaluate costs associated with clinical sequencing.
Role: Co-Investigator
Contact Information at funding agency: Harvey, Zephaun, harveyz@mail.nih.gov, 301 435-7859

Award No. N/A (PI: Maher/Feng/Sharifi/Tomlins 01/01/15 - 12/31/16 1%
Prostate Cancer Foundation $121,000/yr
Identifying Early Biomarkers of Anti-Androgen Treatment Resistance and Lethal Prostate Cancer
Goal(s): Radiation Therapy Oncology Group (RTOG) 96-01 represents a phase III trial of of salvage radiation therapy (RT) alone versus combined therapy (androgen deprivation therapy [ADT] and RT). This represents a highly unique population of 771 patients with aggressive localized prostate cancer following standard treatment options with long-term clinical outcomes (median follow-up of 9 years). The overarching goal of this proposal is to leverage this unique patient population to explore the molecular underpinnings predictive of treatment response and associated with lethal disease.
Role: Co-PI
Contact information at Funding Agency: Audrey Gardner, agardner@pcf.org

Award No. N/A (PI: Rubin/Tomlins) 07/01/15 - 06/30/17 1%
Prostate Cancer Foundation $155,076/yr
Integrative Genomics of Prostate Cancer Progression
Goal(s): Retrospectively collect, review, and perform comprehensive molecular characterization on the original diagnostic biopsy or prostatectomy samples from men with castration resistant prostate cancer (CRPC) participating on the CRPC 500 trial to identify molecular determinants of prostate cancer progression.
Contact information at Funding Agency: Audrey Gardner, agardner@pcf.org

PC13065 (PI: Tomlins) 09/17/14 – 09/16/17 7%
Department of Defense $125,000/yr
Clonal Evaluation of Prostate Cancer by ERG/SPINK1 Status to Improve Prognosis Prediction
Goal(s): Utilize ERG/SPINK1 status to assess the frequency of multiclonality in clinically relevant scenarios and to determine whether incorporating tumor clonality improves prognostic prediction.
Specific Aims: 1) Assess the frequency of multiclonality in clinically important scenarios using dual ERG/SPINK1 IHC; 2) Determine whether multiclonality assessment at biopsy improves prediction of pathology at prostatectomy; 3) Assess whether multiclonality assessment of index foci at prostatectomy improves outcome prediction
Contact information at funding agency: Theresa J. Miller, Ph.D , Phone: 301-619-6875; theresa.j.miller.ctr@mail.mil

OVERLAP

There is no scientific or budgetary overlap.

PREVIOUS, CURRENT, AND PENDING SUPPORT

SCHAEFFER, EDWARD

Active

U01CA196390
Title: Multidiciplinary Integrative Genomic Approach to Distinguish Lethal from Indolent Prostate Cancer in Men of European and African Ancestry
Time Commitment: .60 calendar months (5% effort)
Supporting Agency: NIH/NCI (Pienta - PI)
Name of Procuring Contracting/Grants Officer: Elizabeth Woodhouse
Address of Funding Agency: 9000 Rockville Pike, Bethesda, MD 20892
Performance Period: 9/1/2015 - 8/31/2020
Level of Funding: $85,613
Project Goal: The overall goal of this project is to develop a distinctive molecular signature that can predict the subsequent fates of early lesions distinguishing indolent from progressive disease with lethal potential.
Specific Aims:
1. Develop integrated genomic, epigenomic and expression profiling signatures of indolent and aggressive prostate cancer from both white and African-American men.
2. Validate biomarkers and pathways in active surveillance and autopsy patients.
3. Validate biomarkers in relation to patient outcome, with emphasis on intermediate-risk and African-American patients.
Projects overlap or parallel: None

W81XWH-15-1-0661/PC141474
Title: Comprehensive Molecular Profiling of African-American Prostate Cancer to Inform on Prognosis and Disease Biology
Time Commitment: .96 calendar months (8% effort)
Supporting Agency: DOD/Army via University of Michigan (Tomlins - PI)
Name of Procuring Contracting/Grants Officer: Tom Winter, Grants Specialist, US Army Medical Research Acquisition Activity, Phone: 240-357-1590, Email: thomas.s.winter2.civ@mail.mil
Address of Funding Agency: 1120 Fort Detrick, Frederick, MD 21702
Performance Period: 9/1/2015 - 9/29/2018
Level of Funding: $85,964
Project Goal: The major goal of this project is to create a comprehensive molecular profile of African-American Prostate Cancer to inform on the prognosis and disease biology of the disease.
Specific Aims:
1. Assess the performance of multiple prognostic expression signatures in FFPE RP specimens from a well-annotated cohort of African American men with long term clinical follow-up and anatomical tumor information.
2. Identify novel gene fusions in African American men through multiple approaches.
3. Characterize known somatic genetic alterations in the same cohort of African American men assessed in Aims 1&2.
Projects overlap or parallel: None

Title: A Prospective Validation of a Prostate Cancer Biomarker in African American Men
Time Commitment: .96 calendar months (8% effort)
Supporting Agency: V Foundation for Cancer Research (Murphy - PI)
Name of Procuring Contracting/Grants Officer: Jefferson Parker
Address of Funding Agency: 14600 Weston Parkway, Cary, NC 27513; Tel: 919-380-9505
Performance Period: 11/1/2016 - 10/31/2019
Level of Funding: $600,000

Project Goal: The overall goal of this project is to validate the Prostate Health Index (PHI) screening test in African Americans to reduce cancer outcome disparities in African American men.
Projects overlap or parallel: None

Title: Molecular and Clinical Investigations to Reduce the Morbidity of Prostate Cancer
Time Commitment: .60 calendar months (5% effort)
Supporting Agency: Prostate Cancer Foundation
Name of Procuring Contracting/Grants Officer: Kathy Schwertfeger
Address of Funding Agency: 1250 4th St, Santa Monica, CA 90401: Tel: 310-570-4700
Performance Period: 12/1/2016 - 11/30/2019
Level of Funding: $1,390,000
Project Goal: The overall goal of this project is to perform molecular and clinical investigation to reduce the morbidity of prostate cancer.
Projects overlap or parallel: None

W81XWH-17-1-0608/PC160355
Title: Creation and Validation of a Pre-Biopsy Nomogram for Predicting High-Risk Prostate Cancer in African American Men
Time Commitment: .60 calendar months (5% effort)
Supporting Agency: DOD/Army via Northwestern University (Murphy- PI)
Name of Procuring Contracting/Grants Officer: Mirlene Desir
Address of Funding Agency: 1120 Fort Detrick, Frederick, MD 21702
Performance Period: 9/1/2017 - 6/30/2020
Level of Funding: $795,361
Project Goal: An AA-tailored clinical prediction model will have improved discrimination relative to the PCPT RC for predicting Gleason >6 PCa in AAM undergoing prostate biopsy. Rationale: Many AAM undergo prostate biopsy unnecessarily and many others defer biopsies due to medical mistrust which could be ameliorated with a tailored RC for predicting high-risk PCa.[Halbert CH, Cancer, 2009] Thus, we will innovatively compare the effectiveness of the PCPT RC for high-risk PCa in AAM vs. EAM, tailor and internally validate a model from a retrospective AAM cohort and assess the performance of the AA-tailored prediction model relative to the PCPT RC in prospective recruited AAM eligible for prostate biopsy.
Projects overlap or parallel: None

***W81XWH-17-1-0302/PC160284**
Title: Investigating Long Noncoding RNAs as Biomarkers and Mediators of Prostate Cancer Progression in African American Men
Time Commitment: 1.20 calendar months (10% effort)
Supporting Agency: DOD/Army via University of California, San Francisco (Feng - PI)
Name of Procuring Contracting/Grants Officer: TBD
Address of Funding Agency: 1120 Fort Detrick, Frederick, MD 21702
Performance Period: 10/1/2017 - 9/30/2020
Level of Funding: $138,930
Project Goal: The purpose of this project is to investigate the role of long noncoding RNAs in prostate cancer progression in African American patients.
Specific Aims:
1. Utilize recently developed lncRNA compendia, in tandem with tumor expression data from clinical cohorts, to identify lncRNAs which drive disease progression in African American men.
2. Determine if lncRNAs can serve as non-invasive biomarkers in African American men.
3. Investigate the roles of LNC00883 and RP11-627H22.9.intergenic in PCa progression in African American men, using phenotypical, functional, and mechanistic studies in preclinical models of disease.
Projects overlap or parallel: None

Pending

None

Previous

R01CA134675
Title: High-Specificity Imaging Agents for Aggressive Prostate Cancer
Time commitments: 1.80 calendar months (15% effort)
Supporting Agency: NIH/NCI (Renewal) (Pomper - PI)
Grants Contact: Leota Hall; Program Official; 240-276-6449; halle@gmail.nih.gov
Performance Period: 4/1/2015-3/30/2020
Level of Funding: $443,885
Description of Goals: The goals of this project are to leverage existing but untested agents and to develop new agents for imaging PC, with a focus on aggressive, localized disease.
Aim 1: Imaging of patients with biopsy-proved primary PC with DCFPyL-PET with subsequent correlation of PET signal with histopathology at prostatectomy for PSMA expression, Gleason score and other markers
Aim 2: Synthesis of select PSMA-targeted imaging agents that (a) encompass a new scaffold to engender superior affinity and pharmacokinetics; (b) are hetero-bivalent (HtBv), homing to a rationally chosen co-target (in addition to PSMA); or, (3) enable detection with MR through signal amplification
Aim 3: Development and testing of new agents for imaging the PC microenvironment
Projects overlap or parallel: None

W81XWH-11-1-0336
Title: RNASEH2A-A Putative "Non-Oncogene Addiction" Gene Target and Marker for Radio-sensitivity in High Risk Prostate Cancer
Time Commitment: 1.2 calendar months (10% effort)
Supporting Agency: US Army Medical Research & Materiel Command (Schaeffer - PI)
Name of Procuring Contracting/Grants Officer: Chris Baker
Address of Funding Agency: 820 Chandler St., Fort Dedrick, MD 21702-5014
Performance Period: 9/30/2011 - 9/29/2014
Level of Funding: $0.00
Project Goal: Establish that RNASEH2A is associated with lethal, high grade disease and that it's involved with maintaining chromosomal stability.
Specific Aims:
1: Demonstrate the association of RNASEH2A with lethal prostate cancer.
2: Evaluate the ability of RNASEH2A to modulate radio-sensitivity in prostate cancer cell lines and xenograft models.
3: Investigate RNASEH2A as a marker of radio-sensitivity
Projects overlap or parallel: Minimal overlap with other projects. We utilize biochemical techniques and mouse modeling protocols already established in the lab.

Title: Pathogenic Effect of Cytosolic Phospholipase C Alpha In Prostate Carcinogenesis
Time Commitment: 1.2 calendar months (10% effort)
Supporting Agency: Howard Hughes Medical Institute (Schaeffer - PI)
Name of Procuring Contracting/Grants Officer: Dr. Anh-Chi Le
Address of Funding Agency: Howard Hughes Medical Institute, Office of Grants and Special Programs/EARLY, 4000 Johns Bridge Road, Chevy Chase, Maryland 20815; Phone: 301-215-8879; Fax: 301-215-8888
Performance Period: 8/1/2009 - 7/31/2014
Level of Funding: $0.00

Project Goal: The major goal of this project is to establish an essential role for phospholipase A2 (cPLA2) in prostate carcinogenesis.
Specific Aims:
1: Demonstrate activation of cPLA2 in response to Fgf/Mapk signaling in malignant prostatic epithelium. Prostatic growth is regulated through Fgf/Mapk signaling and in prostate organogenesis Fgf/Mapk signaling activates cPLA2. We hypothesize that Fgf via the Map kinase, Erk 1,2, activates cPLA2 in prostate carcinoma cells lines. A. cPLA2 activation will be assessed by phosphorylation, cPLA2 activity assays and AA production. B. Fgf/Erk activation will be modulated with both endogenous activating ligands and synthetic small molecules inhibitors of FgfR and Erk1,2.
2: Demonstrate that activation of cPLA2 induces prostatic epithelial growth. Signaling through both the FgfR/Mapk pathway and inflammatory cytokines including AA and prostaglandins induce prostate epithelial proliferation. As cPLA2 produces AA and induces prostaglandin production, this aim tests the affect of cPLA2 activity on prostate epithelial growth in vitro and in vivo.
Alterations of cPLA2 expression will be achieved with inducible over expression and siRNA constructs. Modulation of cell growth will be assayed in vitro with colorimetric assays and in vivo with BrdU incorporation/Ki67 staining.
3: Quantify the pathogenic effects of cPLA2 in prostate carcinogenesis.FGF receptor-1 is over expressed in human prostate tumors and mice with prostate epithelial specific inducible FgfR1 (JOCK1 mice) develop, sequentially, hyperplasia, prostatic intraepithelial neoplasia (PIN) and localized and metastatic prostate cancer. Preliminary immunohistochemical analyses
reveal increased cPLA2 expression in all stages (hyperplasia, PIN and Cancer). We propose that cPLA2 is a key component to FgfR induced prostate cancer. FgfR1 induced tumors will be analyzed histologically for activation of cPLA2 and its targets. FgfR1 induced tumor extracts will be assayed biochemically for activation of cPLA2 with phosphorylation specific antibodies, cPLA2 activity assays and measurement of the cPLA2 product, arachadonic acid. JOCK1 mice will be crossed to mice deficient in cPLA2 and sequentially followed by necropsy to determine if absence of cPLA2 delays or
attenuates tumor formation.
Projects overlap or parallel: Overlap minimal. Overlap involves use of the same biochemical techniques to assay Pla2 in developing tissue (K08)and cancer tissue/models (HHMI).

Title: Roles for Phospholipase A2 Signaling in Prostate Development
Time Commitment: 0.6 calendar months (5% effort)
Supporting Agency: American Urological Association Foundation (Schaeffer - PI)
Name of Procuring Contracting/Grants Officer: Rodney Cotton
Address of Funding Agency:
Performance Period: 1/1/2009 - 3/31/2013
Level of Funding: $52,000.00
Project Goal: The major goal of this project is to study and establish an essential role for phospholipase A2 (cPLA2) in prostatic development and patterning, and to become more knowledgeable in molecular genetics and the pathology of human prostatic diseases.
Specific Aims:
1: Correlating spacio-temporal Pla2 expression in prostate organogenesis
2: Demonstrating activation of Pla2 by FGF/Erk1, 2
3: Genetically evaluating the role of Pla2 in prostate development.
Projects overlap or parallel: Overlap minimal. Overlap involves use of the same biochemical techniques to assay Pla2 in developing tissue (K08) and cancer tissue/models (HHMI).

K08DK081019
Title: Roles for Phospholipase A2 Signaling in Prostate Development
Time Commitment: 6 calendar months (50% effort)
Supporting Agency: NIDDK, NIH (Schaeffer - PI)
Name of Procuring Contracting/Grants Officer: Charlette Kenley

Address of Funding Agency: 2 Democracy Plaza, Rm. 711, 6707 Democracy Blvd., Bethesda MD 21092; Telephone: 301-480-8847; Fax: 301-480-3504
Performance Period: 4/1/2008 - 3/31/2013
Level of Funding: $145,600.00
Project Goal: The major goal of this project is to study and establish an essential role for phospholipase A2 (cPLA2) in prostatic development and patterning, and to become more knowledgeable in molecular genetics and the pathology of human prostatic diseases.
Specific Aims:
1: Correlating spacio-temporal Pla2 expression in prostate organogenesis
2: Demonstrating activation of Pla2 by FGF/Erk1, 2
3: Genetically evaluating the role of Pla2 in prostate development.
Projects overlap or parallel: Overlap minimal. Overlap involves use of the same biochemical techniques to assay Pla2 in developing tissue (K08) and cancer tissue/models (HHMI).

W81XWWH-12-1-0473
Title: ASPN, A Novel Inhibitor of TGFbeta and a Putative Biomarker for Aggressive Prostate Cancer
Time Commitment: 0.36 calendar months (3% effort)
Supporting Agency: Congressionally Directed Medical Research (Hurley - PI)
Name of Procuring Contracting/Grants Officer: TBD - Congressionally Directed Medical Research
Address of Funding Agency: U.S. Army Medical Research and Materiel Command, 1077 Patchel Street, Building 1077, Fort Detrick, MD 21702-5024
Performance Period: 9/30/2012 - 9/29/2015
Level of Funding: $76,146.00
Project Goal: We aim to determine if ASPN is a novel marker for high grade aggressive prostate cancer and to evaluate the ability of ASPN genetic variants to contribute to disease progression and to predict clinical outcome.
Specific Aims:
1: Demonstrate the association of ASPN expression in cancer reactive stroma with lethal prostate cancer.
2: Evaluate the ability of allelic variants D13, D14, and D17 of ASPN to promote prostate cancer progression.
3: Evaluate polymorphisms in the aspartic acid repeat domain of ASPN as a genetic biomarker for prostate cancer progression potential.
Projects overlap or parallel: None

90054274
Title: Molecular and Clinical Investigations to Reduce the Morbitity of Prostate Cancer
Time Commitment: 5.4 calendar months (45% effort)
Supporting Agency: Prostate Cancer Foundation (Schaeffer - PI)
Name of Procuring Contracting/Grants Officer: Howard Soule, Ph.D.
Address of Funding Agency: 1250 Fourth Street, Santa Monica, CA 90401
Performance Period: 7/1/2013 - 12/1/2015
Level of Funding: $660,000.00
Project Goal: The overall goal of this project is to use a multi-project approach to decrease the morbitity of prostate cancer.
Specific Aims:
1: To understand the environmental and genetic factors that contribute to the development of prostate cancer.
2: To determine if high dose lovastatin inhibits MYC activity and to determine an optimal does of lovastatin to inhibit MYC activity in men with intermediate/high-grad localized prostate cancer and MYC overexpression after prostatectomy.
3: To determine the pharmacodynamic effects of LDE225 on resected prostate tissue from men undergoing radical prostatectomy for high-risk localized prostate cancer.
Projects overlap or parallel: None

W81XWH-14-1-0284
Title: PC130991 Cell-Free Plasma Tumor DNA as a Biomarker for Guiding Prostate Cancer Therapy
Time Commitment: 0.48 calendar months (4% effort)
Supporting Agency: Congressionally Directed Medical Research (Hurley - PI)
Name of Procuring Contracting/Grants Officer: TBD - Congressionally Directed Medical Research
Address of Funding Agency: U.S. Army Medical Research and Materiel Command, 1077 Patchel Street, Building 1077, Fort Detrick, MD 21702-5024
Performance Period: 7/1/2014 - 12/1/2015
Level of Funding: $124,112.08
Project Goal: The goal of this proposal is to develop a specific and sensitive non-invasive liquid biopsy that recapitulated tumor genetics in real time to allow for physicians to track tumor genetic heterogeneity and evolution.
Specific Aims:
1: Evaluate the efficacy of ptDNA to monitor clonal evolution in response to primary systemic therapy in men with metastatic prostate cancer.
2: Evaluate the efficacy of ptDNA to monitor clonal evolution in response to treatment in men with castration-resistant prostate cancer.
Projects overlap or parallel: None

PREVIOUS, CURRENT, AND PENDING SUPPORT

LOTAN, TAMARA

Active Research Support:

R01 CA200858-01
Title: Molecular and Cellular Mechanisms of Resistance to mTORC1 Inhibition in the Skin
Effort: 3.0 calendar months or 25%
Supporting Agency: US National Institutes of Health
Name of Procuring Contracting/Grants Officer: Romy Reis
Address of Funding Agency: NIH 616 Executive Boulevard, Suite 7013, MSC 8347, Rockville, MD 20852/ NCI Public Inquiries Office 6116 Executive Boulevard Room 3036A Bethesda, MD 20892-8322
Performance Period: 02/03/2016-1/31/2021
Level of Funding: $200,000
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
Projects overlap or parallel: No scientific or budgetary overlap.

Title: Molecular and Clinical investigations to Reduce the Morbidity of Prostate Cancer
Effort: 0.6 calendar or 5% effort
Supporting Agency: Prostate Cancer Foundation
Name of Procuring Contracting/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: $1,320,000
Principal Investigator: Ted Schaeffer
Project Goals: The major goal of this project is to identify molecular profiles of lethal prostate cancer.
Projects overlap or parallel: No scientific or budgetary overlap.

W81XWH-15-1-0661 (Subaward ID 3003957277)
Title: Comprehensive Molecular Profiling of African-American Prostate Cancer to Inform on Prognosis and Disease Biology
Effort: 0.6 calendar months or 5%
Supporting Agency: Regent of the University of Michigan
Name of Procuring Contracting/Grants Officer: TBD
Address of Funding Agency: 109 Zinn Pitcher Place Lab 1858BSRB, Ann Arbor, MI 48109-2200
Performance Period: 09/30/2016-09/29/2019
Level of Funding: $159,797
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.
Projects overlap or parallel: No scientific or budgetary overlap.

W81XWH-16-1-0737
Title: Developing a PTEN-ERG Signature to Improve Molecular Risk Stratification in Prostate Cancer
Effort: 1.2 calendar months or 10%
Supporting Agency: Department of the Army
Name of Procuring Contracting/Grants Officer: Lymor Barnhard
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 09/30/2016-09/29/2019

Level of Funding: $284,751
Principal Investigator: Tamara Lotan (Partnering PI)
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.
Projects overlap or parallel: No scientific or budgetary overlap.

W81XWH-17-1-0286
Title: PC160336-Interaction between the Inflammatory Microenvironment and Somatic Genomic Alterations as a Driver of Prostate Cancer Aggressiveness in African American Men
Effort: 1.2 calendar months or 10%
Supporting Agency: Department of the Army
Name of Procuring Contracting/Grants Officer: TBD
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 09/30/2017-09/29/2020
Level of Funding: $278,311
Principal Investigator: Karen Sfanos (Lotan is Qualified Collaborator)
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.
Projects overlap or parallel: No scientific or budgetary overlap.

W81XWH-17-1-0425
Title: PC160783-Prospective-Retrospective Analysis of PTEN Immunohistochemistry Assay for Prediction of Outcomes in Recurrent and Metastatic Prostate Cancer
Effort: 1.2 calendar months or 10%
Supporting Agency: Department of the Army
Name of Procuring Contracting/Grants Officer: TBD
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 09/30/2017-09/29/2020
Level of Funding: $600,000
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to examine association of PTEN loss and ERG status with outcomes in two large clinical trials for advanced/metastatic prostate cancer (RTOG 9601 and ECOG 3805).
Projects overlap or parallel: No scientific or budgetary overlap.

Pending Research Support:
RSG-17-160-01-CSM
Title: The Function of SPARC1 in Tumor Suppression
Time Commitment: 0.36 calendar months (3% effort)
Supporting Agency: American Cancer Society (Hurley - PI)
Name of Procuring Contracting/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: $165,000
Project Goal: Our long term goal is to understand how SPARCL1 restricts tumor and metastatic progression.
Specific Aims:
1: Elucidate SPARCL1-induced molecular mechanisms that restrict invasion.
2: Determine how SPARCL1 regulates the ECM to restrict tumor progression.
3: Determine the feasibility and utility in targeting SPARCL1 in prostate cancer.
Projects overlap or parallel: None

Title: Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Immunity and Access to Care (RESPOND)
Effort: 1.2 calendar months or 10%
Supporting Agency: US National Institutes of Health
Name of Procuring Contracting/Grants Officer: TBD
Address of Funding Agency: NIH 616 Executive Boulevard, Suite 7013, MSC 8347, Rockville, MD 20852/ NCI Public Inquiries Office 6116 Executive Boulevard Room 3036A Bethesda, MD 20892-8322
Performance Period: 09/01/2017-08/31/2022
Level of Funding: $2,000,000
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.
Projects overlap or parallel: No scientific or budgetary overlap.

R01 CA211695
Title: Regulation of Metastatic Development by Heritable Variants in the Tumor Microenvironment
Time Commitment: 0.36 calendar months (3% effort)
Supporting Agency: NCI (Hurley - PI)
Name of Procuring Contracting/Grants Officer: TBD
Address of Funding Agency: 9000 Rockville Pike, Bethesda, MD 20892
Performance Period: 09/01/2017 – 08/31/2022
Level of Funding: $250,000
Project Goal: 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.
Specific Aims: The overall goal of this project is to map the "sensory GPCRs" landscape and identify novel biomarkers for PCa.
1: Determine the role of ASPN in primary and metastatic prostate cancer development.
2: Determine the role of ASPN D-repeat variants in MSC pluripotency and self-renewal.
3: Elucidate ASPN-mediated molecular mechanisms that regulate MSC pluripotency and renewal.
Projects overlap or parallel: None

Title: Role of miR-21 and PDCD4 in Prostate Cancer Development and Progression
Time Commitment: 0.6 calendar months (5% effort)
Supporting Agency: NCI (Lupold - PI)
Name of Procuring Contracting/Grants Officer: TBD
Address of Funding Agency: 9000 Rockville Pike, Bethesda, MD 20892
Performance Period: 07/01/2018 – 06/30/2023
Level of Funding: $250,000
Project Goal:
Specific Aims: The overall goal of this project is to map the "sensory GPCRs" landscape and identify novel biomarkers for PCa.
1: Determine the role of ASPN in primary and metastatic prostate cancer development.
2: Determine the role of ASPN D-repeat variants in MSC pluripotency and self-renewal.
3: Elucidate ASPN-mediated molecular mechanisms that regulate MSC pluripotency and renewal.
Projects overlap or parallel: None

Title: PTEN IHC and MYC ISH Single Detection in Gleason 3+3 Prostate Cancer
Effort: 0.05 calendar months or (0.5% effort)
Supporting Agency: Ventana Medical Systems

Name of Procuring Contracting/Grants Officer: Bryce Portier, MD PhD
Address of Funding Agency: 1910 E Innovation Park Dr., Tucson, AZ
Performance Period: 08/01/2017-05/31/2018
Level of Funding: $6,000
Principal Investigator: Tamara Lotan
Project Goals: Determine prognostic significance of combined single slide detection of PTEN loss (IHC) and MYC amplification (ISH) for Gleason 3+3 prostate cancer upgrading to Gleason 3+4=7 and above.
Projects overlap or parallel: No scientific or budgetary overlap.

Completed Research Support

K08DK088769
Title: Spatiotemporal Modulation of PIP[3] Signaling in Prostatic Tubulogenesis
Effort: 6.0 calendar or 50% effort
Supporting Agency: NIDDK
Name of Procuring Contracting/Grants Officer: Charlette Kenley
Address of Funding Agency: 2 Democracy Plaza, Room 623, 6707 Democracy Blvd., Bethesda, MD 20892-5458, (301) 594-8847
Performance Period: 9/15/2010-8/31/2015
Level of Funding: $144,700
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to examine the effects of PI3K and PTEN signaling in prostatic morphogenesis.

Title: Role of the PTEN/PIP[3] Signaling Pathway in Prostate Epithelial Morphogenesis
Effort: 0.6 calendar or 5% effort
Supporting Agency: Howard Hughes Medical Institute, Early Career Physician-Scientist Award
Name of Procuring Contracting/Grants Officer: Anh-Chi Le
Address of Funding Agency: 4000 Jones Bridge Road, Chevy Chase, Maryland 20815-6789, (800) 448-4882, ext. 8879
Performance Period: 8/1/2009-7/31/2015 (NCE)
Level of Funding: $75,000
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to define the role of PTEN in regulating epithelial migration during prostate development.

W81XWH1210186
Title: Role of TSC1/2 and mTOR Signaling in Epidermal Cell Differentiation
Effort: 1.2 calendar months or 10% (no salary support)
Supporting Agency: Department of the Army
Name of Procuring Contracting/Grants Officer: Kathryn M. Dunn, Grants Officer,
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 06/01/2012-05/31/2015 (NCE)
Level of Funding: $50,000
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to test whether TSC1/2 function regulates downstream Notch activation in differentiating keratinocytes, and whether the primary cilium coordinates TSC1/2 activity during epidermal development.

R03DK097375
Title: Role of mTORC1 In The Regulation Of Prostatic Branching Morphogenesis
Effort: 0.6 calendar months or 5% (no salary support)

Supporting Agency: NIDDK
Name of Procuring Contracting/Grants Officer: Charlette Kenley
Address of Funding Agency: 2 Democracy Plaza, Room 623, 6707 Democracy Blvd., Bethesda, MD 20892-5458, (301) 594-8847
Performance Period: 09/30/2012-07/31/2015 (NCE)
Level of Funding: $50,000
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to ascertain the molecular and cellular mechanisms by which mTORC1 regulates prostatic branching morphogenesis.

Title: Mechanism and Prognostic Utility of PTEN Protein Inactivation in Prostate Cancer
Effort: 0.6 calendar or 5% effort
Supporting Agency: Prostate Cancer Foundation
Name of Procuring Contracting/Grants Officer: Howard R. Soule
Address of Funding Agency: 1250 Fourth Street, Santa Monica, CA 90401 310-570-4700
Performance Period: 12/1/2011-11/30/2015 (NCE)
Level of Funding: $75,000
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to identify alternative mechanisms of PTEN inactivation in prostate cancer and to evaluate the prognostic utility of an assay to assess PTEN protein levels in prostate tumors.
Projects overlap or parallel: There is no scientific overlap.

W81XWH-13-1-0271
Title: Molecular Profiling of Intraductal Prostate Carcinoma
Effort: 0.60 calendar months or 5%
Supporting Agency: Department of the Army
Name of Procuring Contracting/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: $75,000
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.
Projects overlap or parallel: No scientific or budgetary overlap.

W81XWH-13-2-0070
Title: Toward the Practice of Precision Medicine: A Biomarker Validation Coordinating Center
Effort: 1.2 calendar months or 10%
Supporting Agency: Department of the Army
Name of Procuring Contracting/Grants Officer: Melissa D. Cunningham, Ph.D.
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 10/01/2013-9/30/2016 (NCE)
Level of Funding: $300,000 (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.
Projects overlap or parallel: No scientific or budgetary overlap.

PREVIOUS, CURRENT, AND PENDING SUPPORT

MARCHIONNI, LUIGI

ACTIVE EXTRAMURAL SUPPORT

R01 PA-13-302 (PI: Marchionni)
Title: Hardwiring Mechanism into Predicting Cancer Phenotypes by Computational Learning
Effort: 2.83 calendar months (23.55% effort)
Supporting Agency: National Institutes of Health (NIH)/ National Cancer Institute (NCI)
Name of Procuring Contracting/Grants Officer: Jacquelyn Boudjeda
Address of Funding Agency: 9000 Rockville Pike, Bethesda, Maryland 20892
Performance Period: 04/05/2016-03/31/2021
Level of funding: $257,120
Projects Goal: To develop novel mechanistic algorithms and classifiers for prognostication in cancer
List of the Specific Aims: Aim 1: Develop prediction models based on gene expression regulatory modules; Aim 2: Learn interpretable relationships among signaling pathways; Aim 3: Ground statistical observations with biochemically detailed metabolic networks.
Justification for the requested support: Dr. Marchionni is the PI and will oversee the whole project.
Projects overlap/parallel: There is no scientific or budgetary overlap, the project is synergistic with the current proposal.

DoD – PCRP – 2015 (Marchionni)
Title: Developing a PTEN-ERG Signature to Improve Molecular Risk Stratification in Prostate Cancer
Effort: 3.0 calendar months (25% effort)
Supporting Agency: Congressionally Directed Medical Research Programs – Department of Defense
Name of Procuring Contracting/Grants Officer: Melissa D. Cunningham, Ph.D.
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 09/30/2016-09/29/2019
Level of Funding: $150,926 (direct costs per year)
Principal Investigator: Tamara Lotan
Project Goals: The major goal of this project is to develop a molecular signature associated with PTEN and ERG for better stratification of prostate cancer patients.
List of the 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.
Justification for the requested support: Dr. Marchionni is the PI of the project and he will provide oversight on all research activities and perform analyses.
Projects overlap or parallel: No scientific or budgetary overlap.

P30CA006973 (Nelson)
Title: Regional Oncology Research Center – Bioinformatics Core
Effort: 0.96 calendar months (8% effort)
Supporting Agency: National Institutes of Health (NIH)/National Center Institute (NCI)
Name of Procuring Contracting/Grants Officer: Ms. Judy Sint, NIH, 6120 Executive Blvd., EPS Room 243 Bethesda, MD 20892; phone: 301-496-7240; judy.sint@nih.gov
Performance Period: 07/01/2017-04/30/2022

Level of funding: $141,400
Projects Goal: The major goals of this project are to provide bioinformatics consultation and support to investigators in the Cancer Center.
List of the Specific Aims: To provide comprehensive Bioinformatics expertise to Cancer Center members.
Justification for the requested support: Dr. Marchionni performs bioinformatics analysis for investigators at the cancer center.
Projects overlap/parallel: There is no scientific or budgetary overlap. If any of the pending grant will be funded Dr. Marchionni will reduce his effort on this grant accordingly.

U01CA196390 - (De Marzo - Pienta)
Title: Multidisciplinary Integrative Genomic Approach to Distinguish Lethal from Indolent Prostate Cancer in Men of European and African Ancestry
Effort: 1.2 calendar months (10% effort)
Supporting Agency: National Institutes of Health (NIH)/ National Cancer Institute (NCI)
Name of Procuring Contracting/Grants Officer: NA
Address of Funding Agency: 9000 Rockville Pike, Bethesda, Maryland 20892
Performance Period: 09/10/2015-08/31/2020
Level of Funding: $16,562 (salary only)
Project's Goal: To characterize "multi-omics" profiles in selected population of prostate cancer men.
List of the Specific Aims: Aim 1: Integrated Genomic, Epigenomic and Expression Profiling of Indolent and Aggressive Prostate Cancer from both White and African-American Men; Aim 2: Validation of Biomarkers and Pathways in Active Surveillance and Autopsy Patients; Aim 3: Validation of Biomarkers in Relation to Patient Outcome, with Emphasis on Intermediate Risk and African American Patients.
List of the Specific Aims: No scientific or budgetary overlap.
Justification for the requested support: Dr. Marchionni will provide computational and statistical support.
Projects overlap/parallel: There is no scientific or budgetary overlap; the project is synergistic with the current proposal.

R01CA206027 – NCI Provocative Questions – (Multi-PI: Sidransky/Hoque)
Title: PQ1: Identification and characterization of genetic alterations for the progression of pre-neoplastic lung lesions by using novel PDx models and deep sequencing.
Effort: 1.14 calendar months in year 1 (9.5% effort)
Supporting Agency: National Cancer Institute (NCI)
Name of Procuring Contracting/Grants Officer: NA
Address of Funding Agency: NA
Performance Period: 07/01/2016-06/30/2021
Level of funding: $13,368 (salary only)
Projects Goal: To develop PDX models of early lung lesions for comprehensively identifying molecular markers for lung cancer clinical management.
List of the Specific Aims: Aim 1: To establish patient-derived xenografts (PDX) models of pre-neoplastic lesions, screen detected and interval invasive lung cancers; Aim 2: To identify specific mutational patterns and heterogeneity of early stage adenocarcinoma as a measure of indolence/aggressiveness; Aim 3: Understanding biologic significance and clinical relevance of a given mutational events on a key gene in primary tumors for future preventive and therapeutic strategy development.
Justification for the requested support: Dr. Marchionni will assist with data analysis.
Projects overlap/parallel: There is no overlap in goals of the project.

R01CA208709 (Sidransky/Hoque)
Title: PQ5: Exploring whole mitochondrial genome of screen detected pre-neoplastic lung lesions by novel approaches.
Effort: 0.48 calendar months (4% effort)

Supporting Agency: National Cancer Institute (NCI)
Name of Procuring Contracting/Grants Officer: NA
Address of Funding Agency: NA
Performance Period: 09/13/2016-08/31/2021
Level of Funding: $6,757 (salary only)
Project Goal: To obtain a clear understanding of changes in mitochondrial DNA (mtDNA) along the pathway of lung adenocarcinoma pathogenesis. Results from this proposal will provide new insight in the mechanisms of genesis of pre-neoplastic lesions and its progression.
List of Specific Aims: Aim 1: To understand the heterogeneity of mtDNA at the somatic mutation level along the pathway of early stage lung adenocarcinoma; Aim 2: To understand the heterogeneity of mtDNA at the somatic mutation level as a measure of indolence/aggressiveness in spiral CT screening follow-up cohort; Aim 3: To determine the performance of an optimized plasma test for mtDNA mutation presence in CT detected pre-neoplastic lung lesions patients.
Justification for the requested support: Dr. Marchionni will assist with data analysis.
Projects overlap/parallel: There is no overlap in goals of the project.

R21 AI124776-01 (PI: Romerio) – Subcontract from University of Maryland
Title: PrimeFlow RNA for detection of latently-infected CD4+ T cells
Effort: 1.2 calendar months (10% in year 2)
Supporting Agency: National Institutes of Health (NIH)
Name of Procuring Contracting/Grants Officer: NA **Address of Funding Agency:** NA
Performance Period: 06/01/2017-05/31/2018
Level of funding: $26,897
Projects Goal: to establish a PrimeFlow RNA-based assay for the detection, enumeration, and phenotypic characterization of HIV-1 latently infected cells in clinical samples.
List of the Specific Aims: Aim 1: Estimation of the HIV-1 reservoir in clinical samples by PrimeFlow RNA; Aim 2: Phenotypic analyses of infected cells identified by PrimeFlow RNA in clinical samples.
Justification for the requested support: Dr. Marchionni will oversee genomic analysis in Aim 2.
Projects overlap/parallel: There is no overlap in goals of the project.

W81XWH-16-PCRP-IDA (PI: Lupold)
Title: PC160669 The Role of Alternative Polyadenyaltion in Advanced Prostate Cancer
Effort: 0.59 calendar months (4.95%)
Supporting Agency: Congressionally Directed Medical Research Programs – Department of Defense
Name of Procuring Contracting/Grants Officer: NA **Address of Funding Agency:** NA
Performance Period: 09/01/2017-08/31/2020
Level of funding: $8,362 (salary only)
Projects overlap/parallel: There is no overlap in goals of the project.

AWARDED (not active)

1R01CA211695-01A1 (PI: Hurley)
Title: Regulation of Metastatic Development by Heritable Variants in the Tumor Microenvironment.
Effort: 0.36 calendar months (3%)
Supporting Agency: National Institutes of Health (NIH)
Name of Procuring Contracting/Grants Officer: NA **Address of Funding Agency:** NA
Performance Period: 09/01/2017-08/31/2022
Level of funding: $250,000
Projects Goal: To determine the contribution of ASPN to local tumor growth and metastatic development in autochthonous animal models

List of the Specific Aims: Aim 1: Determine the role of ASPN in primary and metastatic prostate cancer development; Aim 2: Determine the paracrine role of ASPN D-repeat length variants secreted by CAFs in inducing biomechanical mechanisms necessary for cancer cell invasion; Aim 3: Determine the ASPN-mediated molecular mechanisms that regulate cytoskeletal remodeling and ultimately, invasion.
Justification for the requested support: Dr. Marchionni will oversee genomic computational analyses.
Projects overlap/parallel: There is no overlap in goals of the project.

PENDING

None

COMPLETED EXTRAMURAL SUPPORT

R01CA163594 (Sidransky)
Title: Discovery and Characterization of methylation Markers
Effort: 0.6 calendar months (5% effort)
Supporting Agency: NIH
Name of Procuring Contracting/Grants Officer: Dr James V Tricoli, EPN BG, Room 6026, 6130 Executive Blvd, Rockville, MD, 20852; Phone: 301 402-4185; email: james.tricoli@nih.gov
Performance Period: 07/01/2012-04/30/2017
Level of funding: $207,500
Projects Goal: Identify common epigenetic alterations in bladder tumor evolution to help us understand their impact on UCC development, role in cancer progression and biological role in drug resistance.
List of the Specific Aims: Aim 1) To comprehensively screen for novel tumor-specific genes silenced by promoter hypermethylation in primary bladder tumors and UCC cell lines Aim 2) To test multiple promoter hypermethylation markers for bladder UCC in various tissues and bodily fluids from patients with and without disease to establish simple sensitivity and specificity estimates. Aim 3) To test the functional significance and clinical relevance of the novel genes in primary tumors
Justification for the requested support: Dr. Marchionni provides statistical support.
Projects overlap/parallel: There is no scientific or budgetary overlap.

DoD - PCRP 2012 (Lotan)
Title: Molecular Profiling of Intraductal Prostate Carcinoma
Effort: 0.60 calendar months or 5%
Supporting Agency: National Institutes of Health (NIH)
Name of Procuring Contracting/Grants Officer: NA **Address of Funding Agency:** NA
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 10/01/2013-09/29/2016
Level of Funding: $75,000
Principal Investigator: R
Project Goals: The major goal of this project is to ascertain the molecular profile (at DNA and RNA level) of intraductal prostate carcinoma.
List of the Specific Aims: NA
Justification for the requested support: Dr. Marchionni provides statistical and bioinformatics support.
Projects overlap or parallel: No scientific or budgetary overlap.

R01GM083084 (Irizarry)
Title: Prepocessing and Analusis Tools for Contemporary MicroArray.
Effort: 0.48 calendar months or 4%
Supporting Agency: Congressionally Directed Medical Research Programs – Department of Defense

Name of Procuring Contracting/Grants Officer: Melissa D. Cunningham, Ph.D.
Performance Period: 09/30/2013-08/31/2016
Level of Funding: $3,117 (salary only)
Principal Investigator: Rafael Irizarry
Project Goals: To develop the next generation of preprocessing and analysis tools with an emphasis on translational applications.
List of the Specific Aims: NA
Justification for the requested support: Dr. Marchionni provides statistical and bioinformatics support.
Projects overlap or parallel: No scientific or budgetary overlap.

KKESH (Eberhart)
Title: Identifying and Targeting Invasion-Promoting Molecular Pathways In Retinoblastoma
Effort: 0.91 calendar months or 7.56%
Supporting Agency: King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia
Name of Procuring Contracting/Grants Officer: NA
Address of Funding Agency: NA
Performance Period: 02/24/2015-02/28/2017
Level of Funding: $12,431 (salary only)
Principal Investigator: Charles Eberhart
Project Goals: To study the mechanisms and pathways that control invasion into the choroid and optic nerve of retinoblastoma cells causing metastatic spread.
List of the Specific Aims: Aim 1: To identify the molecular pathways associated with retinoblastoma spread into optic nerve and choroid; Aim 2: To confirm their role in promoting tumor invasion in order to develop new prognostic.
Justification for the requested support: Dr. Marchionni provides statistical and bioinformatics support.
Projects overlap or parallel: No scientific or budgetary overlap.

R01 (Ha)
Title: Integrated pathway analysis of altered driver genes in adenoid cystic carcinoma
Effort: 1.53 calendar months (12.75% effort)
Supporting Agency: NIH– NIDCR
Name of Procuring Contracting/Grants Officer: Sundaresan Venkatachalam, venkatachalams@mail.nih.gov, Telephone: 301-594-4812.
Performance Period: 09/01/2012-08/31/2015
Level of funding: $250,000
Projects Goal: to utilize the newest array-based technologies and an integrated pathway-based analysis to identify relevant driver genes in adenoid cystic carcinoma tumorigenesis.
List of the Specific Aims: Aim 1: To perform multiplatform whole-genome analysis including whole genome methylation profiling, RNA sequencing, exome sequencing, and SNP array; Aim 2: Integrative pathway analysis using cancer outlier Gene Profile Sets (coGPS); Aim 3: Validation of pathway analysis and functional analysis of relevant driver gene targets.
Justification for the requested support: Dr. Marchionni provides statistical and bioinformatics support.
Projects overlap/parallel: There is no scientific or budgetary overlap.

PCRP-CDMRP/DoD (Hurley)
Title: ASPN, a Novel Inhibitor of TGF-beta and a Putative Biomarker for Aggressive Prostate Cancer
Effort: 0.42 calendar months (3.5% effort)
Supporting Agency: DoD
Name of Procuring Contracting/Grants Officer: Melissa D. Cunningham, Ph.D., phone: 301-619-4302; Fax: 301-619-7796; email: melissa.cunningham@amedd.army.mil
Performance Period: 09/30/2012-09/29/2015
Level of funding: $5,385 (salary only)

Projects Goal: The major goals of this project are to study the inhibitory role of Asporin on TGF-beta signaling in aggressive prostate cancer, evaluating its role as lethality and progression biomarker.
List of the Specific Aims: Aim 1) Demonstrate the association of ASPN expression in cancer reactive stroma with lethal prostate cancer; Aim 2) Evaluate the ability of allelic variants D13, D14, and D17 of ASPN to promote prostate cancer progression; Aim 3) Evaluate polymorphisms in the aspartic acid repeat domain of ASPN as a genetic biomarker for prostate cancer progression potential.
Justification for the requested support: Dr. Marchionni provides statistical support.
Projects overlap/parallel: There is no scientific or budgetary overlap.

90042859 (Jang)
Title: Developing safe and effective stem cell technology for liver disease modeling and therapy.
Effort: 0.24 calendar months (2% effort)
Supporting Agency: The Maryland Stem Cell Research Commission and The Maryland Stem Cell Research Fund
Name of Procuring Contracting/Grants Officer: Dan Gincel, 410-715-4172, dgincel@marylandtedco.org
Performance Period: 07/01/10 - 06/29/15
Level of funding: $200,000 per year
Projects Goal: The goal of this project is to improve the understanding of stem cell technology for improved modeling and treatment of liver disease.
List of the Specific Aims: AIM 1) To determine the hepatic differentiation potentials and differential epigenetic features of improved human iPS cells generated from different origins; AIM 2) To develop in vitro and in vivo systems for modeling liver diseases by using patient specific iPS cells; AIM 3) To improve gene targeting conditions in patient specific iPS cells for liver disease gene therapy.
Justification for the requested support: Dr. Marchionni analyzes genomic data generated in the context of this project.
Projects overlap/parallel: There is no scientific or budgetary overlap.

W81XWH-11-1-0336 (Schaeffer)
Title: RNASEH2A - a Putative "Non-Oncogene Addiction" Gene Target and Marker for Radio-sensitivity in High Risk Prostate Cancer.
Effort: 0.24 calendar months (2% effort)
Supporting Agency: Department of Defense – Prostate Cancer Research Program
Name of Procuring Contracting/Grants Officer: NA
Performance Period: 10/01/11 - 09/30/14
Level of funding: $738,000
Projects Goal: to study the role of RNASEH2A in prostate cancer radio-sensitivity
List of the Specific Aims: Aim 1) Demonstrate the association of RNASEH2A with lethal prostate cancer; Aim 2) Evaluate the ability of RNASEH2A to modulate radio-sensitivity in prostate cancer cell lines and xenograft models; Aim 3) Investigate RNASEH2A as a marker of radio-sensitivity.
Justification for the requested support: Dr. Marchionni will assist in the analysis of the data generated in the context of this project.
Projects overlap/parallel: There is no scientific or budgetary overlap.

90046933 (Hoque)
Title: Tobacco Induced Epigenetic Alterations in COPD.
Effort: 0.24 calendar months (2% effort)
Supporting Agency: FAMRI
Name of Procuring Contracting/Grants Officer: Elizabeth Kress, 305 579 7007, ekress@famri.org, Flight Attendant Medical Research Institute, 201 S. Biscayne Blvd, Suite 1310, Miami, FL 33131
Performance Period: 07/01/11 - 06/30/14
Level of funding: $300,000

Projects Goal: to study the role of tobacco smoking in determining promoter methylation in COPD.
List of the Specific Aims: Aim 1: To comprehensively screen for novel COPD specific methylated genes in primary tissues obtained from COPD patients; Aim 2: To test multiple promoter hypermethylation markers for COPD in various tissues and bodily fluids from patients with and without disease to establish simple sensitivity and specificity estimates; Aim 3: To evaluate the molecular relationship between COPD and lung cancer.
Justification for the requested support: Dr. Marchionni will analyze genomics data generated during the project and assist with statistical analysis.
Projects overlap/parallel: There is no scientific or budgetary overlap.

R25HG005955 (Wheelan)
Title: Gaining Skills and Collaborating Through Interdisciplinary Education.
Effort: 0.60 calendar months (5% effort)
Supporting Agency: National Human Genome Research Institute (NHGRI) - National Institutes of Health (NIH)
Name of Procuring Contracting/Grants Officer: Vivien Bonazzi, NHGRI – NIH, 5635 Fishers Lane, Suite 4076, MSC 9305, Bethesda, MD 20892, 301-451-8276, bonazziv@mail.nih.gov
Performance Period: 09/22/10-07/31/13
Level of funding: $150,000
Projects Goal: The major goal of this project is to support the training of new investigators in the field of Computational Biology
List of the Specific Aims: Aim 1) To develop methods for cross-disciplinary education in separate disciplines to enable classically trained scientists to collaborate effectively on interdisciplinary projects; Aim 2) To foster collaborations between biological and quantitative scientists to promote innovative, multidisciplinary projects; Aim 3) To establish an interdisciplinary community so that scientists can continue learning and create research groups to work on revolutionary, paradigm-shifting endeavors.
Justification for the requested support: Dr. Marchionni will organize short courses and classes in Bioinformatics.
Projects overlap/parallel: There is no scientific or budgetary overlap.

R21CA158898 (Leach)
Title: High resolution and single cell analyses of PanIN initiation and progression.
Effort: 0.6 calendar months (5% effort)
Supporting Agency: NHI – NCI (NIH - R21 - PA-08-208, Pilot studies in Pancreatic Cancer)
Name of Procuring Contracting/Grants Officer: Grants Management Specialist: Connie Murphy, murphyco@mail.nih.gov, phone 301.846.6832; Program Official: Judy Mietz, mietzj@hin.gov, phone 301.496.9326
Performance Period: 04/01/11 - 03/31/13
Level of funding: $150,000
Projects Goal: The major goal of this project is to identify genomic correlates of PanIN at single cell level.
List of the Specific Aims: Aim 1) To visualize the earliest cellular responses to LSL-GFP:KrasG12D activation in the acinar and ductal compartments using a novel in vitro culture system; Aim 2) To generate and compare high resolution temporal mapping of the pre-PanIN and PanIN transcriptomes following cell type-specific activation of LSL-GFP::KrasG12D in acinar and ductal lineages; Aim 3) To generate and compare high resolution temporal mapping of surface marker expression in individual cells following activation of LSL-GFP:KrasG12D in the acinar and ductal lineages.
Justification for the requested support: Dr. Marchionni will analyze genomics data generated during the project and assist with statistical analysis.

1005994 (Rudin)
Title: Gene expression analysis in lung cancer: discovery of novel therapeutic targets.

Effort: 0.30 calendar months (2.5% effort)
Supporting Agency: Burroughs Wellcome Foundation **Name of Procuring Contracting/Grants Officer:** NA
Performance Period: 07/01/06-06/30/13
Level of funding: $75,000
Projects Goal: To develop novel therapies and treatment approaches in lung cancer.
List of the Specific Aims: NA
Justification for the requested support: Dr. Marchionni provides help with the analysis of public domain gene expression data in lung cancer models.
Projects overlap/parallel: There is no overlap in goals of the project.

Subcontract (Marchionni, 7R21 CA164613-01 - Rosenberg)
Title: Evaluation of a novel urothelial cancer biomarker of lethality
Effort: 1.2 calendar months (10% effort)
Supporting Agency: National Institutes of Health (R21 - PA-10-026) - Sub-Contract – Memorial Sloan Kettering Cancer Center - Rosenberg
Name of Procuring Contracting/Grants Officer: Dr James V Tricoli, EPN BG, Room 6026, 6130 Executive Blvd, Rockville, MD, 20852; Phone: 301 402-4185; email: james.tricoli@nih.gov
Performance Period: 4/1/12 - 3/31/14
Level of funding: $50,000
Projects Goal: To validate a novel biomarker based on copy number variation for urothelial cancer.
List of the Specific Aims: Aim 1) Validate chromosome 1q23.3 gain as a biomarker of lethality in an independent cohort of UC patients; Aim 2) Identify specific genes residing on 1q23.3 that drive lethality in UC.
Justification for the requested support: Dr. Marchionni will provide bioinformatics and biostatistics support.
Projects overlap/parallel: There is no scientific or budgetary overlap.

DMS0342111 (Parmigiani)
Title: Multi-Study Genomic Data Analysis (Co-Investigator)
Effort: 5.40 calendar months (45% effort)
Supporting Agency: National Science Foundation (NSF)
Name of Procuring Contracting/Grants Officer:
Address of Funding Agency: 6116 Executive Boulevard, Suite 7013, MSC 8347, Rockville, MD 20852
Performance Period: 10/1/2004 - 12/30/2009
Level of funding: $219,543
Projects Goal: The major goal of this project is to develop novel data analysis tools for comparison and integration of genomic information across studies, across measurement technologies and across biological systems.
List of the Specific Aims: Aim 1) Development of statistical methods to combine gene expression data; Aim 2) Implement the related software; Aim 3) Validate the statistical models using public domain cancer data to assess reproducibility and classification performance; Evaluation of the applicability of genomic investigation comparability across species.
Justification for the requested support: Dr Marchionni is involved in all aims of the project. He is collecting and curating all data sets used in the study, developing R classes, R methods, and functions to perform the meta-analysis and develop the software. Finally he is performing the validation analysis.
Projects overlap/parallel: There is no overlap in goals of the projects. The project is synergistic.

R01 DK072000 (Berman)
Title: Hedgehog signaling links bladder injury and cancer (Co-Investigator)
Effort: 0.60 calendar months (5% effort)
Supporting Agency: National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Name of Procuring Contracting/Grants Officer: Dr. Christopher Mullins 6807 Democracy Blvd, Rm 637, Bethesda, MD 20892-5460
Performance Period: 07/01/2006 - 04/30/2011
Level of funding: $199,055
Projects Goal: To define molecular events involving the Hedgehog (Hh) pathways in injury and repair and in bladder cancer.
List of the Specific Aims: Aim 1) To characterize the induction of Hh signaling, EMT, and stem cell activation in carcinogenic and non-carcinogenic urothelial injury; Aim 2) To test the effects of Hh pathway blockade on urothelial injury repair; Aim 3) To test whether Hh signaling is necessary for urothelial carcinoma growth; Aim 4) To test whether continuously enforced Hh signaling is sufficient to induce urothelial carcinogenesis.
Justification for the requested support: Dr Marchionni is analyzing public domain data on bladder cancer to find and investigate correlates of Hh pathway activation.
Projects overlap/parallel: There is no overlap in goals of the project.

1R21CA135877 (Karchin)
Title: Tools for Large-Scale Analysis of Driver Pathways (Co-Investigator)
Effort: 1.20 calendar months (10% effort)
Supporting Agency: National Institutes of Health (NIH)/National Center Institute (NCI)
Name of Procuring Contracting/Grants Officer: Daniela Gerhard at NCI, Phone: 301-451-8027
Performance Period: 07/01/2008 - 06/31/2010
Level of funding: $275,000
Projects Goal: The major goal of this project is to establish methods to compare data across genomic scope of analysis, like gene expression, SNPs, CGH, sequencing using the Cancer Genome Atlas (TCGA) data.
List of the Specific Aims: Aim1- Development of algorithms for pathway-based analysis; Aim 2 – Validation with existing TCGA data; Aim3 - caBIGTM compliant implementation of the methods.
Justification for the requested support: Dr Marchionni will develop method for data integration across genomic scope of investigation.
Projects overlap/parallel: There is no overlap in goals of the project. The project is synergistic.

R01MH083738 (Zandi)
Title: METAMOODICS: Meta-analyses and Bioinformatics Display of Mood Disorders Genetics.
Effort: 1.20 calendar months (10% effort)
Supporting Agency: National Institutes of Health (NIH)/ National Institute of Mental Health (NIMH)
Name of Procuring Contracting/Grants Officer: Thomas Lehner, 6001 Executive Boulevard, Room 7190, MSC 9643 301-443-9869, tlehner@mail.nih.gov
Performance Period: 07/01/2009 - 06/31/2012
Level of funding: $275,000
Projects Goal: The major goal of this project is to establish a data base of genomic data on mood disorder, along with the related analytical and visualization tools.
List of the Specific Aims: Aim 1) To carry out and integrate systematic meta-analyses of genetic studies of mood disorders; Aim 2) To develop a web-based bioinformatic resource, that we refer to as "Metamoodics," for presenting the results of the meta-analyses in the context of salient genomic annotation; and Aim 3) To develop a computational tool within "Metamoodics" for conducting gene set enrichment analyses of meta-analyzed data.
Justification for the requested support: Dr Marchionni is co-investigator will performed the analysis proposed in Aim 3.
Projects overlap/parallel: none.

Subcontract (Marchionni, 1R21AI084711-01 - Romerio)
Title: A New Insight into HIV-1 Latency Through a Novel in Vitro System.
Effort: 0.60 calendar months (5% effort)

Supporting Agency: National Institutes of Health / National Institute of Allergy and Infectious Diseases
Name of Procuring Contracting/Grants Officer: Janet M. Young, NIAID, 6700B Rockledge Drive, Room 4152, Bethesda, MD 20892-7626, Telephone: (301) 496-6714
Performance Period: 07/01/2009 - 06/31/2012
Level of funding: $11,000 (sub-contract)
Projects Goal: to determine the determinant of HIV latency using an innovative in vitro system.
List of the Specific Aims: Aim 1: Determine the gene expression profile of in vitro-generated resting, latently infected cells isolated by fluorescence activated cell sorting. Aim 2: Test the hypothesis that CCR5- and CXCR4-tropic HIV-1 strains show different propensities to establish and re-emerge from latency.
Justification for the requested support: Dr Marchionni is co-investigator will performed the analysis proposed in Aim 1.
Projects overlap/parallel: none.

DoD - PCRP 2012 (Lotan)
Title: Molecular Profiling of Intraductal Prostate Carcinoma
Effort: 0.60 calendar months or 5%
Supporting Agency: Congressionally Directed Medical Research Programs – Department of Defense
Name of Procuring Contracting/Grants Officer: Melissa D. Cunningham, Ph.D.
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 10/01/2013-09/29/2016
Level of Funding: $75,000
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.
List of the Specific Aims: NA
Justification for the requested support: Dr. Marchionni provides statistical and bioinformatics support.
Projects overlap or parallel: No scientific or budgetary overlap.

COMPLETED INTRAMURAL SUPPORT

PCW Chair (Schaeffer)
Title: PCW (Schaeffer) Chair The Role of Sox9 in Fibroblast Growth Factor Signaling and Prostate Cancer
Effort: 1.20 calendar months (10% effort)
Supporting Agency: Patrick C Walsh Foundation (Co-Investigator)
Name of Procuring Contracting/Grants Officer: NA
Performance Period: 07/01/2007 - 06/30/2009
Level of funding:
Projects Goal: The project aims at deciphering the role of the Fibroblast Growth Factor Signaling and Sox9 in Prostate Cancer
List of the Specific Aims: Aim 1) Demonstrate activation/induction of Sox9 by Fgf/Erk1 and 2 signaling; Aim 2) Evaluate an essential role for Sox9 in adult prostate glandular homeostasis:
Justification for the requested support: Dr Marchionni is in charge of the analysis of SOX9 expression in public domain expression data in laboratory models of prostate gland homeostasis.
Projects overlap/parallel: There is no overlap in goals of the project. The project is synergistic.

PCW Chair (De Marzo)
Title: MYC induced transformation of prostate epithelial cells.
Effort: 0.60 calendar months (5% effort)
Supporting Agency: Johns Hopkins Medical Institution, Patrick C Walsh Foundation
Name of Procuring Contracting/Grants Officer: NA

Performance Period: 4/1/2009-03/31/2011
Level of funding: $150,000
Projects Goal: The aim of this project is investigate mechanism by which the oncogenic transcription factor MYC transforms prostatic epithelial cells
List of the Specific Aims: 1. Comprehensive Comparative Analysis of Genome-Wide Expression of mRNA of MYC Driven Programs in Mouse Prostate and Human Prostate Cancer Cell lines. 2. Generation of Chromatin "State-Maps" in the Lo-MYC Mouse Prostate
Justification for the requested support: Dr Marchionni will be in charge of the gene expression analysis performed in Aim 1.
Projects overlap/parallel: There is no overlap in goals of the project. The project is synergistic.

JHU Provost Developmental Award (Wheelan-Marchionni)
Title: Nucleating a discipline: creating a leadership in Bioinformatics and Computational Biology.
Effort: 2.40 calendar months (20% effort)
Supporting Agency: Johns Hopkins Medical Institution, The Provost Office
Name of Procuring Contracting/Grants Officer: NA
Performance Period: 04/01/2009 - 03/31/2012
Level of funding: $600,000
Projects Goal: The major goal of this project is to create a collaborative bioinformatics center at Hopkins, to develop short bioinformatics classes, and develop a PhD program in Computational Biology
List of the Specific Aims: NA
Justification for the requested support: Dr Marchionni is Director of the Professional skill development program at the Center for Computational Genomics at Johns Hopkins
Projects overlap/parallel: There is no overlap in goals of the project. The project is synergistic.

90039865 (Eberhart)
Title: Notch and Hedgehog Signaling in Glioblastoma.
Effort: 0.60 calendar months (5% effort)
Supporting Agency: James S. McDonnell Foundation - Sub-Contract Kennedy Krieger
Name of Procuring Contracting/Grants Officer: NA
Performance Period: 08/01/09 - 07/31/11
Level of funding: $149,403
Projects Goal: The goal of this project is to improve the understanding of how the Notch and hedgehog pathways can be effectively targeted in malignant gliomas.
List of the Specific Aims: Aim 1) Identify markers of Notch and Hedgehog therapeutic response in malignant gliomas and GSC; Aim 2) Combining temozolamide and/or glucocorticoids with Notch or Hedgehog blockade. Aim 3) Examine the role of crosstalk between Notch and Hedgehog in GSC Therapeutic response.
Justification for the requested support: Dr. Marchionni analyzes genomic data generated in the context of this project.
Projects overlap/parallel: There is no overlap in goals of the project.