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TITLE: Genetic Variations in SLCO Transporter Genes Contributing to Racial Disparity in Aggressiveness of Prostate Cancer

PRINCIPAL INVESTIGATOR: Yue Wu, PhD

CONTRACTING ORGANIZATION: Health Research, Inc., Roswell Park Division
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Health Research, Inc., Roswell Park Division
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The proposed studies are expected to (1) identify genetic variations in the genes of androgen transporters that are associated with the racial differences in prostate cancer aggressiveness; (2) identify key androgen transporters of which the expression and/or the alteration of expression in cancer relative to benign prostate tissue are associated with racial differences in prostate cancer aggressiveness. Progress in the reporting period includes: 1) Completion of genotyping for all 11 SLCO members using PCaP DNA samples; 2) Finish data processing and preliminary data analyses for genotyping, and identified SNPs that may be associated with prostate cancer characteristics; 3) Continued RNAScope analysis of SLCO transporter in prostate cancer tissue sections and discover unique cell type-specific expression of a SLCO transporter; 4) Further delineation of androgen uptake mechanism on molecular levels.

15. SUBJECT TERMS

Nione provided

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1. INTRODUCTION

Compared to European American (EA) men, African American (AA) men suffer higher incidence of, and greater mortality rate from prostate cancer. Results of multiple studies indicate that prostate cancer in AA men may progress faster than prostate cancer in EA men, and thereby becomes more aggressive. This study is focused specifically on identification of genetic/biological culprits that cause more aggressive types of prostate cancer in AA men. In particular, the proposed studies are focused on the question of how differences in transporter-mediated androgen uptake may contribute to the more aggressive type of prostate cancer in AA versus EA. The proposed studies are expected to (1) identify genetic variations in the genes of androgen transporters that are associated with the racial differences in prostate cancer aggressiveness; (2) identify key androgen transporters of which the expression and/or the alteration of expression in cancer relative to benign prostate tissue are associated with racial differences in prostate cancer aggressiveness.

2. KEYWORDS

Prostate cancer, health disparity, androgen, transporter, genetic variation.

3. ACCOMPLISHMENTS

What were the major goals of the project?

Specific Aim 1 (months 1-18): DNA samples as well as relevant clinical and epidemiological data will be requested for 2258 cases (1130 AA and 1128 EA) from the North Carolina-Louisiana Prostate Cancer Project (PCaP). A total of 952 SNPs along with a panel of 50 ancestry informative markers (AIMs) will be used for genotyping of 11 SLCO transporters. Genotyping will be performed via the GoldenGate Assay by Illumina Bead Station System in the Genomics Core Facility at Roswell Park Cancer Institute (RPCI).

Specific Aim 2 (months 7-30) is to examine in situ expression profiles of SLCO transporters in prostate tissue and investigate associations of the expression profiles with prostate cancer aggressiveness in AA and EA. Expression of SLCO transporters at transcriptional levels will be examined first in tissue microarrays (TMAs) constructed from prostate cancer and distant benign tissues of 92 AA and 92 EA patients from the Pathology Resource Network (PRN) at Roswell Park Cancer Institute (RPCI). The predominantly expressed SLCO transporters in AA or EA, and the transporters with expression significantly altered in cancer relative to benign tissues, will be selected and expression at protein levels will be examined using immunohistochemistry (IHC) on TMAs requested from the PCaP. The data on expression will be combined with the data on disease characteristics from the PCaP to investigate associations of the expression profiles with prostate cancer aggressiveness in AA and EA.

Specific Aim 3 (months 25-36) will characterize functions of candidate SLCO transporters in androgen uptake and evaluate the biological effects on AR signaling in human prostate cancer cell lines. Based on the findings from Aim 1 and Aim 2, candidate SLCO transporters will include the transporters that are predominant in either AA or EA, show significantly altered expression between tumor and benign tissue, or harbor genetic variants that are significantly associated with prostate cancer aggressiveness. Relevant cell models will be constructed using over-expression or siRNA knock-down for functional analysis.

What was accomplished under these goals?

Aim 1. Genotyping has been completed successfully. By the end of the last finding period, the proposed tasks for Aim 1 have been accomplished by 80% before the starting of the EWOF. The work for Aim 1 has been summarized and communicated with the PCaP team as the initiation to prepare a manuscript. The PCaP team reviewed our summary of results and provided very good suggestions. As a result, an abstract was reviewed and approved by the PCaP Committee for submission to the American Urological Association (AUA) 2018 Annual Meeting in Fan Francisco. This abstract was accepted for presentation in a moderated poster section (Abstract # MP21-16), and the abstract was published (J. Urol., Vol. 199, No. 4S, Supplement, Saturday, May 19, 2018, e269).

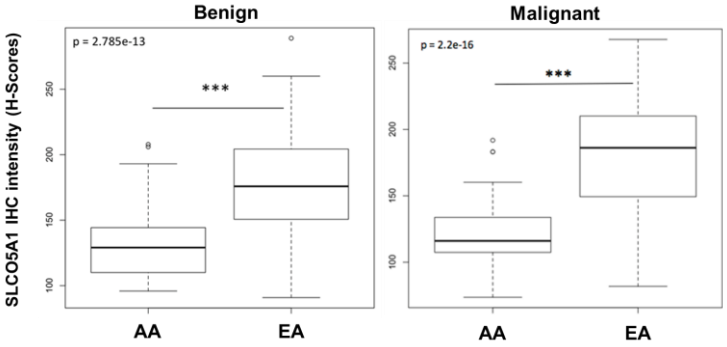

Figure 1. Expression of SLCO5A1 in benign and malignant prostate tissue specimens is higher in EA than AA.

Aim 2. The association study in Aim 1 was critical to decision making on the selection of candidate SLCO transporters for expression level determination on the 92 AA/92 EA TMA from RPCI and the TMA from PCaP. Therefore, decisions were made only after the finalization of the association study. Based on findings in Aim 1, SLCO5A1 and SLCO2A1 were the candidates for Aim 2. We obtained the 92 AA/92 EA TMA sections and finished SLCO5A1 IHC staining and visual scoring. Preliminary analysis of the visual scores has been finished. A comparison of SLCO5A1 between AA and EA revealed that SLCO5A1 expression was higher in EA than in AA, in both benign and malignant prostate tissue specimens (Figure 1). Expression of SLCO5A1 was higher in more aggressive prostate cancer (Figure 2). Another intriguing finding was that the expression of SLCO5A1 increased over the age (Figure 3A-C). The expression was higher in patients who were older at ages of diagnosis (Figure 3A), ages on dates of surgery (Figure 3B), and in general older-aged groups (Figure 3C).

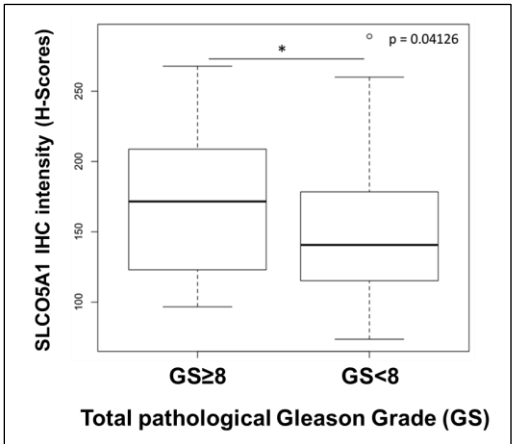

Figure 2. SLCO5A1 expression was higher in

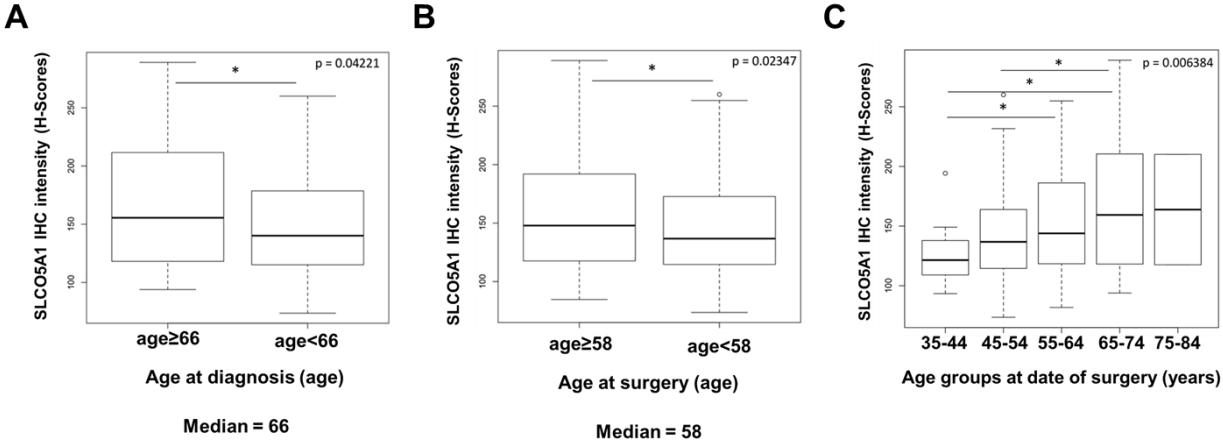

Figure 3. Expression of SLCO5A1 increased over the age.

SLCO2A1 antibodies are commercially available; however, the repeated delays and back orders occurred from multiple resources. Therefore, a custom SLCO2A1 antibody was ordered from Pacific Immunology, an antibody service company. The custom SLCO2A1 antibody was raised against SLCO2A1 epitope and was purified using the same epitope. The antibody was made available to us in the EWOF period. Conditions for IHC staining of SLCO2A1 using the antibody was optimized, and SLCO2A1 was stained on the 92AA/92EA TMA (Figure 4). Slight expression of SLCO2A1 was observed in epithelial cells and cancer cells. SLCO2A1protein was predominantly in the stromal cells, which was in agreement with previous findings using RNAScope for detection of expression at mRNA levels. Due to the unique sub-tissue localization of SLCO2A1, the scoring of IHC positive cells needs to be conducted differently for cancer cells and endothelial cells. The scoring of the SLCO2A1 IHC is still ongoing, and is expected to be completed in 2-3 months.

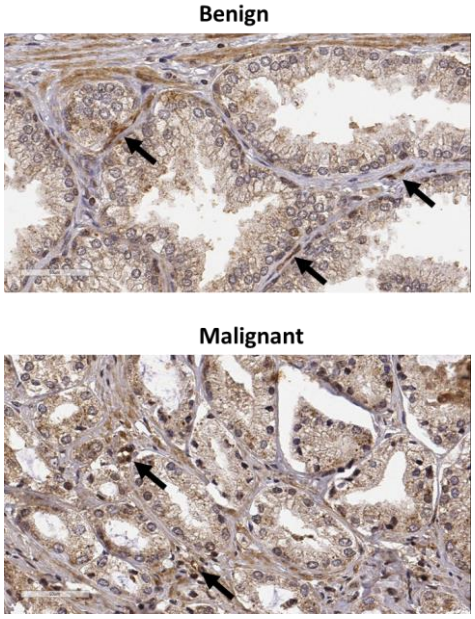

Figure 4. SLCO2A1 IHC staining in benign and malignant prostate tissue. Arrows indicated SLCO2A1 positive cells.

Based on the results, we requested TMA sections from PCaP study for validating findings of SLCO5A1 IHC staining. The TMAs are in house and ready to stain. We request additional 3-5 months for staining and visual/automatic scoring. Since 1-2 months are needed for summarize the final data and for preparing and revising a manuscript for peer-reviewed publication, the total time needed for completion of this study will be 6 months at most.

Aim 3. Characterize functions of candidate SLCO transporters in androgen uptake and evaluate the biological effects on AR signaling in human prostate cancer cell lines. We have summarized our key findings in the Aim and developed a manuscript, which was submitted to Molecular and Cellular Endocrinology. After revision during EWOF, the manuscript has been accepted and is now published.

SLCO5A1 is selected for further testing the role in cell growth or AR signaling due to its predominant expression in benign and malignant prostate tissue. Stable clones that over-express the transporters are the optimal choice for these tasks. This is because transiently transfected cells are not suitable for long-term experiments such as growth, and inconsistent transfection efficiency may cause inconsistent results that are further worsened by double transfection involved in luciferase-based promoter-reporter assay for AR activity. This effort was initiated during EWOF based on the findings from Aim 1 and 2. We already obtained the over-expressing plasmids for the SLCO transporters used puromycin resistance as a selection marker and also established puromycin sensitivities of human prostate cancer cell lines used for the proposed work. We are in the process of establishing stable clones for the biological studies.

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

One of the biggest gain for Dr. Wu is to witness the evolving progression of the analysis of the genotyping data, led by Dr. Tang and Dr. Zhu. As a laboratory-based basic science researcher by training, Dr. Wu would not have had the opportunity to learn from the two co-investigators on the sophisticated statistical models that

were applied to the different data and different study questions. This was the first time for Dr. Wu to interact closely with a molecular epidemiologists and a biostatistician on large-scale data analysis. The experience is invaluable. A lesson that Dr. Wu learned from the interaction with Dr. Mohler and Dr. Azabdaftari was on the complicated issues revolving around the use of TMA, and how important the expertise of a pathologist is to the research using TMA. Dr. Azabdaftari would inspect each core to verify its pathological characteristic, and to exclude unreliable staining caused by misclassifications of the core, or by missing cancer cells in a cancer core. This process refreshed Dr. Wu's previously over simplified view that only relies on the clinical pathological reports for core classification.

How were the results disseminated to communities of interest?

1. Findings in Aim 3 on an active and selective steroid transport system has been published.

   Parsons TK, Pratt RN, Tang L, and Wu Y: An active and selective molecular mechanism mediating the uptake of sex steroids by prostate cancer cells. Mol Cell Endocrinol. 2018 Dec 5; 477:121-131.

2. Findings in Aim 1 have been presented in a moderated poster section (Abstract # MP21-16) in the American Urological Association (AUA) 2018 Annual Meeting in San Francisco.

   Tang L, Zhu Q, Bensen J, Taylor J, Smith G, Pop E, Azabdaftari G, Mohler J, and Wu Y: Associations of genetic polymorphisms in SLCO transporters with clinical aggressiveness of prostate cancer in the North Carolina-Louisiana prostate cancer project. J. Urol., Vol. 199, No. 4S, Supplement, Saturday, May 19, 2018, e269.

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

1) The genotyping and data analyses have been completed during the funding period. We are in the process of preparing a manuscript for a peer-reviewed publication, which may need 3- 6 months for submission and revision pending the review.

2) Complete IHC staining and scoring of SLCO5A1 and SLCO2A1 in the RPCI 92 AA/92 AA TMA, and SLCO5A1 IHC staining and scoring of TMA sections from the PCaP study. This work will need additional 3-5 months for re-optimizing staining procedure and for re-purposing the developed scoring algorisms for the new TMA sections.

3) Genotyping results indicated that SNPs that were associated with prostate cancer characteristics in EA and AA were intronic. This finding complicated the functional study, because evaluation of the functional significance of these genetic variants is fundamentally different from the evaluation of exonic genetic variants. The intronic genetic variants may affect gene splicing, which results in different isoforms of the same gene. During EWOF, we worked closely with our bioinformatics core for functional annotation. None of the identified SNPs was in linkage disequilibrium (LD) with any potential functional SNPs or coding SNPs, nor was nearby splicing boundaries. The finding calls the further search for true signals in the genes. Therefore, a study proposal focusing on SLCO2A1 and SLCO5A1 by targeted gene sequencing is submitted to the DOD, with the goal of revealing the true signals and examining its role in treatment outcome and disease survival.

Meanwhile, we focus on the biological functions of wild-type SLCO5A1. We are in the process of generating stable clones of multiple prostate cancer cell lines for biological studies. Overall, 6 months are needed to complete this part of the study and summarize for manuscript submission and revision.

4. IMPACT

What was the impact on the development of the principle discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGEs/PROBLEMS

Changes in approach and reasons for change.

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them.

A couple of unexpected events delayed the projects. One challenge to the completion of the project was the sudden departure of Dr. Elena Pop (co-I). Dr. Pop was in charge of all the IHC and TMA studies. Her sudden departure caused significant delay of the project. We had to train lab staff to take over IHC staining, and to examine and mark the stained sections in order to collaborate with Dr. Gissou Azabdaftari (pathologist, co-I) to verify cancer cells labeled for scoring. Visual scoring was also delayed because of relocated manpower for the increased work load to compensate and regain the proper expertise. To better address the situation and to obtain more objective data on IHC staining, we collaborated with Roswell Park PNSR to develop algorisms tailored for automatic scoring of SLCO2A1 and SLCO5A1 staining.

Changes that had a significant impact on expenditures.

Nothing to report.

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

Nothing to report.

6. PRODUCTS

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Yue Wu, Ph.D. (2 cal months) – PD/PI

Li Tang, Ph.D. (1 cal month) – Co PD/PI

Elena Pop (1 cal month) – Research Associate

Todd Parsons (1 cal month) – Technician

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes. Updated active other supports of Dr. Yue Wu (PI), Dr. James Mohler (co-I), Dr. Gissou Azabdaftari (co-I), Dr. Qianqian Zhu (co-I), Dr. Elena Pop (co-I) and Dr. John Wilton (co-I) are presented as follows. Nothing to report for Dr. Li Tang (co-PI).

Changes in active support

Wu, Y.

Active to Completed
Title: Deprive prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu)
Time Commitments: 2.40 calendar months
Supporting Agency: NIH/NCI (1R21CA191895-01)
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, Grants Management Specialist, 9609 Medical Center Drive, West Tower, Bethesda, MD 20892, phone: 240-765-5157, viviana.knowles@nih.gov
Performance Period: 09/17/2014-02/28/2018
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:
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

Title: Targeting Usage of Adrenal Androgens for Complete Androgen Deprivation Therapy (Wu)
Time Commitments: 0.60 calendar months
Supporting Agency: New York State Department of Health- DOH01-C30314GG-3450000
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: 12/01/2015-10/31/2017
Level of Funding: $130,430

Brief description of project's goals: The goal of this research is to discover if targeting the highly diverse ability of using different adrenal androgens for CaP cell production of T or DHT is critical to achieving complete ADT.
List of specific aims:
Aim 1. Determine the dynamic changes in the capability of CaP cells to use adrenal androgens for T/DHT production in response to castration
Aim 2. Identify candidate chemicals to block the usage of adrenal androgens to activate AR, and to test the feasibility of blocking the use of adrenal androgens to prevent tumor growth
Aim 3. Evaluate whether co-existing CaP cells that differ in androgen uptake or metabolic abilities synergistically use adrenal androgens for T or DHT production
Overlap: None

Nothing to report for Tang, L.

Mohler, J.L.

Active to Completed
Title: The Thoc1 Ribonucleoprotein as a Novel Biomarker for Prostate Cancer Treatment Assignment (Goodrich - PI)
Time Commitments: 0.30 calendar months
Supporting Agency: USAMRAA PC130746P1
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Lance Nowell, lance.l.nowell.civ@mail.mil, Phone: 301-619-1357
Performance Period: 09/15/2014-09/14/2018
Level of funding: $379,593 (partnering PI)
Brief description of project's goals: The central objective of this application is to test the utility of a novel molecular biomarker, *THOC1*, which may improve assignment of patients to appropriate therapy.
List of specific aims:
1. Characterize pThoc1 levels in independent cohorts of human prostate cancer radical prostatectomy specimens.
2. Characterize pThoc1 levels in a cohort of human prostate cancer patients on active surveillance.
3. Test whether pThoc1 or autoantibodies against pThoc1 can be detected in the blood of prostate cancer patients.

Overlap: None

Title: Cholesterol Lowering Intervention for Prostate Cancer Active Surveillance/Jr. Faculty Award to Alliance NCORP Research Base – Pilot Project (Kim/Mohler - PIs)
Time Commitments: 0.60 calendar months
Supporting Agency: Cedars/NCI
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 – 07/31/2018
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

Title: Deprive 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: 09/17/2014-02/28/2018
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

Azabdaftari, G.

Pending to Active
Title: Decoding the molecular and cellular landscape of the metastatic small renal tumor
Time Commitments: 0.6 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: 11/03/2017-11/02/2018
Level of Funding: $50,000
Brief description of project's goals: To characterize the landscape of molecular and immunologic alterations defining metastatic small renal tumor patients. Identification of alterations differentiating metastatic and nonmetastatic small renal tumors would have immediate opportunity for investigator-initiated clinical trials. Biomarkers for small renal tumor metastasis discovered in this study could be validated prospectively in clinical trials among these new patients and those returning active surveillance patients. Targeted therapies could be offered to those patients with small renal tumors to allow patients to avoid resection; or to supplement resection in the neoadjuvant or adjuvant setting. This proposal will generate several resources available to the RPCI research community. Secondly, the whole genome sequencing and RNA-seq experiments proposed will provide valuable genome-wide mutational and expressional data, which can be queried with future markers of interest.
List of specific aims:
1. Survey the DNA mutational landscape and identify those mutations specific to metastatic small renal tumors relative to nonmetatatic small renal tumors.
2. Identify gene expression alterations at the RNA and protein levels specific to metastatic small renal tumors relative to nonmetastatic small renal tumors.

3. Identify immune cell profiles in patient blood specific to metastatic small renal tumors relative to nonmetastatic small renal tumors.

Overlap: None

Active to Completed

Title: Prognostic role of circulating tumor cells in clear cell carcinoma patients (PI- Kauffman)
Time Commitments: 1.20 calendar months (no salary requested)
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: 09/24/2015- 06/30/2018 (NCE)
Level of Funding: $99,916
Brief description of project's goals: The goal of this project is to determine if circulating tumor cell (CTC) detection in the perioperative setting of clinically localized clear cell RCC (ccRCC) provides a reliable surrogate for metastatic relapse.
List of specific aims:
Aim 1. Validate a multimarker imaging flow-cytometry detection platform for CTC in ccRCC patients
Aim 2. Determine the prognostic value of perioperative CTC for predicting adverse tumor pathology or metastatic relapse in localized ccRCC patients considering nephrectomy
Overlap: None

Title: Deprive prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu – PI)
Time Commitments: 0.60 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: 09/17/2014-02/28/2018
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:
4. Characterize the expression of STS and potential STS regulators in CRPC
5. Evaluate the value of targeting DHEAS usage by prostate cancer cells to prevent post-castration tumor growth
6. Identify DHEAS uptake mechanisms

Overlap: None

Title: The Thoc1 Ribonucleoprotein as a Novel Biomarker for Prostate Cancer Treatment Assignment (Goodrich - PI)
Time Commitments: 0.24 calendar months
Supporting Agency: USAMRAA PC130746P1
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Lance Nowell, lance.l.nowell.civ@mail.mil, Phone: 301-619-1357
Performance Period: 09/15/2014-09/14/2018
Level of funding: $379,593 (partnering PI)

Brief description of project's goals: The central objective of this application is to test the utility of a novel molecular biomarker, *THOC1*, which may improve assignment of patients to appropriate therapy.
List of specific aims:
4. Characterize pThoc1 levels in independent cohorts of human prostate cancer radical prostatectomy specimens.
5. Characterize pThoc1 levels in a cohort of human prostate cancer patients on active surveillance.
6. Test whether pThoc1 or autoantibodies against pThoc1 can be detected in the blood of prostate cancer patients.

Overlap: None

Zhu, Q.

Pending to Active
Title: GMPS-GMPR Axis Melanoma Progression and Therapy (1 R01 CA224434-01A1)
Time Commitments: 0.36 calendar (PI-Nikiforov)
Supporting Agency: NIH
Grants Officer: Neeraja Sathyamoorthy, ns61r@nih.gov
Performance Period: 5/15/18-4/30/23
Level of Funding: $249,000
Brief Description of Project's Goals: The goal of this project will be to test the hypothesis that recruitment of GMEs and physiological modulation of their activity regulate GTP loading on RAC1 and therefore can be exploited therapeutically.
Specific Aims:
1. To characterize the mechanism of RAC1 activation via GME recruitment.
2. To functionally characterize novel EphR-GMPR-RAC1-invasion axis.
3. To establish moderate depletion of GTP as effective anti-melanoma strategy.

Overlap: NONE

Title: Regulation of lactosaminyl glycan biosynthesis in hematopoietic cells (5 P01 HL107146-07)
Time Commitments: 0.60 calendar (PI- Lau)
Supporting Agency: NIH
Grants Officer: Rita Sarkar, sarkarr@nhlbi.nih.gov
Performance Period: 07/01/15-07/31/18
Level of Funding: $618,700
Brief Description of Project's Goals: Goal is to elucidate hematopoietic stem and progenitor cell surface glycan structures and identify the key glycan-modifying enzymatic activities occupying their biosynthetic checkpoints.
List of Specific Aims:
1. To characterize the glycosylation changes in an in vitro system of HSPC differentiation using a multitiered approach.
2. To characterize lactosaminyl glycosylation changes in early HSPC development.
3. To assess the contribution of the extrinsic pathway in HSPC glycan formation.
4. To identify the roles of glycans in HSPC biology and hematopoietic repopulation.
5. To develop systems biology-based modeling framework to describe HSPC glycan biosynthesis.

Overlap: NONE

Title: Genetic underpinnings of ethnic disparities in bone toxicities between Hispanic and non-Hispanic children treated for acute Lymphoblastic leukemia (1 R03 CA223730-01)

Time Commitments: 0.60 calendar (PI-Yao)
Supporting Agency: NCI
Grants Officer: Kelly Filipski, Kelly.filipski@nih.gov
Performance Period: 12/01/17-11/30/19
Level of Funding: $50,000
Brief Description of Project's Goals: This R03 grant seeks to perform a novel pharmacogenomic study based on 05-001 and its successor trial DFCI 11-001 to identify genetic underpinnings of ethnic disparities in bone toxicities. We plan to first test global genetic ancestry with bone toxicities, followed by a bivariate genome-wide association study (GWAS) to jointly analyze osteonecrosis and fracture as two related traits.
List of Specific Aims:
1. Determine whether the composition of genetic ancestry in Hispanic children is an underlying cause for the ethnic disparities in therapy-related bone toxicities, namely osteonecrosis and fracture, in children with ALL in the DFCI 05-001 and 11-001 trials.
2. a). Investigate single variants and polygenic risk scores from previous GWAS of bone-related phenotypes with bone toxicities in children treated for ALL.
b). Identify genetic loci associated with therapy-related bone toxicities by performing bivariate GWAS analyses with directional alignment and meta-analysis in the DFCI 05-001 and 11-001 trials
c). Investigate whether genetic variants and polygenic scores significant in 2a and 2b explain disparities in bone toxicities between Hispanic and non-Hispanic children with ALL.
Overlap: NONE

Active to Completed
Title: NCOR2/SMRT Drives the Onco-Epigenome of Aggressive Prostate Cancer (W81XWH-14-0608)
Time Commitments: 0.30 calendar (PI-Smiraglia)
Supporting Agency: DOD
Grants Officer: Peggi Lesnow, Margaret.a.lesnow.civ@mail.mil
Performance Period: 07/29/14-09/28/18
Level of Funding: $120,216
Brief Description of Project's Goals: The objective of the current study is to define the evolution of the NCOR2/SMRT cistrome and its association with CpG region methylation in ADT-RCaP. We hypothesize that acute environmental and therapeutic stresses in CaP selects for cells in which the NCOR2/SMRT complex drives repressive histone modifications that trigger CpG methylation, at select loci, to generate stable and heritable silencing of subsets of genes.
List of Specific Aims:
1. To reveal the impact of the NCOR2/SMRT cistrome in ADT-RCaP.
2. To measure in vivo the interplay between NCOR2/SMRT and CpG methylation in the emergence of ADT-RCaP.
3. To correlate NCOR2/SMRT expression and CpG methylation with miRNA serum expression levels and clinical outcomes.
Overlap: NONE

Title: Exome Array Analysis of Reproductive Aging and Breast Cancer in African Americans (R03 CA192205)
Time Commitments: 0.72 calendar (PI-Yao)
Supporting Agency: NCI
Grants Officer: Damali Martin; damali,martin@nih.gov; Office: (240) 276-6746
Performance Period:07/01/15-06/30/18
Level of Funding: $175,500

Brief Description of Project's Goals: By leveraging the existing exome array genotype data from a total of 8,350 AA breast cancer cases and healthy controls in the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium, we propose to identify rare and low-frequency coding variants associated with reproductive aging.
List of Specific Aims:
1. To evaluate rare and low-frequency coding variants in the regions identified by previous genome-wide association studies for age at menarche and age at natural menopause.
2. To identify rare and low-frequency coding variants across the genome associated with reproductive aging phenotypes.
Overlap: NONE

Title: Genomic markers predicting tumor response to cytotoxic chemotherapy (R01 CA202354)
Time Commitments: 0.00 calendar (PI-Demant)
Supporting Agency: NIH
Grants Officer: Sudhir B. Kondapaka; sudhir.kondapaka@nih.gov; (240) 276-5365
Performance Period: 12/01/15-11/30/17
Level of Funding: $50,000
Brief Description of Project's Goals: We propose to develop a novel way to determine in advance whether individual cancer patients will benefit from a therapy with a certain anti-cancer drug, or whether they should receive another drug, because their tumor is not likely to be suppressed by the drug considered as the first. The specific advantage of the method we propose is that it is based not only on the current knowledge of pharmacology of anti-cancer drugs, but can discover also reliable predictive factors that are based on novel mechanisms.
List of Specific Aims:
1. Determination of linkage of Tctr genes polymorphic between CcS-2 and CcS-9 will be performed by standard linkage methods in F2 hybrids using a whole polymorphic genome coverage.
2. The linkages detected in the previous experiment will be confirmed in subsequent backcrosses that will serve as starting points for production of congenic lines, each carrying a single Tctr gene, so the functions of each such gene could be investigated separately. However, these congenic lines cannot be completed within the time frame of this project.
Overlap: NONE

Pop, E.

Active to Completed
Title: A Small-Molecule Inhibitor of the Terminal Steps for Intracrine Androgen Synthesis in Advanced Prostate Cancer (Mohler)
Time Commitments: 1.0 calendar months (year 2)
Supporting Agency: NCI-1R21CA205108-01
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Nicole Franklin, Grants Management Specialist, National Cancer Institute, 9609 Medical Center Drive, West Tower, Room 2W556, Bethesda, MD 20892 (regular mail), Phone: 240-276-5210, Email: nicole.franklin@nih.gov
Performance Period: 04/10/2016-04/09/2018
Level of Funding: $ 416,398
Brief description of project's goals: This research seeks to explore if a small-molecule inhibitor of the catalytic site shared by the five 3α−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 3α−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 3α−oxidoreductases
3. Determine whether the inhibitor of the 3α−oxidoreductases decreases tissue T and DHT levels and impairs CRPC growth

Overlap: None

Title: Genetic and Epigenetic Prostate Cancer-Related Alterations in Early-Onset disease in African American Men (Woloszynska-Read)
Time Commitments: 0.60 calendar months
Supporting Agency: NYSDOH
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: 11/01/2015-10/31/2017
Level of Funding: $ 130,430
Brief description of project's goals: Determine the relative frequency of genetic lesions found in prostate cancer in tumors from African Americans and European Americans. Determine the relative frequency of genetic lesions found in prostate cancer in tumors from African Americans and European Americans.
List of specific aims:
1. To determine the relative frequency of common genetic lesions found in prostate cancer in tumors from African Americans and European Americans.
2. To determine potentially relevant transcriptomic and methylomic differences in tumors from African Americans and European Americans.

Overlap: None

Title: Understanding the Relative Contributions of and Critical Enzymes for the 3 Pathways for Intracrine Mebolism (Mohler)
Time Commitments: 0.90 calendar months
Supporting Agency: DoD Idea Development Award
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Tom Winter Grants Specialist, Assistance Agreements Branch 4 U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702 Cell 240-357-1590 Office 301-619-2665 Thomas.s.winter2.civ@mail.mil
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. 3a-oxidoreductases) responsible for primary backdoor DHT synthesis from androstanediol.
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 androstanedione.

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: 09/17/2014-02/28/2018
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

Wilton, J. H.
Active to Completed
Title: Deprive prostate cancer of DHEAS to prevent castration-recurrent prostate cancer (Wu)
Time Commitments: 0.60 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: 09/17/2014-02/28/2018
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:
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

What other organizations were involved as partners?

Nothing to report.