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

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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) approval for IRB protocols that are needed for using DNA samples from the North Carolina-Louisiana Prostate Cancer Project (PCaP), and for IHC and in situ RNA hybridization staining of a TMA set and tissue sections from Roswell Park Cancer Institute (RPCI) and PCaP, respectively; 2) completion of DNA samples processing by PCaP for genotyping at RPCI; 3) selection and ordering of probes of genetic variants for genotyping; 4) optimization of the conditions for IHC and in situ RNA hybridization; and 5) optimization of conditions for in vitro functional characterization of candidate transporters for androgen uptake.

15. SUBJECT TERMS

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

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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?

Major goal of the project for the reporting period (Year 1, months 1-18) is to carry out the research proposed in Specific Aim 1: 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). Three Subtasks were proposed:

Subtask 1 (months 1-3): Obtain approval for IRB protocol and request clinical data and blood DNA samples from the PCaP.

Subtask 2 (months 4-10): Genotype 11 SLCO transporters.

Subtask 3 (months 11-14): Analyze data and to determine the association of genetic variants with prostate cancer aggressiveness.

Tasks were also proposed in the reporting period (Year 1) to fulfill partly Specific Aim 2 which 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 (months 7-30). Subtasks proposed in the reporting period (Year 1) included:

Subtask 1(Months 7-10): Obtain approval for IRB protocol and request clinical data and TMAs from RPCI and PCaP.

Subtask 2 (Months 11-18): Characterize gene expression profiles of SLCO transporters at mRNA levels on TMAs from RPCI using quantitative in situ RNA hybridization technology RNAScope.

What was accomplished under these goals?

Table 1. DNA Samples from PCaP.

Category of DNA samples	Number of participants
Peripheral blood	2015
Mouth wash (buccal cells)	124
Immortalized lymphocytes	35
All DNA samples	2174

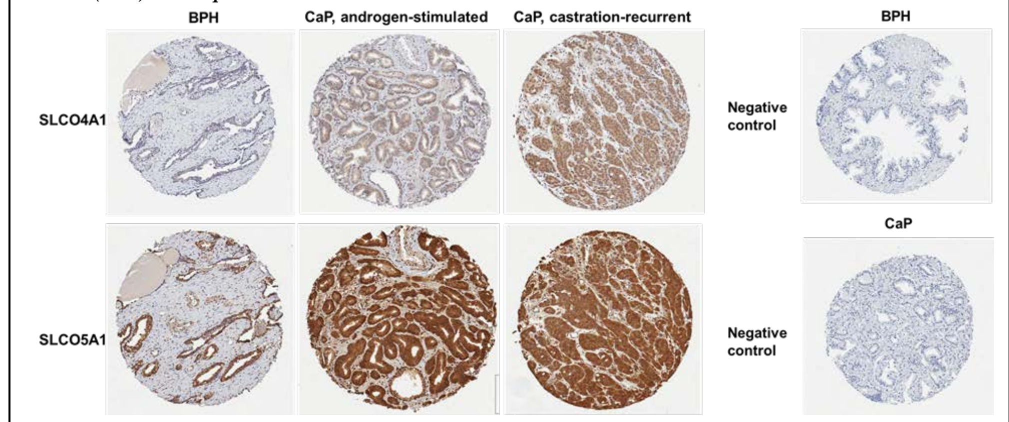
Aim 1. First, Dr. Wu and Dr. Tang successfully obtained the approval for the IRB protocols that are needed for using the PCaP DNA samples (Aim 1, Subtask 1), and for IHC and RNAScope staining of the 92 AA/92 EA TMA from RPCI and the tissue sections from PCaP (Aim 2, Subtask 1). Second, with collaboration with the Cancer Genetics Shared Facility, multiple technical issues such as the concentrations and the total amount and forms of the DNA samples were successfully resolved with PCaP so that the DNA samples are processed for genotyping at RPCI (Aim 1, Subtasks 2&3). Up to date, 20 of the 24 96-well plates of all DNA samples are ready at the University of North Carolina BioSpecimen Processing Facility, the PCaP facility that processes and distribute biospecimens to investigators. The rest of the DNA sample will be ready for shipment to RPCI by October 12th. DNA samples from a total of 2174 PCaP participants are in the process of genotyping. The breakdown of these DNA samples is presented in Table 1. Third, Dr. Tang (co-PI) led the discussions with Dr. Sean Glenn, the director RPCI Cancer Genetics Shared Facility on finalizing the selection of probes of genetic variants for genotyping and the template formation for sample plating (Aim 1, Subtasks 2&3). The list of numbers of SNPs selected for genotyping is presented in Table 2. All reagents, probes have been ordered and are ready to use at the Shared Facility.

Table 2. Numbers of SNPs selected for genotyping.

Genes	Number of SNPs
Ancestry informative markers	128
SLCO6A1	41
SLCO1A2	99
SLCO1B1	102
SLCO1B3	51
SLCO1C1	63
SLCO2A1	79
SLCO2B1	63
SLCO3A1	300
SLCO4A1	40
SLCO4C1	44
SLCO5A1	134
Total number of SNPs	1144

Aim 2. Dr. Wu led a pilot study to optimize the conditions for IHC and RNAScope staining using a TMA set (Aim 2, Subtask 2). The conditions have been optimized and are ready for use once the genotyping data are obtained to guide to selection of candidate SLCO genes. For IHC optimization, rabbit anti-human SLCO4A1 and SLCO5A1 antibodies were used, and a non-immuned rabbit IgG was used at the same titration as primary IgG for negative control (Figure 1). SLCO4A1 and SLCO5A1 were stained positively in benign prostate hyperplasia (BPH), androgen-stimulated prostate cancer (CaP), and castration-recurrent CaP, whereas, the negative IgG control did not stain prostate and CaP tissue specimens. The intensity of IHC staining slightly increased in CaP specimens compared to the benign tissue specimens. Additionally, the intensity of SLCO5A1 was stronger than that of SLCO4A1, although it is noted that the stoichiometry of interaction between individual antibodies and their respective antigens may also contribute to the different intensities. Nevertheless, the IHC intensities agreed with our preliminary qRT-PCR data on the mRNA levels of the two SLCO transporters. RNAScope is a new technology for *in situ* RNA hybridization that is able to

Figure 1. IHC of SLCO4A1 and SLCO5A1 in human benign prostate hyperplasia (BPH) and prostate cancer (CaP) tissue specimens.



quantitate expression of genes of interest at mRNA levels. A probe for SLCO2B1 was designed for condition optimization for RNAScope analyses using TMA sections (Figure 2). According to our preliminary data, expression of SLCO2B1at mRNA level is among the lowest ones of all 11 SLCO transporters. The rationale for using the SLCO2B1 probe for condition optimization lies in the nature of RNAScope methodology, which most likely will produce reliable data once a condition is optimized for one probe of a gene of a family, as long as the probes are applied on the similar tissue specimens, in this case, TMA sections. Therefore, if the condition is able to detect signals of a gene that is expressed at very low levels, the condition will be suitable for detecting genes that are expressed at higher levels. The expression of SLCO2B1 in general was modest in androgen-stimulated CaP tissue, along with benign tissues of other organs. The expression was highest in spleen, and decreased in the order of ovary, liver, kidney, lung, and testis. The low expression levels of SLCO2B1 in prostate and CaP were in agreement with our preliminary data that showed SLCO2B1 was among the lowest expressed SLCO members in total tissue RNA samples. At present it is not clear whether the expression level is increased in castration-recurrent CaP, or is different between African American and European American prostate or CaP. An intriguing finding is that the expression of SLCO2B1 in CaP is sporadic, and preliminary observation suggested that the expression resided in architectures resembling the vasculatures. To further validate the optimized RNAScope condition, a probe specific for the prostate-specific antigen (PSA) was used to detect PSA expression in sections of the same TMA sets (Figure 3). As anticipated, the condition applied to the PSA probe. PSA mRNA was detected in epithelial cells in the BPH tissue, and in cancer/epithelial cells in the CaP tissue. Specificity of the method was confirmed by negative staining using a control probe that is specific to a bacterial gene.

Figure 2. RNAScope condition optimization using SLCO2B1-specific probe. Arrows indicated positive stained cells.

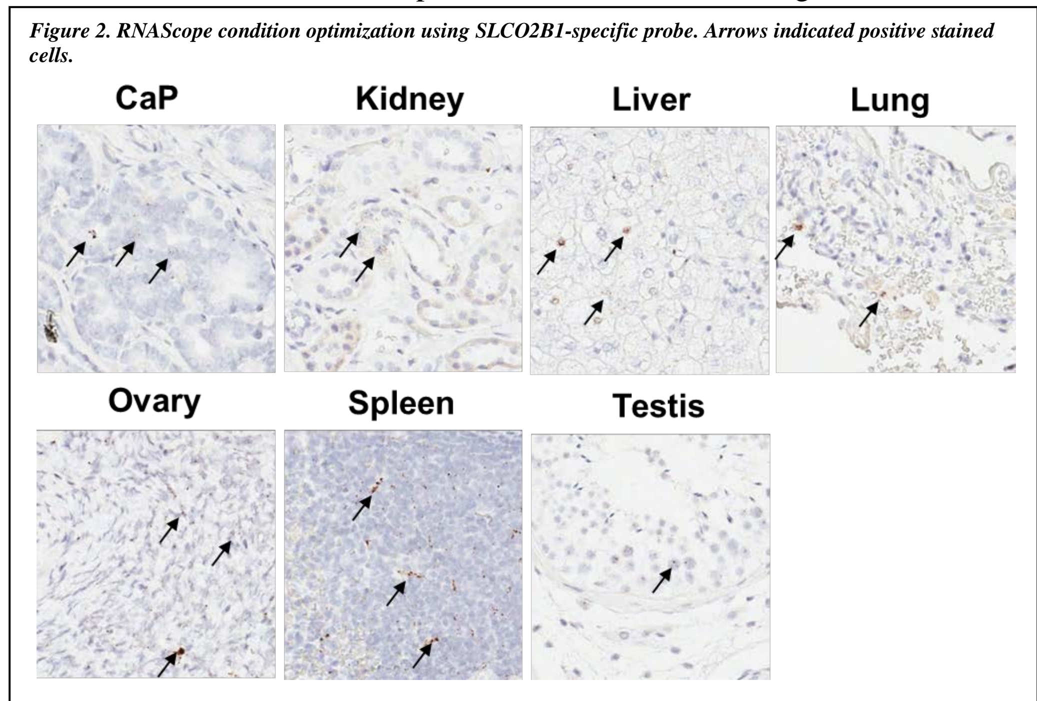
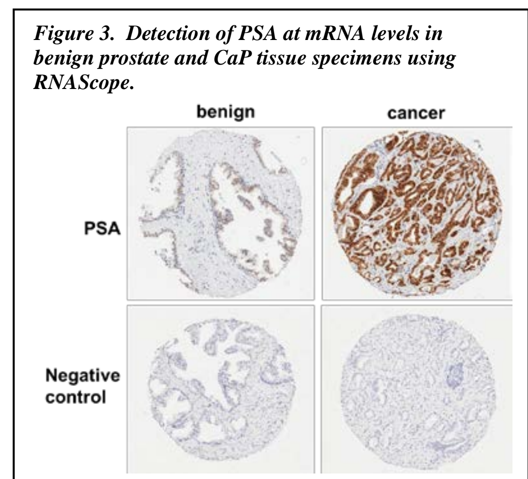
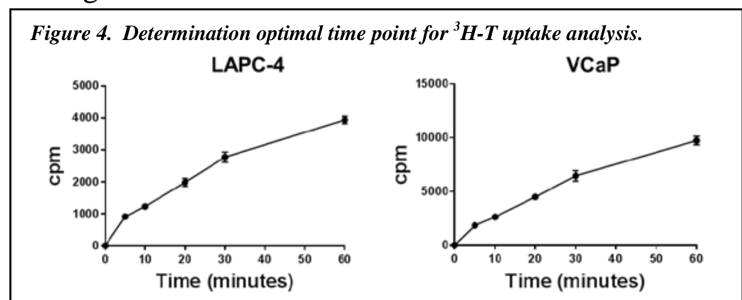


Figure 3. Detection of PSA at mRNA levels in benign prostate and CaP tissue specimens using RNAScope.



Aim 3. Dr. Wu has led in vitro pilot experiments to set up conditions for Specific Aim 3, "Characterize the functions of candidate SLCO transporters in androgen uptake and evaluate the biological effects on AR signaling in human prostate cancer cell lines." A panel of prostate cancer cell lines were tested for their ability to take

Figure 4. Determination optimal time point for ^{3}H-T uptake analysis.



up ^{3}H-labeled testosterone (T). The established experimental protocols identified the baseline for androgen uptake kinetics, and optimized experimental conditions that will be used in Specific Aim 3. The identified reagents included a cell lysis buffer [10 mM Tris (pH 6.8) with 2% SDS and 10% glycerol, when diluted by 2-10 X is compatible for protein determination using BCA], a scintillation fluid that is compatible with detergent-containing cell lysates (Ultra Gold Scintillation fluid, Perkin-Elmer), and a reagent (SOLVABLE, Perkin-Elmer) that stabilizes scintillation/cell lysate mix for high-quality readouts. First, the optimal time point was determined using human prostate cancer cell lines LAPC-4 and VCaP (Figure 4). These cell lines were originated from prostate cancer that harbored wild-type androgen receptor (AR). ^{3}H-T was used at 1 nM in these experiments. The uptake of ^{3}H-T by the cell lines increased over a time period of 30 minutes, and gradually saturated beyond the time point. Therefore, 20 minutes was selected for the duration of treatment to remain in the linear range of the curve and to allow sufficient time for operations. Next, the kinetic of ^{3}H-T uptake was assessed by treating cells with different doses of the androgen for 20 minutes (Figure 5). The inserts show the Schatchard analyses for maximum binding capacity (B_{max}) and the binding affinity (disassociation constant, K_d). The B_{max} and K_d were 1626±247.2 nM and 0.875±0.2825 nM for LAPC-4, and 23719±7688 nM and 3.401±1.417 nM for VCaP. The data indicated that the cell lines were able to uptake T at high capacity. More important, the cell lines differed in their capacities and affinities for T uptake. The kinetics of T uptake by the cell lines verified the existence of a specific uptake mechanism. Two human prostate cancer cell lines, DU145 and PC-3, however, did not show the ability of active T uptake (Figure 6). Cells were treated with 1 nM ^{3}H-T alone or in the presence of 300 nM non-radioactive T (cold T). Cold T blocked ^{3}H-T uptake in LAPC-4 and VCaP cells (Panel A), due to the specific competition for the uptake mechanism for T. The residual readings of radioactivity were caused by non-specific binding (background). ^{3}H-T in DU145 cells and PC-3 cells were detected at levels comparable to the background readings of LAPC-4 and VCaP cells, and were same as the background readings in the presence of cold T (Panel B). Although the cause for the loss of T uptake mechanisms in DU145 and PC-3 cell lines are not clear, the results identified the cell lines as potential models to evaluate the effect of identified transporters in addition to the cell lines that have innate uptake capability.

Figure 5. Kinetic analysis of 3H-T uptake by LAPC-4 and VCaP human prostate cell lines.

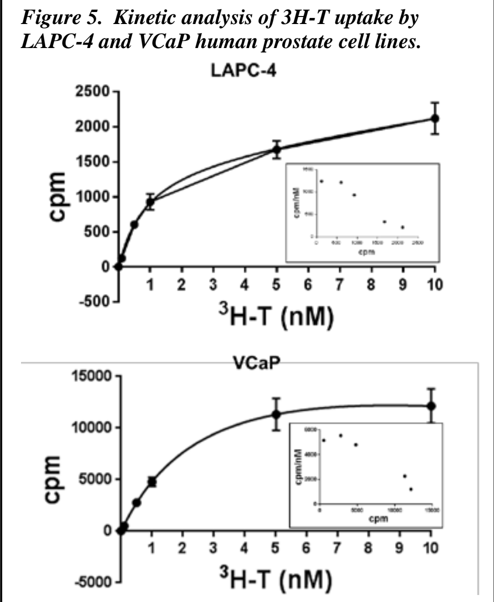
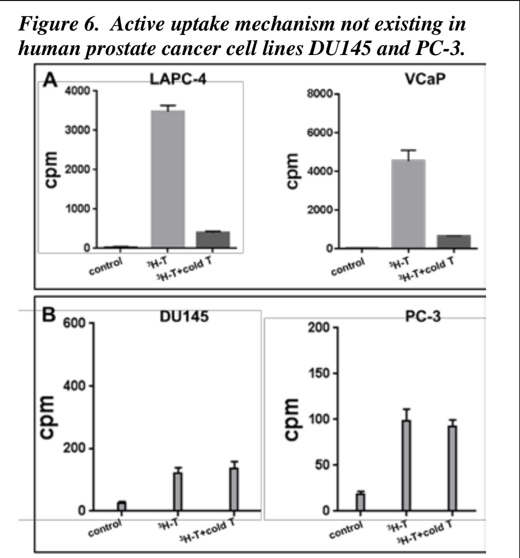


Figure 6. Active uptake mechanism not existing in human prostate cancer cell lines DU145 and PC-3.



In summary, we made good progress and accomplished most of the proposed tasks for Year 1. Genotyping was delayed by nearly 2 months. PCaP had a waiting list of investigators queued for samples, this was one of the reasons that the delivery of the samples was delayed. The most important reason is that the DNA samples provided by PCaP are typically quantitated with NanoDrop, which measures optical density of the samples for DNA quantitation. To assure the most accurate DNA concentrations, the Genetic Shared Facility of RPCI requested the samples to be re-quantitated with PicoGreen. The RPCI team and PCaP team reached to the agreement that PicoGreen would be more appropriate for DNA quantitation for the best quality of genotyping. Due to the large sample number, this adjustment consumed

considerably longer time and increased effort for the PCaP laboratory than what was originally anticipated. However, this is critically important for the quality of our study. We expect that genotyping will start in mid-October. In addition, Dr. Wu's *in vitro* experiments for Aim 3, which was originally proposed for Year 3, compensates the lost time that was necessary for the quality of the DNA samples.

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

The project provides an invaluable opportunity to Dr. Wu and Dr. Tang for interacting with the PCaP study. This project is the first-time collaboration of the investigators to work with the investigators and staff of the PCaP study. During the communications with the PCaP team, we have established constructive collaboration with the PCaP investigator. We also gained insight in material and data processing and infrastructure of the PCaP. The experience not only benefits the investigators to carry out successfully the whole proposed research, but also can be applied to future collaboration with PCaP and other population-based studies. Dr. Wu has learned from Dr. Mohler, a co-investigator and the PI of the PCaP study, about how to initiate interaction with the study, and how to examine study questions from a clinician's perspective. Dr. Wu also gained training in the basics of molecular epidemiology from interactions with Dr. Tang, and the principles and technical details of genotyping through the communication with Dr. Tang and Dr. Glenn. Dr. Gissou Azabdaftari, a pathologist and a co-investigator, also provided training in basics of prostate cancer pathology.

How were the results disseminated to communities of interest?

Nothing to report.

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

During the next reporting period, we will finish the genotyping (Aim 1, Subtask 2), and complete Aim 1 Subtasks 3 and 4, analyze data and to determine the association of genetic variants with prostate cancer aggressiveness, and summarize data and develop a manuscript. We also plan to complete Aim 2 Subtasks 2-4, which are to characterize gene expression profiles of SLCO transporters at mRNA levels on TMAs from RPCI using quantitative in situ RNA hybridization technology RNAScope, analyze data from RNAScope and identify candidate transporters, and confirm expression of the identified candidate transporters at protein level using IHC staining.

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.

One problem we encountered was that the DNA samples provided by PCaP are typically quantitated with NanoDrop, which measures optical density of the samples for DNA quantitation. However, to assure the most accurate of DNA concentrations, the Genetic Shared Facility of RPCI requested the samples to be re-quantitated with PicoGreen. The RPCI team and PCaP team reached to the agreement that PicoGreen would be more appropriate for DNA quantitation for the best quality of genotyping. Due to the large sample number, this adjustment consumed considerable longer time and increased effort for the PCaP laboratory than what was originally anticipated. However, this is critically important for the quality of our study. This issue was solved successfully thanks to the collaborative effort of the two teams.

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

Rachel Pratt (2 cal months) – 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) and Dr. Li Tang (co-PI) are presented as follows.

Changes in active support

Li Tang

Previously active, now completed:

Title: Racial disparity in insertional polymorphisms of human endogenous retroviruses in relation to breast cancer risk and aggressiveness (PI: Tang)
Time Commitment: 15% effort (1.8 calendar months)
Supporting Agency: NIH/NCI R03 CA156645-01A1
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Vaurice Starks
Performance Period: 9/1/11 – 8/30/13 (one year non-cost extension)
Level of Funding:
Brief Description of Project's Goals:
The major goal of this project is to investigator whether the prevalence of HERV-K113 and -K115 insertional polymorphism differs between African American (AA) and European American (EA) women, and whether this disparity is associated with differences in breast cancer characteristics between AA and EA women.
List of Specific Aims:
1. To investigate whether insertional polymorphisms of HERV-K113 and K115 are associated with breast cancer risk in EA and AA women.
2. To investigate whether insertional polymorphisms of HERV-K113 and K115 are associated with early-onset and aggressive characteristics of breast cancer in EA and AA women.
3. To examine the interactions between hormone-related factors and insertional polymorphism of HERV-K113 and -K115 on breast cancer risk and aggressiveness.
Overlap: None

Title: Clinical relevance of intracellular androgen regulators in castration recurrent prostate cancer (PI: Tang)
Time Commitment: As needed
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: 12/03/12 – 11/30/14
Level of Funding: (no cost extension)
Brief Description of Project's Goals:
The overall goal is to examine the expression profiles of androgen regulators in clinical tissue samples of castration-sensitive and castration-resistant prostate cancer.
List of Specific Aims:
1. To examine the expression profiles of SLCO transporters and UGT2B family members in castration-naïve primary prostate cancer and CRPC.
2. To characterize the function of SLCO transporters and UGT2B members in androgen uptake and glucuronidation.
Overlap: None

Previously pending, now active:
Title: Diet and lifestyle in a prospective study of bladder cancer survivors (PI: Kwan/Kushi/Tang)
Time Commitment: 20% effort (2.4 calendar months)
Supporting Agency: NIH/NCI R01 CA172855
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Connie Murphy
Performance Period: 4/1/14 – 3/31/19
Level of Funding:
Brief Description of Project's Goals:
The overall goal is to establish a prospective study of non-muscle invasive bladder cancer cases in order to comprehensively examine the potential beneficial role of cruciferous vegetable intake on bladder cancer recurrence and progression, as well as provide longitudinal data and banked biospecimens for future studies of bladder cancer survival and quality of life.

List of Specific Aims:
1. To determine the associations of cruciferous vegetable intake with bladder cancer recurrence and progression while considering key covariates such as age, sex, race/ethnicity, occupation, and smoking.
2. To examine the modifying effect of genetic variants in ITC-metabolizing genes on the associations between cruciferous vegetable intake and bladder cancer recurrence and progression.
3. To evaluate the effects of the interactions between cruciferous vegetable intake and therapeutic agents on bladder cancer recurrence and progression.

Overlap: None

Yue Wu

Previously active, now completed:
Title: Clinical relevance of intracellular androgen regulators in castration recurrent prostate cancer (Tang)
Time Commitment: 0.60 calendar
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: 12/3/12-11/30/13
Level of Funding: (no cost extension)
Brief Description of Project's Goals:
The overall goal is to examine the expression profiles of androgen regulators in clinical tissue samples of castration-sensitive and castration-resistant prostate cancer.
List of Specific Aims:
Aim 1. Examine the expression profiles of SLCO transporters and UGT2B family members in castration-naïve primary prostate cancer and CRPC
Aim 2. Characterize the function of SLCO transporters and UGT2B members in androgen uptake and glucuronidation
Overlap: None

Previously pending, now active:
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, 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:
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.