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TITLE: The Thoc1 Ribonucleoprotein as a Novel Biomarker for Prostate Cancer Treatment Assignment

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14. ABSTRACT Active surveillance (AS) is an option for men with low risk prostate cancer in order to reduce over treatment, but few men choose it because current prognostic indicators are imperfect. The objectives of this research are to test whether pThoc1 can improve the assignment of prostate cancer patients to therapy. We have made significant progress on the goals articulated in the Statement of Work. IRB/HRPO approval has been obtained for construction and use of new TMAs (PI Mohler and Goodrich). The TMAs from PCaP have been obtained (PI Mohler and Goodrich). Pathology analysis of 1146 patient specimens is complete and construction of TMAs initiated (PI Mohler). Optimization of TMA staining is complete and staining of TMAs initiated (PI Goodrich). IRB/HRPO approval for active surveillance specimens has been obtained (PI Mohler, Goodrich). Enrollment of prostate cancer patients on active surveillance is ongoing (PI Mohler). ELISA assays for measuring pThoc1 and pThoc1 autoantibodies have been successfully developed (PI Goodrich). Analysis of serum samples from a mouse model of prostate cancer has been performed, establishing feasibility (PI Goodrich). IRB/HRPO approval for serum samples has been obtained (PI Mohler, Goodrich). All preparative, optimization, and regulatory approval work has thus been completed, setting the stage for data gathering in year 2 of the grant. Over treatment is complicates the clinical management of prostate cancer. Improving the ability to distinguish aggressive from indolent disease is recognized as an unmet need by the 2013 PCRP Overarching Challenges. Identifying pThoc1 as a biomarker that can help meet this need will have significant impact.						
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1. Introduction

Active surveillance (AS) has been proposed as an option for men with low risk prostate cancer in order to reduce over treatment. Only a fraction of eligible men choose AS, however, because current prognostic indicators are imperfect. Biomarkers that improve upon PSA levels, clinical stage and Gleason score to distinguish between prostate cancers that can be observed safely from those that require immediate treatment could help “right size” recommended treatment. The objectives of this proposal are to test whether pThoc1 can improve the assignment of prostate cancer patients to therapy, to test whether pThoc1 correlates with observed racial disparities in prostate cancer mortality, to determine whether pThoc1 can identify active surveillance patients whose prostate cancer will progress, and to develop methods to quantitate pThoc1 or pThoc1 autoantibody in serum. The general study design is to assay pThoc1 in independent cohorts of clinically annotated prostate cancer biospecimens for which clinical and follow up data is available using previously developed antibody reagents and immunostaining methods. Over treatment is a critical issue complicating the clinical management of prostate cancer. Improving the ability to distinguish aggressive from indolent disease in men newly diagnosed with prostate cancer is recognized as an unmet need by the 2013 PCRP Overarching Challenges. Identifying pThoc1 as a biomarker that can help meet this need will have significant impact.

2. Keywords

Prostate cancer, biomarker, active surveillance, prognostic indicator, tissue microarray, immunostaining, ribonucleoprotein

3. Accomplishments

The Year 1 Tasks for the Mohler laboratory were copied from the Statement of Work and progress reported for each bullet under each task for each specific aim.

Specific Aim 1) Characterize pThoc1 levels in independent cohorts of human prostate cancer radical prostatectomy specimens.

Task 1- Construct prostate TMAs

- Finish construction of 1146 patient TMAs

The construction of the new RPCI tissue microarray (TMA) set that will contain tissue from approximately 1000 radical prostatectomy patients is work in progress. A team of four pathologists just completed the review of the H&E stained tissue sections from each of the patients and the construction of the TMA will be completed by the end of the year.

- Obtain 328 AA and 361 CA patient TMAs from PCaP

The protocol was reviewed and approved by the North Carolina – Louisiana Prostate Cancer Project (PCaP) Management Committee. Their approval was contingent on successful development of the ELISA assay to detect Thoc1 and Thoc1 autoantibodies in serum samples. PCaP tissue sections were released October 2, 2015 since Dr. Goodrich’s laboratory completed the feasibility study and submitted the supporting documentation.

- Obtain HRPO approval, amend IRB protocol

The protocol for this study was amended and reviewed and approved by the RPCI Genito-Urinary Disease Site Research Group (GU DSRG) and by the Office of Research Subject Protection (ORSP). The

approval process took approximately 6 months. DoD PCRPA approval required an additional 9 months when questioned the PCaP and RPCI granted exemption.

Task 2- Immunostain TMAs

- Further optimization of immunostaining

The immunohistochemistry methods have been optimized for immunostaining of Thoc1 and PMP22

- Immunostain RPCI 92 AA and 92 CA patient TMAs
- Immunostain 328 AA and 361 CA patient TMAs
- Immunostain 1146 patient TMAs

Immunostaining of all TMA sections will be performed upon completion of the new RPCI TMA set. Immunostaining at one time is optimal to prevent batch-to-batch variation.

Specific Aim 2) Characterize pThoc1 levels in a cohort of human prostate cancer patients on active surveillance.

Task 1- Immunostain active surveillance patient biopsies

- IRB/HRPO approval for active surveillance specimens

The protocol for this study was amended and reviewed and approved by the RPCI Genito-Urinary Disease Site Research Group (GU DSRG) and by the Office of Research Subject Protection (ORSP). The approval process took approximately 6 months. DoD PCRPA approval required an additional 9 months when questioned the PCaP and RPCI granted exemption.

Task 2- Enroll ~50 prostate cancer patients per year on active surveillance

- Annotate clinical data

Patients continue to be recommended and select active surveillance at RPCI. Each has all demographic, clinical, pathological and oncological outcome data entered prospectively in a relational database by our clinical team and data managers [435 are enrolled as of February 5, 2016, the date of this revised progress report].

- Immunostain biopsy tissue sections

385 patients are enrolled on active surveillance at RPCI [as of October 14, 2015, the date of the original progress report]. Diagnostic prostate biopsy tissue specimens are available for only 53 patients. All other patients had prostate biopsies performed at other facilities. Obtaining them from individual pathology laboratories would be costly and time consuming, based on previous PCaP experience. The study group will be expanded by including diagnostic biopsy tissue sections from RPCI and PCaP patients who would have qualified for active surveillance (NCCN very low, low or favorable intermediate [T1c, Gleason grade 3+4, PSA < 10] prostate cancer). Approximately 250 research subject meet these criteria and could have prostate biopsy sections available for study.

DSRG and ORSP approvals were obtained at RPCI and from the PCaP Management Committee. The approval process took approximately 6 months. DoD PCRPA approval required an additional 9 months when questioned the PCaP and RPCI granted exemption.

PCaP provided diagnostic prostate biopsies from 183 men October 2, 2015, which have been

immunostained and visual scoring has begun. The RPCI diagnostic biopsy tissue sections are being prepared by the RPCI Pathology Resource Network.

Specific Aim 3) Test whether pThoc1 or autoantibodies against pThoc1 can be detected in the serum of prostate cancer patients.

Task 2- Assay serum pThoc1 or pThoc1 autoantibodies in human prostate cancer serum samples

- IRB/HRPO approval for serum samples

The protocol for this study was amended and reviewed and approved by the RPCI Genito-Urinary Disease Site Research Group (GU DSRG) and by the Office of Research Subject Protection (ORSP). The approval process took approximately 6 months. DoD PCRPA approval required an additional 9 months when questioned the PCaP and RPCI granted exemption.

In summary, we are on schedule in all areas except RPCI TMA construction has taken longer than anticipated. All blocks have been selected and the TMA set designed. The TMA set will consist of approximately 18 blocks and block 10 is under construction (anticipated completion date April 15, 2016).

4. Impact

None

5. Changes/Problems

None

6. Products

None

7. Participants & Other Collaborating Organizations

James L. Mohler, MD	Partnering PI	1 calendar months
Gissou Azabdaftari, MD	Co-Investigator	<1 calendar months
Elena Pop, MD	Co-Investigator	1 calendar months
Kristopher Attwood, PhD	Biostatistician	<1 calendar months
John Stocking	Lab technician	6 calendar months

No other organizations are involved in the research.

Changes in Other Support

James Mohler, MD

No Cost Extension Granted

Title: Prostate Cancer: Transition to Androgen Independence, Project 1: Interference with the Androgen Receptor and Its Ligands in Recurrent Prostate Cancer (French - PI)

Time Commitments: 2.04 calendar months

Supporting Agency: National Cancer Institute P01-CA77739

Name and address of the Funding Agency's Procuring Contracting/Grants Officer:

Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295

102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015, mkramer@med.unc.edu

Performance Period: 04/01/2005-03/31/2016 (NCE)

Level of Funding: \$2,292,618

Brief description of project's goals: Renewal of a project that tests the hypothesis that recurrence of prostate cancer during androgen deprivation therapy can be prevented or delayed by preventing the accumulation of tissue androgens and/or inhibiting the androgen receptor.

List of specific aims:

1. Prevent the changes in androgen metabolism that provide AR ligand(s) in the immediate post-castration period
2. Degrade AR ligand(s) formed in the immediate post-castration period
3. Diminish or eliminate AR in the immediate post-castration period

Overlap: None

No Cost Extension Granted

Title: Prostate Cancer: Transition to Androgen Independence, Core A: Administration (Mohler – PI)

Time Commitments: 1.16 calendar months

Supporting Agency: National Cancer Institute P01-CA77739

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295

102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015, mkramer@med.unc.edu

Performance Period: 04/01/2005-03/31/2016 (NCE)

Level of Funding: \$519,640

Brief description of project's goals: Renewal of an administrative core that provides the leadership for the overall Program Project in the daily execution of administrative matters common to the three projects and ImmunoAnalysis and Tumor Management Core B.

List of specific aims:

The objective of the Administration Core A is to provide leadership, direction and administrative services for the purposes of enhancing research productivity and maintaining a stimulating research environment conducive to study of prostate cancer biology. Administration Core A will foster exchange of ideas and promote collaboration through its interactions with the Project Leaders and research groups. A major effort will be to encourage and facilitate collaboration in translational research among investigators within the Program Project and other investigators within or outside UNC-Lineberger Comprehensive Cancer and Roswell Park Cancer Institute. Administration Core A will have direct responsibility for organization and facilitation of the monthly research conferences and annual review of the Program Project by the 5 external consultants. Administration Core A will monitor activities of ImmunoAnalysis and Research Specimen Management Core B, in particular, and the entire program, in general, to improve the efficiency and effectiveness of the entire program.

Overlap: None

No Cost Extension Granted

Title: Prostate Cancer: Transition to Androgen Independence, Core B: ImmunoAnalysis and Tumor Management (French – PI)

Time Commitments: 0.48 calendar months

Supporting Agency: National Cancer Institute P01-CA77739

Name and address of the Funding Agency's Procuring Contracting/Grants Officer:

Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295

102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015, mkramer@med.unc.edu

Performance Period: 04/01/2005-03/31/2016 (NCE)

Level of Funding: \$903,203

Brief description of project's goals: Renewal of a core that serves two primary functions to the three projects: Core B is involved in all aspects of clinical specimen and prostate cancer xenograft management and Core B processes and stores the invaluable prostate biopsy specimens obtained from men with advanced prostate cancer prior to and at regular intervals after beginning androgen deprivation therapy.

List of specific aims:

The ImmunoAnalysis and Research Specimen Management Core B will provide 3 primary services to the Program Project.

1. Core B will provide high quality, reliable and cost-effective technical services to participants of the Program Project for immunohistochemistry and quantitative image analysis.
2. Core B will manage the research specimens critical to the conduct of the research proposed by the Program Project.
3. Core B will provide expertise in biostatistics and genitourinary pathology.

Overlap: None

Change in PI Effort

Title: Cancer Center Support Grant (Johnson - PI)

Time Commitments: 2.40 calendar months

Supporting Agency: National Cancer Institute

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Kimerly Griffin, NCI Shady Grove, 9609 Medical Center Drive, West Tower, 2nd floor, Room 2W520, Rockville, MD 20850. 240-276-6315

Performance Period: 06/26/2014-04/30/2019

Level of Funding: \$2,315,456

Brief description of project's goals:

Roswell Park Cancer Institute's Cancer Center Support Grant (CCSG) includes six programs and 13 cores resources. Support is provided for leadership, developmental funds, planning and evaluation and administration.

List of specific aims:

The resource provides a complete service from methods development and validation to sample handling and analysis to PK/PD modeling and simulation leading to informed decision-making about dosing, dose scheduling and drug combinations.

Overlap: None

Previously Pending, now Current

Title: Genetic variations in SLCO transporter genes contributing to racial disparity in aggressiveness of prostate cancer (Wu - PI)

Time Commitments: 0.12 calendar months

Supporting Agency: USAMRAA W81XWH-14-1-0453

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mirlene Desir, Grant Specialist, Assistance Branch 4, MCMR-AAA-AD, USAMRAA, 820 Chandler Street, Fort Detrick, MD 21702, phone: 301-619-7733, fax: 301-619-9656, mirlene.desir@civ@mail.mil

Performance Period: 09/15/2014-09/14/2017

Level of funding: \$764,100

Brief description of project's goals: The objective seeks to address how transporter-regulated androgen availability to cancer cells may contribute to the difference in prostate cancer aggressiveness between African American (AA) and European American (EA) men. The hypothesis is: Genetic variations in solute carrier family of organic anion transporting peptides (SLCO) androgen transporter genes and expression profiles of SLCO androgen transporters in prostate tissue are associated with aggressiveness of

prostate cancer, and contribute to racial differences in prostate cancer aggressiveness. (Recommended for funding)

List of specific aims:

1. Examine genetic variations in SLCO transporters genes and to investigate the associations of the variations with prostate cancer aggressiveness in AA and EA.
2. Examine *in situ* expression profiles of SLCO transporters in prostate tissue and to investigate the associations of the expression profiles with prostate cancer aggressiveness in AA and EA.
3. Characterize the functions of candidate SLCO transporters in androgen uptake and to evaluate the biological effects on AR signaling in human prostate cancer cell lines.

Overlap: None

New Funding

Title: Qualifying multi-transcript signatures for active surveillance in prostate cancer (Kim/Mohler - PIs)

Time Commitments: 0.60 calendar months

Supporting Agency: National Institutes of Health 1R01CA182438-01A1

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 09/01/2014-08/31/2019

Level of funding: \$195,510 (sub contract)

Brief description of project's goals: The vast majority of men diagnosed with prostate cancer do not die of their disease, yet prostate cancer remains the second leading cause of cancer-death in men. We propose to qualify prognostic transcriptomic signatures to predict the risk of adverse prostate cancer pathology and disease progression using prostate needle biopsies from men considering active surveillance as a strategy to delay and even avoid the treatment of prostate cancer. A qualified test will help with treatment decisions at the time of prostate cancer diagnosis. Another objective addresses the glaring absence of well-established criteria for active surveillance in non-Caucasian men. We propose to qualify our signatures in African-American men. Qualified signatures of cancer severity will improve outcomes prediction and identify the most appropriate candidates for active surveillance, and ultimately reduce the public health burden of prostate cancer.

List of specific aims:

1. Qualify biomarkers to predict adverse pathology and progression using prostate biopsies in men considering active surveillance.
2. Test the effects of African-American ethnicity on the biomarker signatures.

Overlap: None

New Funding

Title: Alliance NCORP Research Base (Kim/Mohler - PIs)

Time Commitments: 0.60 calendar months

Supporting Agency: Alliance Foundation

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Subcontract with Cedars Sinai. Cedars-Sinai Medical Center, Attention: Margaret Jenkins, Administrative Program Coordinator

Department of Surgery, Research Division, 8635 W. 3rd Street, Suite 973W, Los Angeles, CA 90048
margaret.jenkins@cshs.org

Performance Period: 04/01/2015 – 03/31/2016

Level of funding: \$93,955 (sub contract)

Brief description of project's goals: The proposed research tests the hypothesis that intensive cholesterol lowering will decrease the growth rate of benign and malignant prostate epithelium. The proposed research could provide the data necessary to justify a phase III clinical trial to address one of the major problems in urologic oncology how to prevent the progression of low risk prostate cancer to provide men higher levels of confidence for selection of active surveillance.

Overlap: None

No Cost Extension Granted

Title: Defining intra- and intertumoral genomic heterogeneity in prostate cancer (Mohler - PI)

Time Commitments: 0.60 calendar months

Supporting Agency: Roswell Park Alliance Foundation

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14203, Judith.Epstein@RoswellPark.org

Performance Period: 12/10/2013-12/31/2015

Level of funding: \$92,384

Brief description of project's goals:

Intra- and inter-tumoral CaP genomic heterogeneity necessitates extensive sampling of a radical prostatectomy specimen.

List of specific aims:

1. Determine intra- and inter-tumoral heterogeneity in CaP's mutational landscape using whole exome sequencing to determine heterogeneity within and among CaP foci derived from radical prostatectomy specimens from patients with high-risk disease who are expected to develop metastatic disease and require ADT
2. Define intra- and inter-tumoral CaP heterogeneity in structural gene rearrangement and gene expression patterns using RNA-Seq and RNA derived from the same CaP samples used in Aim 1

Overlap: None

Previously Active, now Completed

Title: Genetic variations in mitochondria and prostate cancer aggressiveness and progression in Caucasian and African American men (Zhao - PI)

Time Commitments: 0.60 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer:

Sherie Wesley, Research Contract Specialist, Legal Services Department, LEGAL SERVICES, Unit 537, P. O. Box 301439, Houston, Texas 77230-1439 Email: swesley@mdanderson.org Phone: 713.794.1507 Fax: 713.792.6878

Performance Period: 07/01/2012-06/30/2015

Level of Funding: \$936,256

Brief description of project's goals: The hypothesis is that genetic variations (sequence and copy number) in mtDNA are associated with prostate cancer aggressiveness at diagnosis and prostate cancer progression. The proposed study will represent the first study to address the roles of mtDNA variations in prostate cancer aggressiveness and progression as well as racial difference.

List of specific aims:

1. Evaluate whether genetic variations in mtDNA are associated with aggressive tumor characteristics of prostate cancer at diagnosis and progression of prostate cancer in CA and AA men, and whether the associations are different between CA and AA men.
2. Evaluate whether mtDNA CNVs are associated with aggressive tumor characteristics of prostate cancer at diagnosis and progression of prostate cancer in CA and AA men, and whether the associations are different between CA and AA men.
3. Exploratory Aim: Perform whole mitochondrial DNA sequencing to identify novel genetic variants in AA and CA prostate cancer patients.

Previously Active, now Completed

Title: Role of Androgen Axis in the Racial Differences of Prostate Cancer Mortality (Mohler - PI)

Time Commitments: 1.20 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Ayi Ayayi, Contract Specialist, U.S. Army Medical Research Acquisition Activity, MCMR-AAA-E, 820 Chandler Street, Fort Detrick, MD 21702-5014 Phone: (301) 619-4018 ayi.ayayi@us.army.mil

Performance Period: 09/30/2010-09/29/2014

Level of Funding: \$817,716 NCE

Brief description of project's goals: The study will provide complete analysis of the androgen receptor and androgen-regulated genes and relate it to prostate cancer in a large sample of men to test whether racial differences in prostate cancer mortality may be due, in part, to racial differences in androgenic stimulation of prostate cancer. Greater androgenic stimulation of the African American prostate could explain the two-fold difference in prostate cancer risk and increased aggressiveness of clinical disease in African compares to Caucasian Americans.

List of specific aims:

The central hypothesis of the proposed research is that racial differences in the tissue androgen axis contribute to CaP aggressiveness. Greater androgenic stimulation of the African-American prostate may contribute to increased incidence of, and higher mortality rates from, CaP. Quantifying the androgen axis in a large number of men with CaP will determine whether or not CaP receives race-dependent differences in androgenic stimulation that may affect CaP outcome. In order to test the central hypothesis, we propose three specific aims:

1. Determine whether AR protein levels differ in CaP of African and Caucasian Americans
2. Determine whether AR protein levels correlate with proteins expressed from androgen-regulated genes (PSA, Nkx3.1, hK2, *TRMPRSS2/ERG* fusions)
3. Determine whether AR protein levels correlate with CaP growth rate, extent and tumor differentiation

Kristopher Attwood, PhD

Previously Active, now Completed

Title: Is Immune Response against Breast Cancer Inhibited by Lack of Available Metabolic Energy?

Time Commitments: 0.30 calendar (PI-Repasky)

Supporting Agency: NYSDOH

Grants Officer: Kenneth Peek; Phone: (518) 474-7002; kep03@health.state.ny.us

Performance Period: 09/01/13-08/31/15

Level of Funding: \$150,000

Brief description of project's goals: The goal of this proposal is to test this provocative hypothesis in a murine breast cancer (4T1) model.

List of specific aims:

- 1) Will test the impact of supporting body temperature on primary and metastatic tumor growth, on the function of critical immune effector cells and cytokines and on therapeutic efficacy of radiation and immunotherapy.
- 2) Tests whether there are changes in energy-related signaling pathways and the tumor microenvironment.
- 3) Will test the exciting possibility that energy conservation may even help to control tumors in mice given high fat diets, in which tumor progression is known to be accelerated.

Overlap: NONE

Previously Pending, now Current

Title: Deprive Prostate Cancer of DHEAS to Prevent Castration-Recurrent Prostate Cancer (5 R21 CA191895-02)

Time Commitments: 0.60 calendar (PI-Wu)

Supporting Agency: NIH

Grants Officer: Neeraja Sathyamoorthy; neeraja.sathyamoorthy@nih.gov; Phone: (240) 276-6220

Performance Period: 09/01/15-08/30/16

Level of Funding: \$229,028

Brief description of project's goals: The proposed studies are required to validate the concept that DHEAS is an important source of precursors for intracrine production of T and DHT by prostate cancer cells. In addition, the transporters, STS, and STS regulators provide potential targets for therapy.

List of specific aims:

- 1) Characterize the expression of STS and potential STS regulators in CRPC.
- 2) Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth.
- 3) Identify DHEAS uptake mechanisms.

Overlap: NONE

Previously Pending, now Current

Title: Targeting Granzyme B to Separate GVH from GVL Responses (1 R01 CA184728-01)

Time Commitments: 0.60 calendar (PI-Cao)

Supporting Agency: NIH

Grants Officer: Susan McCarthy; susan.mccarthy@nih.gov; Phone: (240) 276-6200

Performance Period: 04/01/15-03/31/20

Level of Funding: \$401,456

Brief description of project's goals: The goal of this work is to examine this new paradigm regarding GzmB function after allogeneic HSCT. We hypothesize that the dual detrimental role for GzmB function may provide a long-desired target, allowing separation between GVH and GVL responses.

List of specific aims:

- 1) Will determine the contributions of hematopoietic APCs versus non-hematopoietic tissues to GzmB-mediated GVHD pathogenesis.
- 2) Will study the mechanisms by which GzmB diminishes CD8+ T cell-mediated GVL response.
- 3) Will study the clinical relevance of Granzyme function in allogeneic HSCT patients.

Overlap: NONE

New Funding

Title: Multicenter phase 2 trial of nintedanib (BIBF 1120) in patients with carcinoid tumors (NCCN NINT 0016)

Time Commitments: 0.30 calendar (PI-Iyer)

Supporting Agency: NCCN

Grants Officer: Diane Paul, NCCN, 275 Commerce Drive, Suite 300, Fort Washington, PA, 19034, (215) 690-0232, paul@nccn.org

Performance Period: 11/25/14-11/24/18

Level of Funding: \$480,611

Brief description of project's goals: We hypothesize that since fibroblast proliferation is a major driver of disease and clinical progression in non-pancreatic carcinoids that is shown in animal models to be driven by serotonin (5-HT) through FGFR2 (Hisaoka et al) that targeting angiogenesis and FGFR merits study in this tumor.

List of specific aims:

1. Targeting angiogenesis and the fibroblast growth factor pathway with nintedanib will result in clinical benefit measured as progression free survival (PFS) and radiographic response or stable disease in patients with progressing carcinoid tumors within the 12 months prior to study entry.
2. This therapy will be safe and tolerable in combination with octreotide. This will also lead to improved QOL measured using the Norfolk QOL-NET tool.
3. Using a previously developed PK/PD model, using decrease in circulating cytokines such as soluble vascular endothelial growth factor receptor (sVEGFR), VEGF, fibroblast growth factor (FGF) and FGFR by ELISA before and serially q12 week with steady state PK draw to correlate with drug level following start of therapy compared to pre therapy will correlate with clinical benefit and maybe a valuable biomarker.

4. Tumor expression of fibroblast growth factor receptor isoforms FGFR IIIb and IIIc, Ki-67 and microvessel density measured by immunohistochemistry (IHC) will correlate with clinical benefit.

Overlap: NONE

New Funding

Title: Cancer Center Support Grant – Biostatistical Core (RPCI subcontract) (5 P30 CA16056-36)

Time Commitment: 1.20 calendar (PI-Johnson/Brady)

Supporting Agency: NIH

Funding Agency's Procuring Contracting/Grants Officer: Wooddill, Joseph; Phone: (301) 496-8635

Performance Period: 05/01/97-04/30/19

Level of Funding: \$2,392,072

Project Goals: The major goal of this project is to provide biostatistical support for cancer clinical trials.

Specific Aims:

1. Facilities: Physical facilities dedicated to the conduct of cancer focused research, and to the center's shared resources, administration, and research dissemination efforts, should be appropriate and adequate to the task.
2. Organizational Capabilities: The center should be organized to take maximum advantage of institutional capabilities in cancer research, and to appropriately plan and evaluate center strategies and activities.
3. Transdisciplinary Collaboration and Coordination: Substantial coordination, interaction, and collaboration among center members from a variety of disciplines should enhance and add value to the productivity and quality of research in the center.
4. Cancer Focus: A defined scientific focus on cancer research should be clear from the center members' grants and contracts, and from the structure and objectives of its formal Programs.
5. Institutional Commitment: The center should be recognized as a formal organizational component with sufficient space, positions, and discretionary resources to insure its stability and fulfill the center's objectives.
6. Center Director: The director should be a highly qualified scientist and administrator with leadership experience and institutional authority appropriate to manage the center and further its scientific mission and objectives.

Overlap: None

New Funding

Title: Image-Guided Photodynamic Therapy of Lung Cancer (1R21 CA176154-01A1)

Time Commitments: 2.50 calendar (PI-Nwogu)

Supporting Agency: NCI

Grants Officer: Anil Wali; anil.wali@nih.gov; Phone: (240) 276-6183

Performance Period: 08/01/14-07/31/16

Level of Funding: \$229,028

Brief description of project's goals: Lung cancer is the most frequent cause of cancer death in both men and women in the United States and will account for about 27% of all estimated cancer deaths in 2013. This project seeks to study the ability of a novel compound to simultaneously image lung cancer using positron emission tomography (PET) and ablate it with photodynamic therapy (PDT).

List of specific aims:

- 1) Compare the effectiveness of 124I-PS2 and 18F-Fluorodeoxyglucose (FDG) in imaging of lung tumors and lymph node metastases using an orthotopic lung cancer model in SCID mice.
- 2) Compare the effectiveness of photodynamic therapy using PS2 and Porfimer Sodium (Photofrin®) in human NSCLC xenografts established subcutaneously in SCID mice.

Overlap: NONE

Elena Pop, MD

Previously Active, now Completed

Title: Role of Androgen Axis in the Racial Differences of Prostate Cancer Mortality (PI – Mohler)

Time Commitments: 1.20 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Ayi Ayayi,
Contract Specialist

U.S. Army Medical Research Acquisition Activity, MCMR-AAA-E, 820 Chandler Street, Fort Detrick,
MD 21702-5014

Phone: (301) 619-4018 ayi.ayayi@us.army.mil

Performance Period: 09/30/2010-09/29/2014

Level of Funding: \$817,716 NCE

Brief description of project's goals: The study will provide complete analysis of the androgen receptor and androgen-regulated genes and relate it to prostate cancer in a large sample of men to test whether racial differences in prostate cancer mortality may be due, in part, to racial differences in androgenic stimulation of prostate cancer. Greater androgenic stimulation of the African American prostate could explain the two-fold difference in prostate cancer risk and increased aggressiveness of clinical disease in African compares to Caucasian Americans.

List of specific aims:

The central hypothesis of the proposed research is that racial differences in the tissue androgen axis contribute to CaP aggressiveness. Greater androgenic stimulation of the African-American prostate may contribute to increased incidence of, and higher mortality rates from, CaP. Quantifying the androgen axis in a large number of men with CaP will determine whether or not CaP receives race-dependent differences in androgenic stimulation that may affect CaP outcome. In order to test the central hypothesis, we propose three specific aims:

4. Determine whether AR protein levels differ in CaP of African and Caucasian Americans
5. Determine whether AR protein levels correlate with proteins expressed from androgen-regulated genes (PSA, Nkx3.1, hK2, *TRMPRSS2/ERG* fusions)
6. Determine whether AR protein levels correlate with CaP growth rate, extent and tumor differentiation

PI Moved to a different Institution

Title: Towards selective androgen deprivation by targeting androgen activation of SRF (Heemers)

Time Commitments: 2.4 calendar months (in years 4 and 5)

Supporting Agency: National Institutes of Health- R01

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 06/19/2014-05/31/2019

Level of funding: \$2,137,388

Brief description of project's goals:

The SRF-responsive subset of androgen-regulated genes is responsible for the aggressive CaP phenotype via androgen activation of the RhoA signaling axis and the RhoA effectors, PKN1 and CIT.

List of specific aims:

Aim 1. Define the contribution of RhoA, PKN1 and CIT in androgen regulation of SRF target genes

Aim 2. Determine the preclinical role of the SRF-responsive subset of androgen-regulated genes in CaP cell motility and invasive behavior

Aim 3. Determine the clinical relevance of RhoA-, PKN1-, and CIT-dependent androgen-responsive SRF action

Overlap: None

No Cost Extension Granted

Title: Prostate Cancer: Transition to Androgen Independence, Core B: ImmunoAnalysis and Tumor Management (French – PI)

Time Commitments: 9.0 calendar months

Supporting Agency: National Cancer Institute P01-CA77739

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295, 102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015, mkramer@med.unc.edu

Performance Period: 04/01/2005-03/31/2017 (NCE)

Level of Funding: \$903,203

Brief description of project's goals: Renewal of a core that serves two primary functions to the three projects: Core B is involved in all aspects of clinical specimen and prostate cancer xenograft management and Core B processes and stores the invaluable prostate biopsy specimens obtained from men with advanced prostate cancer prior to and at regular intervals after beginning androgen deprivation therapy.

List of specific aims:

Aim 1. Core B will provide high quality, reliable and cost-effective technical services to participants of the Program Project for immunohistochemistry and quantitative image analysis.

Aim 2. Core B will manage the research specimens critical to the conduct of the research proposed by the Program Project.

Aim 3. Core B will provide expertise in biostatistics and genitourinary pathology.

Overlap: None

Moved from Pending to Current

Title: Genetic variations in SLCO transporter genes contributing to racial disparity in aggressiveness of prostate cancer (Wu)

Time Commitments: 0.60 calendar months

Supporting Agency: CDMRP (W81XWH-14-1-0453)

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mirlene Desir, Grant Specialist, Assistance Branch 4, MCMR-AAA-AD, USAMRAA, 820 Chandler Street, Fort Detrick, MD 21702, phone: 301-619-7733, fax: 301-619-9656, mirlene.desir@civ@mail.mil

Performance Period: 09/15/2014-09/14/2017

Level of funding: \$764,100

Brief description of project's goals: The objective seeks to address how transporter-regulated androgen availability to cancer cells may contribute to the difference in prostate cancer aggressiveness between African American (AA) and European American (EA) men. The hypothesis is: Genetic variations in solute carrier family of organic anion transporting peptides (SLCO) androgen transporter genes and expression profiles of SLCO androgen transporters in prostate tissue are associated with aggressiveness of prostate cancer, and contribute to racial differences in prostate cancer aggressiveness.

List of specific aims:

Aim 1. Examine genetic variations in SLCO transporters genes and to investigate the associations of the variations with prostate cancer aggressiveness in AA and EA.

Aim 2. Examine *in situ* expression profiles of SLCO transporters in prostate tissue and to investigate the associations of the expression profiles with prostate cancer aggressiveness in AA and EA.

Aim 3. Characterize the functions of candidate SLCO transporters in androgen uptake and to evaluate the biological effects on AR signaling in human prostate cancer cell lines.

Overlap: None

New funding

Title: Deplete prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu)

Time Commitments: 1.80 calendar months

Supporting Agency: NIH/NCI 1R21CA191895-01

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-276-5157, viviana.knowles@nih.gov

Performance Period: 09/17/2014-08/31/2016 **Level of Funding:** \$466,950

Brief description of project's goals: This research seeks to address the racial differences in prostate cancer aggressiveness from a biological perspective.

List of specific aims:

Aim 1. Characterize the expression of STS and potential STS regulators in CRPC

Aim 2. Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth

Aim 3. Identify DHEAS uptake mechanisms

Overlap: None

8. Special Reporting Requirements

This grant funds a Synergistic Idea Development Award in collaboration with Dr. David Goodrich (Partnering PI, Roswell Park Cancer Institute). Dr. Goodrich will be submitting an independent annual report describing his aspect of the work.

MOHLER, JAMES L.

Current

Title: Prostate Cancer: Transition to Androgen Independence, Project 1: Interference with the Androgen Receptor and Its Ligands in Recurrent Prostate Cancer (French - PI)

Time Commitments: 2.04 calendar months

Supporting Agency: National Cancer Institute P01-CA77739

Name and address of the Funding Agency's Procuring Contracting/Grants Officer:

Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295
102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015,
mkramer@med.unc.edu

Performance Period: 04/01/2005-03/31/2017 (NCE)

Level of Funding: \$2,292,618

Brief description of project's goals: Renewal of a project that tests the hypothesis that recurrence of prostate cancer during androgen deprivation therapy can be prevented or delayed by preventing the accumulation of tissue androgens and/or inhibiting the androgen receptor.

List of specific aims:

1. Prevent the changes in androgen metabolism that provide AR ligand(s) in the immediate post-castration period
2. Degrade AR ligand(s) formed in the immediate post-castration period
3. Diminish or eliminate AR in the immediate post-castration period

Overlap: None

Title: Prostate Cancer: Transition to Androgen Independence, Core A: Administration (Mohler – PI)

Time Commitments: 1.16 calendar months

Supporting Agency: National Cancer Institute P01-CA77739

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295

102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015,
mkramer@med.unc.edu

Performance Period: 04/01/2005-03/31/2017 (NCE)

Level of Funding: \$519,640

Brief description of project's goals: Renewal of an administrative core that provides the leadership for the overall Program Project in the daily execution of administrative matters common to the three projects and ImmunoAnalysis and Tumor Management Core B.

List of specific aims:

The objective of the Administration Core A is to provide leadership, direction and administrative services for the purposes of enhancing research productivity and maintaining a stimulating research environment conducive to study of prostate cancer biology. Administration Core A will foster exchange of ideas and promote collaboration through its interactions with the Project Leaders and research groups. A major effort will be to encourage and facilitate collaboration in translational research among investigators within the Program Project and other investigators within or outside UNC-Lineberger Comprehensive Cancer and Roswell Park Cancer Institute. Administration Core A will have direct responsibility for organization and facilitation of the monthly research conferences and annual review of the Program Project by the 5 external consultants. Administration Core A will monitor activities of ImmunoAnalysis and Research Specimen Management Core B, in particular, and the entire program, in general, to improve the efficiency and effectiveness of the entire program.

Overlap: None

Title: Prostate Cancer: Transition to Androgen Independence, Core B: ImmunoAnalysis and Tumor Management (French – PI)

Time Commitments: 0.48 calendar months

Supporting Agency: National Cancer Institute P01-CA77739

Name and address of the Funding Agency's Procuring Contracting/Grants Officer:

Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295
102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015,
mkramer@med.unc.edu

Performance Period: 04/01/2005-03/31/2017 (NCE)

Level of Funding: \$903,203

Brief description of project's goals: Renewal of a core that serves two primary functions to the three projects: Core B is involved in all aspects of clinical specimen and prostate cancer xenograft management and Core B processes and stores the invaluable prostate biopsy specimens obtained from men with advanced prostate cancer prior to and at regular intervals after beginning androgen deprivation therapy.

List of specific aims:

The ImmunoAnalysis and Research Specimen Management Core B will provide 3 primary services to the Program Project.

1. Core B will provide high quality, reliable and cost-effective technical services to participants of the Program Project for immunohistochemistry and quantitative image analysis.
2. Core B will manage the research specimens critical to the conduct of the research proposed by the Program Project.
3. Core B will provide expertise in biostatistics and genitourinary pathology.

Overlap: None

Title: Cancer Center Support Grant (Johnson - PI)

Time Commitments: 3.30 calendar months

Supporting Agency: National Cancer Institute

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Kimerly Griffin, NCI Shady Grove, 9609 Medical Center Drive, West Tower, 2nd floor, Room 2W520, Rockville, MD 20850. 240-276-6315

Performance Period: 06/26/2014-04/30/2019

Level of Funding: \$2,315,456

Brief description of project's goals:

Roswell Park Cancer Institute's Cancer Center Support Grant (CCSG) includes six programs and 13 cores resources. Support is provided for leadership, developmental funds, planning and evaluation and administration.

List of specific aims:

The resource provides a complete service from methods development and validation to sample handling and analysis to PK/PD modeling and simulation leading to informed decision-making about dosing, dose scheduling and drug combinations.

Overlap: None

Title: Diet changes among prostate cancer patients under expectant management (Marshall - PI)

Time Commitments: 0.60 calendar months

Supporting Agency: National Cancer Institute

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Program Official: Howard L. Parnes, Email: hp24c@nih.gov Phone: 301-594-0920 Fax: 301-435-1564

Performance Period: 09/28/2009-01/31/2016

Level of Funding: \$55,818

Brief description of project's goals: The focus of this study is to assess whether a diet emphasizing plant consumption decreases the probability that low grade, low-volume prostate cancer (LGLV) in expectant management (EM) patients progresses to a more aggressive form of cancer that merits active treatment. The intervention will be conducted through one of the leading cooperative oncology research groups: Cancer and Leukemia Group B (CALGB).

List of specific aims:

1. Assess the effect of a telephone-based dietary intervention on PSA, PSA doubling time, Gleason score and tumor extension in LGLV prostate cancer patients treated with EM.
2. Assess the effect of a telephone-based dietary intervention on treatment seeking, anxiety and coronary heart disease in prostate cancer patients treated with EM.

Overlap: None

Title: Defining intra- and intertumoral genomic heterogeneity in prostate cancer (Mohler - PI)

Time Commitments: 0.60 calendar months

Supporting Agency: Roswell Park Alliance Foundation

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14203, Judith.Epstein@RoswellPark.org

Performance Period: 12/10/2013-12/31/2015

Level of funding: \$92,384

Brief description of project's goals:

Intra- and inter-tumoral CaP genomic heterogeneity necessitates extensive sampling of a radical prostatectomy specimen.

List of specific aims:

1. Determine intra- and inter-tumoral heterogeneity in CaP's mutational landscape using whole exome sequencing to determine heterogeneity within and among CaP foci derived from radical prostatectomy specimens from patients with high-risk disease who are expected to develop metastatic disease and require ADT
2. Define intra- and inter-tumoral CaP heterogeneity in structural gene rearrangement and gene expression patterns using RNA-Seq and RNA derived from the same CaP samples used in Aim 1

Overlap: None

Title: Network Lead Academic Participating Site Grant from the Roswell Park Cancer Institute (Adjei, Lele, Levine, Singh - PIs)

Time Commitment: 0.60 calendar months

Supporting Agency: NIH: NCI NCTN Program IU10 CA180866-01

Funding Agency's Procuring Contracting/Grants Officer: Margaret M. Mooney, Program Official, BG 9609 RM 5W412, 9609 Medical Center Drive, Rockville, MD 20850, phone 240-276-6560, mooneym@mail.nih.gov

Performance Period: 05/06/2014-02/28/2019

Level of Funding: \$3,080,000

Brief description of project's goals: The aim of inter-Institutional cooperative clinical research is to advance our understanding of malignant diseases and, thereby, improve our ability to treat people afflicted with them. These aims are accomplished by resolving scientific questions of importance regarding cancer biology and therapy through the cooperation of selected Institutions that can pool their intellectual, technical, and patient resources. The rapid accumulation of clinical data and experience through cooperative research expedites progress in cancer therapy.

List of specific aims: The Roswell Park Cancer Institute has had a long tradition of contributing to the national cooperative groups over many decades. Those contributions have been scientific, administrative, and participatory (over 1200 patients have been enrolled in cooperative group trials over the last 5 years). This application summarizes the intent of its 4 Co-PIs (Levine/Adjei/Lele/Singh) and the membership of RPCI to sustain its commitment to the many strengths inherent to cooperative group research: therapeutic advances; a better understanding of the biology of cancer; cancer prevention; means to improve the quality of life of cancer patients; piloting of new drugs and radiology and radiation and surgical techniques; establishing the relevance of new cellular and molecular advances to the predictive, prognostic, and therapeutic approaches to patients;

and the advancement of patient advocacy. Investigators at RPCI and its supporting staff fully recognize the essential importance of the timely and accurate submission of data and specimens to achieve these aims.

Overlap: None

Title: Genetic variations in SLCO transporter genes contributing to racial disparity in aggressiveness of prostate cancer (Wu - PI)

Time Commitments: 0.12 calendar months

Supporting Agency: USAMRAA W81XWH-14-1-0453

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mirlene Desir, Grant Specialist, Assistance Branch 4, MCMR-AAA-AD, USAMRAA, 820 Chandler Street, Fort Detrick, MD 21702, phone: 301-619-7733, fax: 301-619-9656, mirlene.desir@civ@mail.mil

Performance Period: 09/15/2014-09/14/2017

Level of funding: \$764,100

Brief description of project's goals: The objective seeks to address how transporter-regulated androgen availability to cancer cells may contribute to the difference in prostate cancer aggressiveness between African American (AA) and European American (EA) men. The hypothesis is: Genetic variations in solute carrier family of organic anion transporting peptides (SLCO) androgen transporter genes and expression profiles of SLCO androgen transporters in prostate tissue are associated with aggressiveness of prostate cancer, and contribute to racial differences in prostate cancer aggressiveness. (Recommended for funding)

List of specific aims:

1. Examine genetic variations in SLCO transporters genes and to investigate the associations of the variations with prostate cancer aggressiveness in AA and EA.
2. Examine *in situ* expression profiles of SLCO transporters in prostate tissue and to investigate the associations of the expression profiles with prostate cancer aggressiveness in AA and EA.
3. Characterize the functions of candidate SLCO transporters in androgen uptake and to evaluate the biological effects on AR signaling in human prostate cancer cell lines.

Overlap: None

Title: Deplete prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu – PI)

Time Commitments: 0.12 calendar months

Supporting Agency: NIH/NCI 1R21CA191895-01

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-276-5157, viviana.knowles@nih.gov

Performance Period: 09/17/2014-08/31/2016

Level of Funding: \$419,884

Brief description of project's goals: This research seeks to address the racial differences in prostate cancer aggressiveness from a biological perspective.

List of specific aims:

1. Characterize the expression of STS and potential STS regulators in CRPC
2. Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth
3. Identify DHEAS uptake mechanisms

Overlap: None

Title: Qualifying multi-transcript signatures for active surveillance in prostate cancer (Kim/Mohler - PIs)

Time Commitments: 0.60 calendar months

Supporting Agency: National Institutes of Health 1R01CA182438-01A1

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 09/01/2014-08/31/2019

Level of funding: \$195,510 (sub contract)

Brief description of project's goals: The vast majority of men diagnosed with prostate cancer do not die of their disease, yet prostate cancer remains the second leading cause of cancer-death in men. We propose to qualify prognostic transcriptomic signatures to predict the risk of adverse prostate cancer pathology and disease progression using prostate needle biopsies from men considering active surveillance as a strategy to delay and even avoid the treatment of prostate cancer. A qualified test will help with treatment decisions at the time of prostate cancer diagnosis. Another objective addresses the glaring absence of well-established criteria for active surveillance in non-Caucasian men. We propose to qualify our signatures in African-American men. Qualified signatures of cancer severity will improve outcomes prediction and identify the most appropriate candidates for active surveillance, and ultimately reduce the public health burden of prostate cancer.

List of specific aims:

1. Qualify biomarkers to predict adverse pathology and progression using prostate biopsies in men considering active surveillance.
2. Test the effects of African-American ethnicity on the biomarker signatures.

Overlap: None

Title: Alliance NCORP Research Base (Kim/Mohler - PIs)

Time Commitments: 0.60 calendar months

Supporting Agency: Alliance Foundation

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Subcontract with Cedars Sinai. Cedars-Sinai Medical Center, Attention: Margaret Jenkins, Administrative Program Coordinator Department of Surgery, Research Division, 8635 W. 3rd Street, Suite 973W, Los Angeles, CA 90048
margaret.jenkins@cshs.org

Performance Period: 04/01/2015 – 03/31/2016

Level of funding: \$93,955 (sub contract)

Brief description of project's goals: The proposed research tests the hypothesis that intensive cholesterol lowering will decrease the growth rate of benign and malignant prostate epithelium. The proposed research could provide the data necessary to justify a phase III clinical trial to address one of the major problems in urologic oncology how to prevent the progression of low risk prostate cancer to provide men higher levels of confidence for selection of active surveillance.

Overlap: None

Pending

Title: Development of an inhibitor for 3alpha-oxidoreductases, the enzymes common to the last step in DHT production by the primary and secondary backdoor pathways (Mohler - PI)

Time Commitments: 1.20 calendar months

Supporting Agency: DoD Idea Development Award W81XWH-15-PCR-IDA

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 04/01/2016-03/31/2019

Level of funding: \$591,672

Brief description of project's goals: Abiraterone expense (\$6000/mo) and its relative lack of efficacy (extends survival 4 mo) impede development of pharmaceuticals that target intracrine androgen metabolism. An actively coordinated attack upon intracrine androgen metabolism may lower DHT better, improve efficacy of primary or secondary ADT, and reduce the need for new treatments. We have recognized that the 5 enzymes critical for the terminal steps in T and DHT production via 2 backdoor pathways share a catalytic site, which we proved important by mutating then deleting it. Potential inhibitors will be tested in preclinical models to deliver a 3 α -oxidoreductase inhibitor for clinical trial. The new drug used alone or in combination with abiraterone should reduce the death rate from CaP, the 3rd PCR-IDA theme.

List of specific aims:

1. Identify a candidate inhibitor against the catalytic site shared by the five 3 α -oxidoreductases
2. Synthesize and test re-designed candidate inhibitors and conduct PK/PD and toxicity studies to produce a lead compound inhibitor of the five 3 α -oxidoreductases

3. Determine whether the inhibitor of the five 3 α -oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth

Overlap: None

Title: Understanding the Relative Contributions of and Critical Enzymes for the 3 Pathways for Intracrine Metabolism (Mohler - PI)

Time Commitments: 1.70 calendar months

Supporting Agency: DoD Idea Development Award

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 04/01/2016-03/31/2019

Level of funding: \$660,315

Brief description of project's goals:

Better understanding of intracrine androgen metabolism during ADT will identify new targets to reduce T and DHT production.

List of specific aims:

1. Determine the relative use of the 3 pathways for intracrine androgen metabolism in vitro, in vivo and in clinical specimens.
2. Identify the principal androgen metabolism enzymes (ie. 3 α -oxidoreductases) responsible for primary backdoor DHT synthesis from androstenediol.
3. Determine the requirements for SRD5A1-3 in the frontdoor pathway of DHT synthesis from T and its precursors and of SRD5A1 and HSD17B3 in the secondary backdoor pathway of DHT synthesis from androstenedione.

Overlap: None

Title: Leveraging the North Carolina-Louisiana Prostate Cancer Project (PCaP) Data and Biorepository with Oncological Outcome (Mohler – PI)

Time Commitments: 1.20 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 04/01/2016 – 03/31/2019

Level of funding: \$767,096

Brief description of project's goals: Project is the largest population-based study of newly diagnosed prostate cancer ever completed. Project sought to partition the reasons for increased prostate cancer mortality in African compared to Caucasian Americans among racial differences in 3 categories: 1) interaction between the prostate cancer patient and the American healthcare system; 2) biology of the host (diet, genetics and environment); and 3) biology of the tumor. The value of the Project will grow by connecting 10-year outcome to this invaluable data and biorepository to provide further insight into the reasons for the racial disparity in prostate cancer mortality.

List of specific aims:

1. Contact research subjects and their physicians to update treatments received, repeat the quality of life assessments performed at baseline and follow-up, and query them on the financial impact of cancer
2. Provide mortality and cause of death information for research subjects at least annually
3. Provide the administrative structure and manage the liquid and tissue biorepositories necessary to facilitate additional grants and manuscripts

Overlap: None

Title: A Small-Molecule Inhibitor of the Terminal Steps for Intracrine Androgen Synthesis in Advanced Prostate Cancer (Mohler)

Time Commitments: 1.20 calendar months

Supporting Agency: NCI- Omnibus R21

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not yet assigned

Performance Period: 04/01/2016-03/31/2018

Level of Funding: \$ 660,315

Brief description of project's goals: This research seeks to explore if a small-molecule inhibitor of the catalytic site shared by the five 3 α -oxidoreductases will decrease T and DHT metabolism through the frontdoor and backdoor pathways.

List of specific aims:

1. Identify a candidate inhibitor against the catalytic site shared by the five 3 α -oxidoreductases
2. Synthesize and test re-designed candidate inhibitors and conduct PK/PD and toxicity studies to produce a lead compound inhibitor of the five 3 α -oxidoreductases
3. Determine whether the inhibitor of the 3 α -oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth

Overlap: None

Title: Establishment of a CRPC Biorepository from Caucasian and African Americans by Collaboration among Advocaters, Physicians, Scientists and Organ Donation Services (Foster)

Time Commitments: 0.6 calendar months

Supporting Agency: DoD Idea Development Award W81XWH-15-PCR-IDA

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 04/01/2016-03/31/2019

Level of funding: \$600,000

Brief description of project's goals: To establish a pipeline to collection the lethal phenotype from African American and Caucasian men using local prostate cancer support networks with education and mentoring, physicians and local organ procurement organization. The goal is to collect over the 3 year period tissues from 45 donors with the lethal phenotype of prostate cancer of which 15 are African American. A biorepository will be established in which the following biospecimens will be available from each donor: primary cancer from soft and bone metastasis (formalin fixed paraffin embedded (FFPE), flash frozen (FF)), patient derived xenografts (PDX) and organoids.

List of specific aims:

1. Establish a registry of men with mCRPC that want to donate tissues for research purposes.
2. Establish with MANUP and Us TOO an outreach program in the AA community for CaP education and peer support for men with CaP to insure that at least 33% of the enrollees are AA.
3. Establish a biobank of mCRPC tissues having 33% AA which contains formalin fixed paraffin embedded samples, flash frozen samples, and renewable resources of xenografts and organoids; thereby, establishing an invaluable repository of mCRPC rich in AA biospecimens for genomic and molecular study.
4. RTAP will partner with Buffalo's organ procurement organization for the collection of tissues and clinical data from mCRPC donors.
5. As a proof of scientific value, mCRPC samples are used to determine if the mutational profile of the AR is different in mCRPC of AA and if AR mutations differ in multiple metastatic sites of an individual.

Overlap: None

Previous

Title: Genetic variations in mitochondria and prostate cancer aggressiveness and progression in Caucasian and African American men (Zhao - PI)

Time Commitments: 0.60 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer:

Sherie Wesley, Research Contract Specialist, Legal Services Department, LEGAL SERVICES, Unit 537, P. O. Box 301439, Houston, Texas 77230-1439 Email: swesley@mdanderson.org Phone: 713.794.1507 Fax: 713.792.6878

Performance Period: 07/01/2012-06/30/2015

Level of Funding: \$936,256

Brief description of project's goals: The hypothesis is that genetic variations (sequence and copy number) in mtDNA are associated with prostate cancer aggressiveness at diagnosis and prostate cancer progression. The proposed study will represent the first study to address the roles of mtDNA variations in prostate cancer aggressiveness and progression as well as racial difference.

List of specific aims:

1. Evaluate whether genetic variations in mtDNA are associated with aggressive tumor characteristics of prostate cancer at diagnosis and progression of prostate cancer in CA and AA men, and whether the associations are different between CA and AA men.
2. Evaluate whether mtDNA CNVs are associated with aggressive tumor characteristics of prostate cancer at diagnosis and progression of prostate cancer in CA and AA men, and whether the associations are different between CA and AA men.
3. Exploratory Aim: Perform whole mitochondrial DNA sequencing to identify novel genetic variants in AA and CA prostate cancer patients.

Title: Racial Differences in Prostate Cancer: Influence of Health Care and Host and Tumor Biology, Project 7: The Androgen Axis in Prostate Cancer (Mohler - PI)

Time Commitments: 0.60 calendar months

Supporting Agency: U.S. Army Medical Research, DAMD17-03-2-0052

Name and address of the Funding Agency's Procuring Contracting/Grants Officer:

Nrusingha.Mishra, Nrusingha.Mishra@amedd.army.mil 301-619-7782

Performance Period: 09/01/2004-08/31/2010

Level of Funding: \$938,663

Brief description of project's goals: Test the hypothesis that CaP mortality is greater in African Americans than Caucasian Americans because CaP receives greater androgenic stimulation. In order to test this hypothesis, we will evaluate the androgen axis in men selected geographically to demonstrate three different categories of CaP aggressiveness – African Americans from North Carolina (high risk), African Americans from Louisiana (intermediate risk) and Caucasians from both states (low risk). Quantifying the androgen axis in a large number of men with CaP will determine whether or not CaP receives race-dependent differences in androgenic stimulation that may affect CaP outcome.

List of specific aims:

1. Determine whether AR protein levels differ in CaP of African and Caucasian Americans.
2. Determine whether AR protein levels correlate with CaP extent, differentiation and growth rate.
3. Determine whether AR trinucleotide repeat lengths and serum levels of androgen affect AR protein levels.

Title: Racial Differences in Prostate Cancer: Influence of Health Care and Host and Tumor Biology, Core 3: Tissue Microarray and ImmunoAnalysis Core (Mohler - PI)

Time Commitments: 0.48 calendar months

Supporting Agency: U.S. Army Medical Research, DAMD17-03-2-0052

Name and address of the Funding Agency's Procuring Contracting/Grants Officer:

Nrusingha.Mishra, Nrusingha.Mishra@amedd.army.mil 301-619-7782

Performance Period: 09/01/2003-10/31/2010

Level of Funding: \$441,169

Brief description of project's goals: The Tissue MicroArray and ImmunoAnalysis Core 3 will provide high quality, reliable and cost-effective technical services to the projects of the DOD Consortium.

List of specific aims:

The Tissue MicroArray and ImmunoAnalysis Core 3 will provide high quality, reliable and cost effective technical services to the projects of the DOD Consortium. Core 3 will construct tissue microarrays from diagnostic biopsies and provide microarray sections to the individual Projects. When requested, Core 3 will perform for, or assist the Projects with, immunohistochemical/immunofluorescence staining, in situ hybridization and quantitative analysis of immunostained sections using image analysis. Core 3 will rely on the high level of expertise of the research personnel that has been developed by serving the needs of Dr. Mohler's

P01, Prostate Cancer: Transition to Androgen-Independence, and its Projects led by Drs. Mohler, French and Smith, Dr. Mohler's DOD award, Prevention of Development of Recurrent Growth of Prostate Cancer, Dr. Gregory's DOD award, The Role of Nuclear Receptor Coactivators in Recurrent Prostate Cancer, Dr. Ornstein's R21, Proteomic Studies of Androgen-Independent Prostate Cancer and Dr. Mohler's past DOD award, A Novel Approach to the Elucidation of the Mechanism of Development of Androgen-Independent Growth of Prostate Cancer. In addition to the services necessary for the DOD Consortium, Core 3 also performs standard microdissection¹ and laser-capture microdissection^{2,3} for DNA extraction, PCR amplification and androgen receptor mutational analysis.

Title: Racial Differences in Prostate Cancer: Influence of Health Care and Host and Tumor Biology, Core 4: Scientific Management, Communication, Administration (Mohler - PI)

Time Commitments: 0.48 calendar months

Supporting Agency: U.S. Army Medical Research, DAMD17-03-2-0052

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Nrusingha.Mishra, Nrusingha.Mishra@amedd.army.mil 301-619-7782

Performance Period: 09/01/2003-10/31/2010

Level of Funding: \$416,532

Brief description of project's goals: The Communications and Administration Plan will facilitate interaction among all Consortium personnel.

List of specific aims:

The Consortium was comprised by 9 Projects that were supported by 3 scientific cores and the Communications and Administration Plan (Figure). The scientific management of the Consortium relies upon the close relationships between the investigators that existed previously, and has been strengthened as a result of the Prostate Cancer Consortium Development Award activities. With these relationships as a baseline, a Scientific Management Plan was constructed that took advantage of the scientific expertise of the investigators, the guidance of prostate cancer survivors and minority community activists and state-of-the-art information technology to direct and monitor progress toward the goals of the Consortium.

Title: Dependency on Src-Family Kinases for Recurrence of Androgen-Independent Prostate Cancer (Gelman - PI)

Time Commitments: 0.60 calendar months

Supporting Agency: Department of Defense Prostate Cancer Synergistic Idea award

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Marielena McGuire, Ph.D. Grants Manager Prostate Cancer Research Program Congressionally Directed Medical Research Programs United States Army Medical Research and Materiel Command, 1077 Patchel St., Fort Detrick, Maryland 21702 Tel: 301-619-8969, Fax: 301-619-7796 email: marielena.mcguire@amedd.army.mil

Performance Period: 04/01/2008-03/31/2011

Level of Funding: \$749,997

Brief description of project's goals: The goal of this study is to perform preclinical studies to collect the data necessary to establish the foundation for clinical studies to use SFK inhibitors such as KX2-391 as adjuvants to androgen deprivation therapy in order to prevent castration-recurrent -CaP.

List of specific aims:

1. Characterize the requirement of SFK activity for the recurrence of AI-CaP after castration
2. The role of SFK in NE cell expansion after castration
3. Src and Lyn activity in the NE proliferation, NE-secretion of mitogenic neuropeptides and the NE-mediated promotion of AI-CaP recurrence and proliferation

Title: Health Care Access and Prostate Cancer Treatment in North Carolina: HCaP-NC (Bensen - PI)

Time Commitments: 0.60 calendar months

Supporting Agency: American Cancer Society

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Ronit Elk, Ph.D., Scientific Program Director, Cancer Control and Prevention Research, Director, Research Targeted at the Poor

and Underserved, American Cancer Society, 250 Williams St. NW (6th floor), Atlanta, GA, 30303, Ronit.Elk@cancer.org, (404) 417-5957 or (404)329-5740

Performance Period: 01/01/2008 - 12/31/2011

Level of Funding: \$190,937

Brief description of project's goals: This study will inform public health efforts to reduce racial disparities by identifying potentially modifiable intermediates in the causal pathway linking African American race/ethnicity to adverse prostate cancer outcomes.

List of specific aims:

1. Develop a data collection instrument and measures of the quality of prostate cancer treatment based on characteristics of providers and facilities and concordance with consensus recommendations defined by patient characteristics, disease and treatment.
2. Quantify the extent of racial differences in the quality of prostate cancer treatment and evaluate health insurance, individual access to care, and healthcare availability as potential causes of differences in treatment quality.
3. Quantify the extent of racial differences in the health-related quality of life (HRQOL) of prostate cancer patients and evaluate health insurance healthcare access and availability, type of treatment, and quality of treatment as potential causes of differences in HRQOL

Title: A Clinical Trial of Selenium and Prostate Biomarkers (Marshall – PI)

Time Commitments: 0.45 calendar months

Supporting Agency: National Cancer Institute R01-CA116673-03

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Sean Hine, Grants Management Officer, National Cancer Institute, Email: hines@mail.nih.gov Phone: 301-846-1005

Performance Period: 01/01/2007-12/31/2012

Level of Funding: \$312,817

Brief description of project's goals: This study will provide key in vivo, human data on the mechanisms of selenium's action in the prostate, and greatly help interpret the results of the important chemoprevention trials such as HGPIN and SELECT.

List of specific aims:

Primary aim: Evaluate down regulation of androgen receptor (AR) in the prostate by short-term selenium supplementation.

Secondary aims:

1. Evaluate down-regulation by short-term selenium supplementation of AR regulated genes, such as PSA, KLK2, CDC6, and DHCR24, in the prostate.
2. Evaluate down-regulation by short-term selenium supplementation of prostatic expression of HNF3a, a transcription factor that interacts physically with AR in AR signaling.
3. Determine whether the thiol methyltransferase (TMT) phenotype modifies the prostatic response to short-term selenium supplementation.

Title: Translational Research of Finasteride and Selenium Prevention of Prostate cancer. Project 1: Mechanism of selenium potentiation of finasteride efficacy

Time Commitments: 1.20 calendar months

Supporting Agency: NIH P01-CA126804

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Howard Parnes, M.D. Chief, Prostate and Urologic Cancer Research Group, Division of Cancer Prevention, National Cancer Institute Executive Plaza North, Room 2100, 6130 Executive Blvd., Bethesda, MD 20892, (301)594-0920, parnesh@mail.nih.gov

Performance Period: 09/01/2007-08/31/2013

Level of Funding: \$1,315,352

Brief description of project's goals: The objective of the program project is to develop a novel mechanism-driven strategy for prostate cancer prevention. Project 1 is to delineate how finasteride and selenium work cooperatively to modulate certain molecular events in controlling the clonal expansion of prostate cancer cells.

Special emphasis is placed on the functional analysis of key targets and pathways responsible for the induction of apoptosis following treatment with finasteride/selenium. Microenvironmental hypoxia is frequently seen in a colony of proliferating cancer cells due to abnormalities of the vasculature. It is well known that hypoxia produces a variety of molecular changes as a selective pressure for survival. There is recent evidence suggesting that hypoxia facilitates AR activation and the transcription of androgen-responsive genes. The above process is mediated by a redox-regulating protein called peroxiredoxin-1, or Prx1. Prx1 is preferentially elevated in prostatic intraepithelial neoplasia and prostate cancer cells.

List of specific aims:

1. Determine (a) whether the combination of finasteride/selenium will result in a further suppression of androgen signaling when compared to the single agent, and (b) whether finasteride has other effects on AR signaling beyond its known function of blocking 5 α -reductase.
2. Investigate the role of FOXO1A, a transcription factor negatively regulated by AR, in mediating the anticancer effect of finasteride and selenium.
3. Study (a) the activation of initiator caspases and executioner caspases by finasteride or selenium, or both; and (b) whether restoration of AR signaling reverses the effect of each agent on caspase activation and caspase-mediated apoptosis.
4. To validate the anticancer efficacy of finasteride/selenium and the accompanying molecular changes (information obtained from Aims 1 to 3) in human prostate cancer xenograft models.

Title: Translational Research of Finasteride and Selenium Prevention of Prostate cancer. Project 3: A Clinical Trial with Finasteride and Selenium (Marshall - PI)

Time Commitments: 0.60 calendar months

Supporting Agency: NIH P01-CA126804

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Howard Parnes, M.D. Chief, Prostate and Urologic Cancer Research Group, Division of Cancer Prevention, National Cancer Institute Executive Plaza North, Room 2100, 6130 Executive Blvd., Bethesda, MD 20892, (301)594-0920, parnesh@mail.nih.gov

Performance Period: 09/01/2007-08/31/2013

Level of Funding: \$1,355,357

Brief description of project's goals: The overall objective of the program project is to develop a novel and unique mechanism-driven strategy targeting the androgen signaling axis as a viable approach to prostate cancer prevention.

List of specific aims:

1. Evaluate whether selenium enhances the efficacy of finasteride in depressing AR signaling in patients with localized prostate cancer by using PSA expression as the indicator.
2. Evaluate the induction of apoptosis by the finasteride/selenium combination.
3. Determine whether the responsiveness to finasteride/selenium is related to the level of Prx1 expression.

Title: Steroid 5 α -reductase-3 promotes the progression of prostate cancer to recurrent prostate cancer (Titus - PI)

Time Commitments: 0.30 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Jennifer Shankle, Grant Specialist, U.S. Army Medical Research Acquisition Activity, MRMC-AAA-E, 820 Chandler Street, Ft. Detrick, MD 21702-5014 Phone: 301-619-2193 Fax: 301-619-3500

Performance Period: 04/20/2010-04/19/2013

Brief description of project's goals: Data from this project will enhance the understanding of prostate cancer tumor biology, identify a new target enzyme for therapy and define a biomarker that may determine therapeutic response to inhibitors of steroidogenesis.

List of specific aims:

1. Quantify 5 α -reductase-3 gene expression and protein location in androgen-stimulated benign prostate and androgen-stimulated prostate cancer and castration-recurrent prostate cancer.
2. Determine the relative substrate selectivity of 5 α -reductase-3 for conversion of the Δ 4-3-keto steroids, testosterone, androstenedione, progesterone and cortisol.
3. Determine the androgen metabolic profile in tumor tissue and serum using androgen-stimulated and androgen-independent prostate cancer cell line xenograft models

Title: Serum response factor as a novel therapeutic target in prostate cancer (Heemers - PI)

Time Commitments: 0.30 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Ayi Ayayi, Contract Specialist U.S. Army Medical Research Acquisition Activity, MCMR-AAA-E, 820 Chandler Street, Fort Detrick, MD 21702-5014 Phone: (301) 619-4018 ayi.ayayi@us.army.mil

Performance Period: 07/15/2010-01/14/2014

Level of funding: \$388,667

Brief description of project's goals: The proposed aims to test this hypothesis employ *in vitro* and *in vivo* preclinical models of PCa to determine the molecular mechanisms underlying androgen regulation of SRF/RhoA signalling and their potential as novel targets for therapeutic intervention.

List of specific aims: Androgen activation of SRF signaling is important for PCa cell proliferation and invasive potential and that the RhoA/SRF signaling pathway represents a novel therapeutic target downstream of AR action.

1. Mechanistically corroborate the involvement of RhoA signaling in androgen regulation of SRF target genes
2. Determine the molecular mechanism(s) by which androgens stimulate SRF signaling
3. Determine the therapeutic potential of targeting SRF signaling using preclinical PCa models

Title: PKN1 as a novel therapeutic target to block clinically relevant androgen action in prostate cancer (Heemers - PI)

Time Commitments: 0.24 calendar months

Supporting Agency: Roswell Park Alliance Foundation

Name and address of the Funding Agency's Procuring Contracting/Grants Officer:

Judith Epstein, Director Grants & Foundation Office, Roswell Park Cancer Institute, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14203, Judith.Epstein@RoswellPark.org

Performance Period: 04/02/2013 – 04/01/2014

Level of Funding: \$50,000

Brief description of project's goals:

The RhoA effector PKN1 that is responsible for conveying androgen-responsiveness to SRF represents an attractive novel target to inhibit selectively clinically relevant androgen action downstream of AR

List of specific aims:

1. Determine the therapeutic consequences of inhibition or mutation of PKN1 using a PKN1 inhibitor and site-directed mutations of PKN1 in sites that are necessary for RhoA interaction, and a preclinical CaP xenograft model
2. Determine the clinical relevance of PKN1 using immunohistochemistry and tissue microarrays (TMAs) that contain 715 CaP and control tissues for which complete clinical and outcome data is available

Title: A Phase I Study of Methylseleno-L-Cysteine in Prostate Cancer Patients (Marshall - PI)

Time Commitments: 0.18 calendar months

Supporting Agency: Northwestern University/NIH

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Bruce Elliott, Jr., PhD – Director, Office for Sponsored Research b-elliott@northwestern.edu Phone: 312-503-7955 Fax: 312-503-2234

Performance Period: 05/01/2011-06/30/2014

Level of Funding: \$318,700

Brief description of project's goals: This project is a continuation of a previous 1-arm study of Methylseleno-L-Cysteine in prostate cancer patients. This study adds 3 cohorts of 13 subjects each.

List of specific aims: To determine the individual toxicity profiles of MSC, SeMet and selenite administered to cohorts of men daily for 12 weeks, with dose escalation with each successive cohort.

Title: Role of Androgen Axis in the Racial Differences of Prostate Cancer Mortality (Mohler - PI)

Time Commitments: 1.20 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Ayi Ayayi, Contract Specialist, U.S. Army Medical Research Acquisition Activity, MCMR-AAA-E, 820 Chandler Street, Fort Detrick, MD 21702-5014 Phone: (301) 619-4018 ayi.ayayi@us.army.mil

Performance Period: 09/30/2010-09/29/2014

Level of Funding: \$817,716 NCE

Brief description of project's goals: The study will provide complete analysis of the androgen receptor and androgen-regulated genes and relate it to prostate cancer in a large sample of men to test whether racial differences in prostate cancer mortality may be due, in part, to racial differences in androgenic stimulation of prostate cancer. Greater androgenic stimulation of the African American prostate could explain the two-fold difference in prostate cancer risk and increased aggressiveness of clinical disease in African compares to Caucasian Americans.

List of specific aims:

The central hypothesis of the proposed research is that racial differences in the tissue androgen axis contribute to CaP aggressiveness. Greater androgenic stimulation of the African-American prostate may contribute to increased incidence of, and higher mortality rates from, CaP. Quantifying the androgen axis in a large number of men with CaP will determine whether or not CaP receives race-dependent differences in androgenic stimulation that may affect CaP outcome. In order to test the central hypothesis, we propose three specific aims:

1. Determine whether AR protein levels differ in CaP of African and Caucasian Americans
2. Determine whether AR protein levels correlate with proteins expressed from androgen-regulated genes (PSA, Nkx3.1, hK2, *TRMPRSS2/ERG* fusions)
3. Determine whether AR protein levels correlate with CaP growth rate, extent and tumor differentiation

PHS 398/2590 OTHER SUPPORT

Attwood, Kristopher

ACTIVE:

Title: Targeting Granzyme B to Separate GVH from GVL Responses (1 R01 CA184728-01)

Time Commitments: 0.60 calendar (PI-Cao)

Supporting Agency: NIH

Grants Officer: Susan McCarthy; susan.mccarthy@nih.gov; Phone: (240) 276-6200

Performance Period: 04/01/15-03/31/20

Level of Funding: \$401,456

Brief description of project's goals: The goal of this work is to examine this new paradigm regarding GzmB function after allogeneic HSCT. We hypothesize that the dual detrimental role for GzmB function may provide a long-desired target, allowing separation between GVH and GVL responses.

List of specific aims:

- 1) Will determine the contributions of hematopoietic APCs versus non-hematopoietic tissues to GzmB-mediated GVHD pathogenesis.
- 2) Will study the mechanisms by which GzmB diminishes CD8+ T cell-mediated GVL response.
- 3) Will study the clinical relevance of Granzyme function in allogeneic HSCT patients.

Overlap: NONE

Title: Distinguishing Tumor- and Stromal- Mediated Mechanisms of Resistance and Rebound in Models of Metastatic Renal Cell Carcinoma (W81XWH-14-1-0210)

Time Commitments: 0.50 calendar (PI-Ebos)

Supporting Agency: DOD

Grants Officer: Wendy A. Baker, Contracting Officer; wendy.a.baker.civ@mail.mil; Phone: (301) 619-2034

Performance Period: 07/01/14-06/30/16

Level of Funding: \$602,996

Brief description of project's goals: The purpose of the proposed studies is to investigate the contributions of stromal and tumor 'reactions' to antiangiogenic therapy in clinically-relevant metastatic models of RCC. The hypothesis guiding this research is that both tumor and host-stroma reactions collude to elicit metastatic cell behavior that drives resistance and rebound growth when therapy is halted.

List of specific aims:

- 1) To use an operative-metastatic RCC model to evaluate stromal host 'reactions' following therapy withdrawal in rebound and resistance 'reversibility'.
- 2) To identify whether tumor-stromal molecular gene signatures complement to activate pathways that promote drug-resistance and metastasis.
- 3) To assess the benefit of VEGF pathway inhibition in the neoadjuvant treatment setting.

Overlap: NONE

Title: FACT as a Novel Marker and Target and Target of Aggressive Breast Cancer (CCR13264604)

Time Commitments: 0.60 calendar (PI-Gurova)

Supporting Agency: Susan G Komen National Foundation

Grants Officer: Nancy Martin; Phone: (972) 701-2085; fax: (972) 701-2121; nmartin@komen.org

Performance Period: 04/01/13-03/31/16

Level of Funding: \$253,427

Brief description of project's goals: Our hypothesis is that we can measure FACT in BC to predict if a patient will develop metastatic disease and, therefore, requires additional treatment. We also propose that drug(s) which reduce or eliminate FACT would be effective in these types of patients and safe since FACT is not present in an adult organism (it is present only in so called "stem cells" of some organs and cells of embryos).

List of specific aims:

- 1) To confirm association of FACT expression with aggressive metastatic breast cancer.

- 2) To understand how FACT provides tumor cells with more aggressive features.
- 3) To define if artificial decrease in FACT activity or level would result in reduced tumor growth and loss of metastatic behavior of tumor cells in mouse models of BC.

Overlap: NONE

Title: Multicenter phase 2 trial of nintedanib (BIBF 1120) in patients with carcinoid tumors (NCCN NINT 0016)

Time Commitments: 0.30 calendar (PI-Iyer)

Supporting Agency: NCCN

Grants Officer: Diane Paul, NCCN, 275 Commerce Drive, Suite 300, Fort Washington, PA, 19034, (215) 690-0232, paul@nccn.org

Performance Period: 11/25/14-11/24/18

Level of Funding: \$480,611

Brief description of project's goals: We hypothesize that since fibroblast proliferation is a major driver of disease and clinical progression in non-pancreatic carcinoids that is shown in animal models to be driven by serotonin (5-HT) through FGFR2 (Hisaoka et al) that targeting angiogenesis and FGFR merits study in this tumor.

List of specific aims:

1. Targeting angiogenesis and the fibroblast growth factor pathway with nintedanib will result in clinical benefit measured as progression free survival (PFS) and radiographic response or stable disease in patients with progressing carcinoid tumors within the 12 months prior to study entry.
2. This therapy will be safe and tolerable in combination with octreotide. This will also lead to improved QOL measured using the Norfolk QOL-NET tool.
3. Using a previously developed PK/PD model, using decrease in circulating cytokines such as soluble vascular endothelial growth factor receptor (sVEGFR), VEGF, fibroblast growth factor (FGF) and FGFR by ELISA before and serially q12 week with steady state PK draw to correlate with drug level following start of therapy compared to pre therapy will correlate with clinical benefit and maybe a valuable biomarker.
4. Tumor expression of fibroblast growth factor receptor isoforms FGFR IIIb and IIIc, Ki-67 and microvessel density measured by immunohistochemistry (IHC) will correlate with clinical benefit.

Overlap: NONE

Title: Cancer Center Support Grant – Biostatistical Core (RPCI subcontract) (5 P30 CA16056-36)

Time Commitment: 1.20 calendar (PI-Johnson/Brady)

Supporting Agency: NIH

Funding Agency's Procuring Contracting/Grants Officer: Wooddill, Joseph; Phone: (301) 496-8635

Performance Period: 05/01/97-04/30/19

Level of Funding: \$2,392,072

Project Goals: The major goal of this project is to provide biostatistical support for cancer clinical trials.

Specific Aims:

1. **Facilities:** Physical facilities dedicated to the conduct of cancer focused research, and to the center's shared resources, administration, and research dissemination efforts, should be appropriate and adequate to the task.
2. **Organizational Capabilities:** The center should be organized to take maximum advantage of institutional capabilities in cancer research, and to appropriately plan and evaluate center strategies and activities.
3. **Transdisciplinary Collaboration and Coordination:** Substantial coordination, interaction, and collaboration among center members from a variety of disciplines should enhance and add value to the productivity and quality of research in the center.
4. **Cancer Focus:** A defined scientific focus on cancer research should be clear from the center members' grants and contracts, and from the structure and objectives of its formal Programs.

5. Institutional Commitment: The center should be recognized as a formal organizational component with sufficient space, positions, and discretionary resources to insure its stability and fulfill the center's objectives.
6. Center Director: The director should be a highly qualified scientist and administrator with leadership experience and institutional authority appropriate to manage the center and further its scientific mission and objectives.

Overlap: None

Title: Prosaposin: a novel biomarker of prostate cancer progression in African Americans (5 R01 MD005824-05)

Time Commitments: 0.30 calendar (PI- Koochekpour)

Supporting Agency: NIH

Grants Officer: Nishadi Rajapakse; chandima.rajapakse@nih.gov

Performance Period: 07/01/12-06/30/15

Level of Funding: \$391,670

Brief description of project's goals: We hypothesized that PSAP contributes to PCa progression and has the characteristics of a novel biomarker discriminating the aggressive tumors from non-aggressive ones in African American patients.

List of specific aims:

- 1) Define the clinical significance of serum-PSAP as a marker of PCa progression or aggressiveness in African Americans.
- 2) Determine the association between tissue expression of PSAP and clinical and histopathological predictors or prognosticators of PCa progression or aggressiveness in African Americans.
- 3) Determine the association between PSAP and invasive and metastatic phenotypes in PSAP-overexpressed or -silenced African American PCa cells.

Overlap: NONE

Title: Metabotropic Glutamate Receptor 1 in African American Prostate Cancer (R21 CA183892-01)

Time Commitments: 0.30 calendar (PI-Koochekpour)

Supporting Agency: NIH

Grants Officer: Elizabeth Woodhouse; elizabeth.woodhouse@nih.gov; Phone: (240) 276-6205

Performance Period: 04/01/14-03/31/16

Level of Funding: \$184,658

Brief description of project's goals: Data generated from this exploratory study will define biological and/or clinicohistopathological significance or relevance of GRM1 expression in African American prostate cancer and may prove useful in discriminating clinically or biologically aggressive tumors from indolent (non-aggressive) tumors and minimizing prostate cancer disparity in African Americans.

List of specific aims:

- 1) Determine the association between tissue expression of GRM1 and clinicohistopathological predictors or prognosticators of prostate cancer progression or aggressiveness in African Americans.
- 2) Determine the association between GRM1 expression levels and invasive and metastatic phenotypes in African American prostate cancer cells.

Overlap: NONE

Title: Therapeutic Efficacy of Riluzole in Prostate Cancer (1 R21 CA181152-01A1)

Time Commitments: 0.30 calendar (PI-Koochekpour)

Supporting Agency: NIH

Grants Officer: Michael Alley; michael.alley@nih.gov; Phone: (301) 624-1246

Performance Period: 07/01/14-06/31/16

Level of Funding: \$221,589

Brief description of project's goals: This is a translational prostate cancer research aimed at determining the effect of glutamate receptor antagonist on tumor growth and metastatic ability, fatty acid synthase (FAS)

expression and apoptotic markers in prostate cancer. This study will investigate the underlying mechanisms by which glutamate receptor antagonist down regulates FAS expression in prostate cancer cell lines.

List of specific aims:

- 1) Determine the therapeutic efficacy of Riluzole in in-vivo tumorigenesis assays.
- 2) Determine the association between Riluzole treatment and androgen receptor expression in tumor xenografts and prostate cancer cell lines.

Overlap: NONE

Title: Image-Guided Photodynamic Therapy of Lung Cancer (1R21 CA176154-01A1)

Time Commitments: 2.50 calendar (PI-Nwogu)

Supporting Agency: NCI

Grants Officer: Anil Wali; anil.wali@nih.gov; Phone: (240) 276-6183

Performance Period: 08/01/14-07/31/16

Level of Funding: \$229,028

Brief description of project's goals: Lung cancer is the most frequent cause of cancer death in both men and women in the United States and will account for about 27% of all estimated cancer deaths in 2013. This project seeks to study the ability of a novel compound to simultaneously image lung cancer using positron emission tomography (PET) and ablate it with photodynamic therapy (PDT).

List of specific aims:

- 1) Compare the effectiveness of 124I-PS2 and 18F-Fluorodeoxyglucose (FDG) in imaging of lung tumors and lymph node metastases using an orthotopic lung cancer model in SCID mice.
- 2) Compare the effectiveness of photodynamic therapy using PS2 and Porfimer Sodium (Photofrin®) in human NSCLC xenografts established subcutaneously in SCID mice.

Overlap: NONE

Title: MiRNA Profiling to Predict Recurrence after Resection of Early Lung Cancer (5 K23 CA149076-03)

Time Commitments: 0.30 calendar (PI-Yendamuri)

Supporting Agency: NIH

Grants Officer: Susan Lim; Phone: (240) 276-5630

Performance Period: 09/07/11-08/31/17

Level of Funding: \$186,729

Brief description of project's goals: MicroRNAs are short (18-25 nt) RNAs that are thought to control the expression of at least one third of the human genome. In this project, we propose refining and prospectively validating a microRNA signature to predict recurrence after resection of early lung cancer. We also aim to identify serum microRNAs that can serve as biomarkers of the lung cancer disease state.

List of specific aims:

- 1) To conduct a retrospective validation study of a microRNA signature in 80 stage I NSCLC patients.
- 2) To conduct a clinical trial to prospectively validate the microRNA signature for prognosis.
- 3) Development of a blood based microRNA profile for detection of lung cancer recurrence.

Overlap: NONE

Title: Deplete Prostate Cancer of DHEAS to Prevent Castration-Recurrent Prostate Cancer (5 R21 CA191895-02)

Time Commitments: 0.60 calendar (PI-Wu)

Supporting Agency: NIH

Grants Officer: Neeraja Sathyamoorthy; neeraja.sathyamoorthy@nih.gov; Phone: (240) 276-6220

Performance Period: 09/01/15-08/30/16

Level of Funding: \$229,028

Brief description of project's goals: The proposed studies are required to validate the concept that DHEAS is an important source of precursors for intracrine production of T and DHT by prostate cancer cells. In addition, the transporters, STS, and STS regulators provide potential targets for therapy.

List of specific aims:

- 1) Characterize the expression of STS and potential STS regulators in CRPC.
- 2) Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth.
- 3) Identify DHEAS uptake mechanisms.

Overlap: NONE

PENDING

Title: Treating prostate cancer by combined targeting of androgen and CCL2 signaling

Time Commitments: 0.60 calendar (PI-Krolewski)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 04/01/16-03/31/21

Level of Funding: \$2,968,877

Brief description of project's goals: Our preliminary and our (and other's) published data shows one limitation in the treatment of CRPC is therapy-induced metastasis. This paradoxical effect occurs via the tumor microenvironment and is mediated by CCL2, which in turn is regulated by paracrine TNF and/or intracellular Stat3 signaling. We propose to investigate and test two approaches to counter this type of resistance to anti-androgen therapy for CRPC.

List of specific aims:

- 1) Mechanistically dissect the role of TNF signaling in CCL2 mediated metastasis, in response to anti-androgens.
- 2) Mechanistically dissect the role of Stat3 signaling in CCL2 mediated metastasis, in response to anti-androgens.
- 3) Test the efficacy of combining enzalutamide with therapies directed at CCL2, versus ASC-J9 alone, to reduce metastases in fully blinded, rigorous, adequately powered pre-clinical trials employing mouse models of prostate cancer.

Overlap: NONE

Title: Role of Mitochondria Dysfunction in Prostate Cancer Health Disparities

Time Commitments: 0.30 calendar (PI-Chandra)

Supporting Agency: NCI

Grants Officer: Pending

Performance Period: 04/01/16-03/31/21

Level of Funding: \$2,122,500

Brief description of project's goals: The goal of this proposal is to understand underlying mechanisms of racial disparities in prostate cancer between African American and Caucasian American men and how the findings could help in designing/prediction of new anticancer agents for PCa therapy in American men.

List of specific aims:

- 1) Define mitochondrial priming via BH3 profiling for cytochrome c release in PCa cells.
- 2) Define the apoptosome formation and function in PCa cells.
- 3) Identify mtDNA mutations and impact of apoptosome dysfunction in PCa health disparity.

Overlap: NONE

Title: soluble PD-L1 as a surrogate biomarker for cancer and cancer therapy

Time Commitments: 0.00 calendar (PI-Ebos)

Supporting Agency: Damon Runyon Cancer Research Foundation

Grants Officer: Pending

Performance Period: 01/01/16-12/31/18

Level of Funding: \$300,000

Brief description of project's goals: The hypothesis driving these studies is that circulating sPD-L1 may correlate with membrane bound PD-L1

levels and, in turn, be exploited as a surrogate marker for metastatic disease, PD-1 pathway inhibition, and resistance to current antiangiogenic therapies.

List of specific aims:

1. Molecular Characterization of sPD-L1 and its role in tumor growth.
2. To examine sPD-L1 level changes following PD-1 pathway inhibition.
3. sPD-L1 as a surrogate biomarker for antiangiogenic drug resistance.

Overlap: NONE

Title: R-loops, chromosome translocations, and prostate cancer progression

Time Commitments: 0.36 calendar (PI-Goodrich)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 04/01/16-03/31/21

Level of Funding: \$2,756,505

Brief description of project's goals: We conclude that high levels of pThoc1 are required by aggressive prostate cancer cells to support gene expression and to prevent accumulation of genotoxic R-loops. The experiments proposed in this application will extend preliminary data to test whether R-loops influence oncogenic chromosome translocations and prostate cancer progression.

List of specific aims:

1. Identify the genome wide location of R-loops and test whether these locations overlap potential chromosome translocation breakpoints. We propose to characterize the genome wide locations of R-loops, DSBs, and translocations in the LNCaP prostate cancer cell line using next generation sequencing based approaches. The primary goal is to test whether R-loops and DSBs overlap at translocation breakpoints.
2. Test whether manipulating R-loops affects the generation of oncogenic chromosome translocations in vitro. Spontaneous generation of TMPRSS2-associated chromosome translocations can be detected during in vitro culture of the LNCaP prostate cancer cell line. We propose to test whether manipulating R-loop levels affects the frequency of TMPRSS2-associated chromosome translocations. We will identify mechanisms leading from R-loops to chromosome translocations using gene silencing approaches.
3. Determine whether R-loops influence cancer progression in vivo. We propose to genetically manipulate R-loop levels in prostate cancer mouse models to test whether R-loops influence spontaneous cancer progression in vivo.
4. Assess whether R-loop formation is detectable in human prostate cancer specimens. R-loop, THO complex proteins, DNA damage, senataxin, and RNaseH levels will be characterized in prostate cancer patient specimens to test whether they are correlated with each other and cancer aggressiveness.

Overlap: NONE

Title: Preventing Progression of EGFR Mutant Lung Cancers with Vitamin D Compounds

Time Commitments: 0.30 calendar (PI-Hershberger)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 07/01/15-06/30/20

Level of Funding: \$2,191,760

Brief description of project's goals: Our studies implicate dietary vitamin D3 (VD3) supplementation as a safe, effective, and affordable approach to prevent TGF β -mediated erlotinib failure and disease progression in patients diagnosed with EGFR mt NSCLC.

List of specific aims:

1. To establish the significance of genomic antagonism between VDR and SMAD signaling in *EGFR* mt NSCLC cells.
2. To test the prediction that dietary VD3 prevents progression of *EGFR* mt NSCLC by supporting tumor production of 1,25(OH)2D3 and epithelial differentiation.

3. To establish the integrity of the vitamin D signaling axis and its association with disease progression in *EGFR* mt NSCLC patients treated with erlotinib

Overlap: NONE

Title: Development of Primary Cell Line Resources for Prostate Cancer Disparity Research

Time Commitments: 0.30 calendar (PI-Koochekpour)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 12/01/15-11/30/20

Level of Funding: \$2,193,750

Brief description of project's goals: In this proposal, we plan to develop, maintain, characterize, and assemble a comprehensive primary AA-PCa cell line resource, which includes up to 12 PCa cell lines and matched stromal cells, custom-designed TMA blocks, and gDNA/RNAs extracted from matched PCa and stromal cells and tissues. This AA-PCa cell-based model system and resources will be shared with investigators and more specifically, within PCa racial disparity research communities in the U.S., African-Caribbean Cancer Consortium, and others.

List of specific aims:

1. In Aim 1, taking advantage of a novel methodological approach and institutional infrastructural resources and without using any chemical or biological transforming or immortalizing agents, we will establish and maintain a set of AA-PCa cell lines and tumor-derived stromal cells, perform chromosome karyotyping, and confirm African ancestry.
2. Aim 2 will focus on molecular characterization of the established AA-PCa and stromal cells using epithelial, stromal, and prostatic cytodifferentiation markers. Additional characterization will include growth and colony formation assays, whole genome expression analysis, and integrated whole-exome and transcriptome sequencing and profiling. Frozen stocks of the AA-PCa and stromal cells and their respective genomic (g)DNAs and RNAs will be prepared at passage 5 to 75. Tissue microarray (TMA) paraffin blocks will be also constructed from the AA-PCa cells and tissues.
3. Aim 3 will focus on determination of genetic alterations in AR and expression profiling of AR-target genes and AR-regulated microRNAs in the AA-PCa cells. Wild or mutant-AR will be examined for their transcriptional activity, transactivation potential, and growth response to androgens, anti-androgens, and non-androgenic steroids.
4. Aim 4 will examine growth, invasive, and metastatic potential of the AA-PCa cells lines in vivo. As in vitro model systems and resources, matched AA-PCa cell lines and stromal cells, gDNA/RNA, and TMAs could be used for basic and translational research aimed at reducing or minimizing PCa disparities.

Overlap: NONE

Title: Cortisol induces prostate cancer growth and invasiveness in African Americans

Time Commitments: 0.60 calendar (PI-Koochekpour)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 04/01/16-03/31/21

Level of Funding: \$2,193,750

Brief description of project's goals: With respect to inter-ethnic differences for the association between SGK1 expression and clinical or pathological predictors or prognosticators of prostate cancer (PCa), no knowledge is available. Based on our data, we hypothesize that stress hormone induces PCa growth and invasiveness in African Americans.

List of specific aims:

1. Determine the effect of chronic stress on SGK1 expression and tumor growth and metastasis in AA-PCa cells.
2. Determine the association between alterations in SGK1 expression levels and invasive and metastatic phenotypes in AA-PCa cells in vivo.

3. Determine the association between SGK1 tissue expression and clinicohistopathological predictors or prognosticators of PCa progression or aggressiveness and outcome in AAs versus CAs.

Overlap: NONE

Title: Role of PIM kinases in vitamin D signaling in renal cancer

Time Commitments: 0.60 calendar (PI-Luo)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 12/01/15-11/30/20

Level of Funding: \$2,193,361

Brief description of project's goals: The goal of this study is to elucidate the role of serine-threonine kinase PIM in vitamin D signaling and to develop new therapeutic strategies targeting PIM kinases in combination with vitamin D for renal cell carcinoma.

List of specific aims:

1. To determine whether PIM affects vitamin D signaling and the underlying mechanisms by examining:
 - a) The effect of PIM on genome-wide VDR binding profile, VDR transcriptional activity and the expression profile of 1,25D3-responsive genes;
 - b) The potential interaction between PIM and VDR and the effect of PIM on VDR phosphorylation; and
 - c) The effect of PIM on VDR cytoplasmic and nuclear localization and the association of VDR with VDR-interacting protein complex.
2. To determine the effect of PIM on vitamin D metabolism and the anti-tumor action of the combination of 1,25D3 and PIM kinase inhibitor JP_11646 by examining:
 - a) The effect of PIM on CYP24A1 enzyme activity, 1,25D3-mediated anti-proliferative and vitamin D catabolism; and
 - b) The *in vivo* efficacy of PIM kinase inhibitor JP_11646 in combination with 1,25D3 in human RCC mouse xenograft models.
3. To determine whether PIM expression is associated with the alteration of vitamin D signaling in existing RCC TMA by examining:
 - a) The expression of PIM, vitamin D metabolism enzymes and target genes in human RCC tissues; and
 - b) The association of PIM expression, tumor tissue 25-hydroxycholecalciferol (25D3) and 1,25D3 levels, and VDR target genes with tumor progression and overall survival in patients with RCC. The results obtained from studies proposed above will provide important information for the understanding

Overlap: NONE

Title: Image-Guided Photodynamic Therapy with Multifunctional Nanoparticles

Time Commitments: 0.60 calendar (PI-Pandey)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 04/01/16-03/31/20

Level of Funding: \$2,939,325

Brief description of project's goals: The overall goal of this project is to develop an all-in-one targeting, detecting and therapeutic agent based on appropriately functionalized nanoparticle (NP) platforms.

List of specific aims:

1. To evaluate *in vitro* the target-specificity of near 800 nm PS and the corresponding cRGD/iRGD conjugates to gliomas. Tumor-specificity of the PS will be achieved from the tumor-avid nature of the PS and from the corresponding PS-cRGD or PS-iRGD peptide recognized by the $\alpha_v\beta_3$ integrin known for its over-expression in human gliomas.
2. To assess the efficacy of OVV-CXCR4-A-Fc and OVV-EGFP viruses after systemic (i.v.) delivery alone or in combination with NIR-PDT against syngeneic and xenograft models of GBM. We will

analyze inhibition of tumor growth, virus dissemination within the tumor tissue, and neurotoxicity after each treatment.

3. To dissect the mechanisms responsible for the enhanced efficacy of the NIR-PDT/OVV-CXCR4-A-Fc treatment against GBM.

Overlap: NONE

Title: Targeting Stress Pathways for Improved Tumor Immunity Following Cancer Therapies

Time Commitments: 0.24 calendar (PI-Repasky)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 04/01/16-03/31/21

Level of Funding: \$2,193,750

Brief description of project's goals: The overall goal of this proposal is to examine the impact of β -AR signaling on the balance between pro-tumorigenic immunosuppression and anti-tumor immune effector function, and on tumor cell survival pathways.

List of specific aims:

1. To test the hypothesis that adrenergic signaling limits the anti-tumor efficacy of checkpoint inhibitors alone and in combination with radiation therapy.
2. To test the hypothesis that adrenergic signaling regulates immune activity in the tumor microenvironment and draining lymph nodes.
3. To test the hypothesis that adrenergic signaling alters the phenotype of bulk and/or CSCs in ways that will promote tumor resistance to immune cell killing or radiation therapy.

Overlap: NONE

Title: Leveraging the methionine salvage pathway as a novel therapy for prostate cancer

Time Commitments: 0.30 calendar (PI-Smiraglia)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 04/01/16-03/31/21

Level of Funding: \$2,335,917

Brief description of project's goals: The overall objective of the proposed research is to determine the therapeutic potential of polyamine catabolism upregulation and methionine salvage pathway inhibition, either alone or in combination, to enhance the extent and/or duration of clinical benefit of ADT.

List of specific aims:

1. We propose to test MTAP inhibition and pharmacological enhancement of SSAT activity in a panel of androgen sensitive and androgen independent CaP cell lines to test for synergy both with and without androgen.
2. We propose to identify individual and combined therapeutic approaches to treat androgen independent CWR22Rv1 and LNCaP C4-2 s.q. xenografts grown in castrate nude mice.
3. We propose to test if these approaches can prevent recurrence during ADT using the LuCaP and CWR22 xenograft models of castration recurrence.

Overlap: NONE

Title: ADT-Induced Therapeutic Window for Treatment of Organ-Localized Prostate Cancer

Time Commitments: 0.24calendar (PI-Smith)

Supporting Agency: NIH

Grants Officer: Pending

Performance Period: 04/01/16-03/31/21

Level of Funding: \$2,826,287

Brief description of project's goals: This project proposes to develop an alternative minimally-invasive therapeutic modalities management paradigm with no/acceptable collateral morbidity for patients with organ-

localized, high-risk CaP, but that potentially could be extended to patients with low-risk CaP that are not comfortable with “watchful waiting” or patients with clinically significant benign prostate enlargement.

List of specific aims:

1. Correlate prostate cancer-dependent variations in the “opening and closing” of the “therapeutic window” induced by T-D (ADT) and the reparative re-endothelialization” after the “therapeutic window, with changes in the transcriptome of ECs and CaP cells.
2. Identify classes of chemotherapeutic agents that demonstrate prostate-specific cytotoxicity to human CaP cells when introduced during the “therapeutic window”.
3. Characterize the nature of the EC-mediated permeability barrier that regenerates after T-D, or after treatment with an anti-angiogenic agent, to close the “therapeutic window”.

Overlap: NONE

Title: Mitochondria dysfunction in prostate cancer health disparities

Time Commitments: 0.30 calendar (PI-Yadav)

Supporting Agency: NCI

Grants Officer: Pending

Performance Period: 12/01/15-11/30/20

Level of Funding: \$2,193,750

Brief description of project’s goals: The goal of this proposal is to understand the underlying mechanisms of racial disparities in prostate cancer (PCa) between African American (AA) and Caucasian American (CA) men and how the findings could help in designing/prediction of new anticancer agents for PCa therapy in American men.

List of Specific Aims:

1. Define mitochondrial priming via BH3 profiling for cytochrome c release in PCa cells.
2. Define the apoptosome formation and function in PCa cells.
3. Identify mtDNA mutations and impact of apoptosome dysfunction in PCa health disparity.

COMPLETED

Title: Significance of a Novel Germline AR Mutation in Black Men with Prostate Cancer (7 R21 CA149137)

Time Commitments: 0.30 calendar (PI- Koochekpour)

Supporting Agency: NIH/NCI

Grants Officer: Suresh Mohla; mohlas@mail.nih.gov; Phone: (301) 435-1878; Fax (301) 480-0864

Performance Period: 12/01/11-08/31/13

Level of Funding: \$134,374

Brief description of project’s goals: Race and family history are the widely accepted risk factors for prostate cancer (PCa). The incidence, mortality rate and stage-specific aggressiveness of PCa in African American (AA) men are significantly higher than in Caucasians. Our discovery of a novel germline AR mutation in a high-risk AA family might have predictive significance that would provide us a more effective diagnostic approach in AAs with familial PCa.

List of specific aims:

- 1) We will determine the relative incidence of the AR-A1675T mutation and its attribution to familial PCa in African Americans. The analysis for the AR-A1675T mutation will be extended to 400 members of 40 high-risk African American and Caucasian families, each containing at least three men diagnosed with PCa and to a pool of 400 unrelated individuals from both ethnic cohorts who have not been diagnosed with PCa. Mutations will be identified using allele-specific oligonucleotide hybridization, restriction enzyme-based genotyping, and PCRbased automated sequencing.
- 2) We will determine the biological characteristics of the AR-A1675T mutation in AR-negative PCa cells or immortalized African American-derived prostate epithelial cells. The effect of the AR-A1675T mutation on growth, DNA-binding affinity, transcriptional activity and transactivation response to androgens, steroid hormones, and non-steroidal anti-androgens will be determined using methods routine in the laboratory.

Overlap: NONE

Title: Laser-Capture Microdissection-Assisted Identification of Epithelial microRNA Expression Signatures for Prognosis of Stage I NSCLC (W81XWH-10-1-0614)

Time Commitments: 0.60 calendar (PI-Yendamuri)

Supporting Agency: USAMRAA

Grants Officer: Elayne Seiler; elayne.k.seiler.civ@mail.mil

Performance Period: 09/07/10-09/06/13

Level of Funding: \$552,601

Brief description of project's goals: We intend to develop, for the first time, a prognostic signature for early non-small cell lung cancer based on miRNA profiling of the epithelial and stromal components separately. These components will be separated using laser capture microdissection. We hypothesize that the measurement of the expression of miRNAs in these clearly defined components of tumors will improve the signal to noise ratio of such measurements.

List of specific aims:

- 1) To identify epithelium- and stroma- specific miRNA signatures for the prediction of recurrence after resection of early stage NSCLC.
- 2) To develop a miRNA in situ hybridization assay with performance characteristics comparable to a miRNA microarray for prediction of recurrence after resection of early stage NSCLC using epithelium-specific data obtained with Specific Aim 1.
- 3) To study the role of two miRNAs predicting prognosis in regulation of the phenotype of lung cancer.

Overlap: NONE

Title: MiRNA Expression Profiling to Predict Recurrence after Resection of Stage I NSCLC (HHS000109SF)

Time Commitments: 0.60 calendar (PI-Yendamuri)

Supporting Agency: S.A.S. Foundation for Cancer Research

Grants Officer: Mary Ann J. Hrywnak, Phone: (607) 624-5843

Performance Period: 12/18/09-12/31/12

Level of Funding: \$50,000

Brief description of project's goals: The study will attempt to utilize the stability of miRNAs in blood to identify serum miRNAs to serve as biomarkers of the lung cancer state. This will be done by comparing blood miRNA profiles of lung cancer patients before and after resection and comparing it the of the serum profile obtained after recurrence.

List of specific aims:

- 1) To refine our microRNA signatures for lung cancer recurrence using an external retrospective cohort.
- 2) To prospectively validate the final microRNA signature developed from specific aim 1.
- 3) To develop serum microRNA biomarkers of the lung cancer disease state by comparing the microRNA profiles of pre- and post-resection serum samples.

Overlap: NONE

Title: Is Immune Response against Breast Cancer Inhibited by Lack of Available Metabolic Energy?

Time Commitments: 0.30 calendar (PI-Repasky)

Supporting Agency: NYSDOH

Grants Officer: Kenneth Peek; Phone: (518) 474-7002; kep03@health.state.ny.us

Performance Period: 09/01/13-08/31/15

Level of Funding: \$150,000

Brief description of project's goals: The goal of this proposal is to test this provocative hypothesis in a murine breast cancer (4T1) model.

List of specific aims:

- 1) Will test the impact of supporting body temperature on primary and metastatic tumor growth, on the function of critical immune effector cells and cytokines and on therapeutic efficacy of radiation and immunotherapy.
- 2) Tests whether there are changes in energy-related signaling pathways and the tumor microenvironment.

- 3) Will test the exciting possibility that energy conservation may even help to control tumors in mice given high fat diets, in which tumor progression is known to be accelerated.

Overlap: NONE

OTHER SUPPORT

Pop, Elena

Current

Title: Prostate Cancer: Transition to Androgen Independence, Core B: ImmunoAnalysis and Tumor Management (French – PI)

Time Commitments: 9.0 calendar months

Supporting Agency: National Cancer Institute P01-CA77739

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mark Kramer, Administrative Director, UNC Lineberger Comprehensive Cancer Center Campus Box 7295, 102 Mason Farm Road, Chapel Hill, NC 27599-7295, Phone: (919) 966-0233, Fax: (919) 966-3015, mkramer@med.unc.edu

Performance Period: 04/01/2005-03/31/2017 (NCE)

Level of Funding: \$903,203

Brief description of project's goals: Renewal of a core that serves two primary functions to the three projects: Core B is involved in all aspects of clinical specimen and prostate cancer xenograft management and Core B processes and stores the invaluable prostate biopsy specimens obtained from men with advanced prostate cancer prior to and at regular intervals after beginning androgen deprivation therapy.

List of specific aims:

Aim 1. Core B will provide high quality, reliable and cost-effective technical services to participants of the Program Project for immunohistochemistry and quantitative image analysis.

Aim 2. Core B will manage the research specimens critical to the conduct of the research proposed by the Program Project.

Aim 3. Core B will provide expertise in biostatistics and genitourinary pathology.

Overlap: None

Title: Genetic variations in SLCO transporter genes contributing to racial disparity in aggressiveness of prostate cancer (Wu)

Time Commitments: 0.60 calendar months

Supporting Agency: CDMRP (W81XWH-14-1-0453)

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Mirlene Desir, Grant Specialist, Assistance Branch 4, MCMR-AAA-AD, USAMRAA, 820 Chandler Street, Fort Detrick, MD 21702, phone: 301-619-7733, fax: 301-619-9656, mirlene.desir@civ@mail.mil

Performance Period: 09/15/2014-09/14/2017

Level of funding: \$764,100

Brief description of project's goals: The objective seeks to address how transporter-regulated androgen availability to cancer cells may contribute to the difference in prostate cancer aggressiveness between African American (AA) and European American (EA) men. The hypothesis is: Genetic variations in solute carrier family of organic anion transporting peptides (SLCO) androgen transporter genes and expression profiles of SLCO androgen transporters in prostate tissue are associated with aggressiveness of prostate cancer, and contribute to racial differences in prostate cancer aggressiveness.

List of specific aims:

Aim 1. Examine genetic variations in SLCO transporters genes and to investigate the associations of the variations with prostate cancer aggressiveness in AA and EA.

Aim 2. Examine *in situ* expression profiles of SLCO transporters in prostate tissue and to investigate the associations of the expression profiles with prostate cancer aggressiveness in AA and EA.

Aim 3. Characterize the functions of candidate SLCO transporters in androgen uptake and to evaluate the biological effects on AR signaling in human prostate cancer cell lines.

Overlap: None

Title: Deprive prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu)

Time Commitments: 1.80 calendar months

Supporting Agency: NIH/NCI 1R21CA191895-01

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-276-5157, viviana.knowles@nih.gov

Performance Period: 09/17/2014-08/31/2016 **Level of Funding:** \$466,950

Brief description of project's goals: This research seeks to address the racial differences in prostate cancer aggressiveness from a biological perspective.

List of specific aims:

Aim 1. Characterize the expression of STS and potential STS regulators in CRPC

Aim 2. Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth

Aim 3. Identify DHEAS uptake mechanisms

Overlap: None

Pending

Title: Leveraging the North Carolina-Louisiana Prostate Cancer Project (PCaP) Data and Biorepository with Oncological Outcome (Mohler – PI)

Time Commitments: 1.20 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 04/01/2016 – 03/31/2019

Level of funding: \$767,096

Brief description of project's goals: Project is the largest population-based study of newly diagnosed prostate cancer ever completed. Project sought to partition the reasons for increased prostate cancer mortality in African compared to Caucasian Americans among racial differences in 3 categories: 1) interaction between the prostate cancer patient and the American healthcare system; 2) biology of the host (diet, genetics and environment); and 3) biology of the tumor. The value of the Project will grow by connecting 10-year outcome to this invaluable data and biorepository to provide further insight into the reasons for the racial disparity in prostate cancer mortality.

List of specific aims:

1. Contact research subjects and their physicians to update treatments received, repeat the quality of life assessments performed at baseline and follow-up, and query them on the financial impact of cancer
2. Provide mortality and cause of death information for research subjects at least annually
3. Provide the administrative structure and manage the liquid and tissue biorepositories necessary to facilitate additional grants and manuscripts

Overlap: None

Title: Development of an inhibitor for 3alpha-oxidoreductases, the enzymes common to the last step in DHT production by the primary and secondary backdoor pathways (Mohler - PI)

Time Commitments: 0.60 calendar months (Years 2 and 3)

Supporting Agency: DoD Idea Development Award W81XWH-15-PCRP-IDA

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 04/01/2016-03/31/2019

Level of funding: \$591,672

Brief description of project's goals: Abiraterone expense (\$6000/mo) and its relative lack of efficacy (extends survival 4 mo) impede development of pharmaceuticals that target intracrine androgen metabolism. An actively coordinated attack upon intracrine androgen metabolism may lower DHT better, improve efficacy of primary or secondary ADT, and reduce the need for new treatments. We have recognized that the 5 enzymes critical for the terminal steps in T and DHT production via 2 backdoor pathways share a catalytic site, which we proved important by mutating then deleting it. Potential inhibitors will be tested in preclinical models to deliver

a 3 α -oxidoreductase inhibitor for clinical trial. The new drug used alone or in combination with abiraterone should reduce the death rate from CaP, the 3rd PCRP theme.

List of specific aims:

1. Identify a candidate inhibitor against the catalytic site shared by the five 3 α -oxidoreductases
2. Synthesize and test re-designed candidate inhibitors and conduct PK/PD and toxicity studies to produce a lead compound inhibitor of the five 3 α -oxidoreductases
3. Determine whether the inhibitor of the five 3 α -oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth

Overlap: None

Title: Understanding the Relative Contributions of and Critical Enzymes for the 3 Pathways for Intracrine Metabolism (Mohler - PI)

Time Commitments: 0.90 calendar months

Supporting Agency: DoD Idea Development Award

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Not assigned yet

Performance Period: 04/01/2016-03/31/2019

Level of funding: \$660,315

Brief description of project's goals:

Better understanding of intracrine androgen metabolism during ADT will identify new targets to reduce T and DHT production.

List of specific aims:

1. Determine the relative use of the 3 pathways for intracrine androgen metabolism in vitro, in vivo and in clinical specimens.
2. Identify the principal androgen metabolism enzymes (ie. 3 α -oxidoreductases) responsible for primary backdoor DHT synthesis from androstenediol.
3. Determine the requirements for SRD5A1-3 in the frontdoor pathway of DHT synthesis from T and its precursors and of SRD5A1 and HSD17B3 in the secondary backdoor pathway of DHT synthesis from androstenedione.

Overlap: None

Previous

Title: Role of Androgen Axis in the Racial Differences of Prostate Cancer Mortality (PI – Mohler)

Time Commitments: 1.20 calendar months

Supporting Agency: Department of Defense

Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Ayi Ayayi, Contract Specialist

U.S. Army Medical Research Acquisition Activity, MCMR-AAA-E, 820 Chandler Street, Fort Detrick, MD 21702-5014

Phone: (301) 619-4018 ayi.ayayi@us.army.mil

Performance Period: 09/30/2010-09/29/2014

Level of Funding: \$817,716 NCE

Brief description of project's goals: The study will provide complete analysis of the androgen receptor and androgen-regulated genes and relate it to prostate cancer in a large sample of men to test whether racial differences in prostate cancer mortality may be due, in part, to racial differences in androgenic stimulation of prostate cancer. Greater androgenic stimulation of the African American prostate could explain the two-fold difference in prostate cancer risk and increased aggressiveness of clinical disease in African compares to Caucasian Americans.

List of specific aims:

The central hypothesis of the proposed research is that racial differences in the tissue androgen axis contribute to CaP aggressiveness. Greater androgenic stimulation of the African-American prostate may contribute to

increased incidence of, and higher mortality rates from, CaP. Quantifying the androgen axis in a large number of men with CaP will determine whether or not CaP receives race-dependent differences in androgenic stimulation that may affect CaP outcome. In order to test the central hypothesis, we propose three specific aims:

1. Determine whether AR protein levels differ in CaP of African and Caucasian Americans
2. Determine whether AR protein levels correlate with proteins expressed from androgen-regulated genes (PSA, Nkx3.1, hK2, *TRMPRSS2/ERG* fusions)
3. Determine whether AR protein levels correlate with CaP growth rate, extent and tumor differentiation

Overlap: None