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CONTRACTING ORGANIZATION: Johns Hopkins School of Medicine, Baltimore, MD

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13. SUPPLEMENTARY NOTES

14. ABSTRACT This report concerns Year 1 of the award. The objective of this project is to determine if there are intrinsic biological differences in prostate cancer (PCa) phenotypes that contribute to the disparity in outcomes between African American (AA) and European American (EA) men. The project is a matched case-control study of biochemical recurrence (BCR) in AA and EA PCa patients based on evaluating metabolomics and epigenetic differences between the groups, using prostatic fluid as the substrate for measuring analytes. In each race group 65 cases with BCR occurring in less than 5 years are matched on age and year of prostatectomy to 65 PCa patients without BCR for 5 or more years. Prostatic fluid previously collected and banked from each man at prostatectomy will be aliquotted and sent to our industry partner Metabolon Inc. for metabolomics analyses, and to the lab of Dr. Yegnasubramanian for epigenetic analyses. Progress to date was severely affected by the COVID-19 pandemic and the resulting requirement of remote work for many of the study team. In particular, it limited the time available to the Research Specialist to identify patients with banked prostatic fluid, determine eligibility and sample volume, and work with the PI to select appropriately matched cases & controls. We are currently continuing this process now that on-site work has increased. Other progress includes approval of the protocol by the Johns Hopkins IRB and by the USAMRDC Human Research Protection Office (HRPO), and finalization of the contract with Metabolon Inc.

15. SUBJECT TERMS African American, biochemical recurrence, prostatic fluid, metabolomics, epigenomics, matched case-control study, penalized conditional logistic regression, gene set enrichment analyses

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1. INTRODUCTION

African American (AA) men have long been known to have higher prostate cancer (PCa) incidence and cancer-specific mortality than European American (EA) men, and this disparity continues to the present. Studies that have attempted to disentangle disparity due to intrinsically biological differences vs. disparities in socioeconomic status, environmental exposures and lifestyle have produced inconsistent results. Some studies have indicated that the disparity is eliminated or greatly diminished in settings of equal access to care. However, in other studies differences remain after accounting for measurable socioeconomic and related factors. Although a number of differences in gene expression have been identified, they generally don't characterize relevant cancer phenotypes at the functional level, nor do they provide clues to potential risk modifying strategies. An especially promising approach that may be closer to the functional biology of the racial disparity would be to integrate metabolomics with epigenomics. We propose to conduct metabolomic and epigenomic analyses of prostatic fluid in a matched case-control study of AA and EA men with and without biochemical recurrence (BCR). In each race group 65 cases with BCR occurring in less than 5 years are matched on age, year of prostatectomy, and prostatectomy Gleason Grade Group (GGG) to 65 PCa patients without BCR for 5 or more years. Prostatic fluid previously collected and banked from each man at prostatectomy will be aliquotted and sent to our industry partner Metabolon Inc. for metabolomics analyses, and to the lab of Dr. Yegnasubramanian for epigenomic analyses. We hypothesize that comparison of prostatic fluid metabolomic and epigenomic profiles between AA and EA PCa patients, and their association with BCR may provide novel information about functional differences – if any – in the biology of PCa between AA and EA patients, and potentially inform future studies of biomarkers that can be detected in expressed prostatic secretions after prostate massage.

2. KEYWORDS

African American, biochemical recurrence, prostatic fluid, metabolomics, epigenomics, matched case-control study, penalized conditional logistic regression, gene set enrichment analyses.

3. ACCOMPLISHMENTS

There were 2 major goals for Year 1; we will describe them and the progress toward each of these goals, as follows:

1. Develop study procedures (months 1-12 in SOW). This included clarifying tasks, objectives, and potential problems, developing a protocol and submitting it to the IRB, and following approval, to HRPO, and creating a statistical analysis plan.

Progress. We have defined tasks for all study team members, and described them in the IRB protocol. Potential problems identified include subjects with insufficient volume of stored prostatic fluid, and determining the closeness of matching that is feasible on age at prostatectomy, year of prostatectomy, and GGG. We are addressing the former by identifying more than the required number of 65 matched BCR and non-BCR pairs from both race groups so that patients found to have insufficient volume in the biorepository can be replaced. For the latter we have determined that of the AA and EA patients with samples in the biorepository, the percentage of potential pairs with exact matches and matches within 3 years are 43% and 99%, respectively for year of surgery, and 28% and 96% for age. For GGG 30% are exact matches and 79% are within 1 grade group.

Our IRB protocol was approved by the Johns Hopkins IRB on 12/20/21, and approved by HRPO on 5/13/22.

The formal statistical analysis plan has not been developed yet. Although Drs. Trock and Yegnasubramanian have laid out in the grant application the methods to be used for metabolomics, whole genome DNA methylation analysis, and their integration, they are considering whether there are advantages to any new methods that have become available in the 2 years since the grant application was written. If any such changes deviate substantially from the plans in the grant application, we will first submit a request to include the changes and their rationale to the Grants Officer, as required. We expect to have the formal statistical analysis plan completed by the end of July 2022.

2. Identify eligible AA and EA men with sufficient banked prostatic fluid (months 7-12 in SOW). This included identifying men of both races in our IRB-approved prostatectomy database who had prostatectomy from 2008-2016, weren't missing key clinical variables, and developed BCR within 5 years, or were free of BCR for more than 5 years. This has been accomplished, and we have extended the eligibility to prostatectomy in 2017

since these men will have at least 5 years of follow-up at the time the case-control matching is finalized. These men will be matched against the biorepository of prostatic fluid from men who underwent prostatectomy in 2008-2017 and have sufficient sample. Because there are far fewer AA than EA men in the database, the case-control selection will be based on the matching criteria of AA men with prostatectomy 2008-2017 who did and did not have BCR; currently there are 88 and 166, respectively, in the database. These will be matched against the prostatic fluid database to identify eligible AA patients with available prostatic fluid. 65 case-control pairs will be assembled from these men, and EA case-control pairs will be selected to match the distribution of the AA pairs.

If we are unable to obtain 65 AA matched pairs meeting the required criteria we will include men with prostatectomy from 2005-2017; if this provides more than 65 AA matched pairs we will select the most recent 65. We expect this to be completed by the end of July 2022. We realize that there is potential that fewer metabolites can be detected in samples that are too old. We have previously had good metabolite detection in prostatic fluid samples back to 2008. If we need to use samples that are older than 2008 we will first send a pilot set of samples from 2005 to 2017 to determine whether sample age impacts the number of metabolites detectable. In the unlikely event that we are unable to assemble 65 AA matched pairs with suitable sample age, we will submit a request to our Grants Officer to change the study design to a case-cohort design.

In addition to the above we finalized a contract with Metabolon, Inc., our industry partner who will perform global metabolomic analyses and complex lipid profiling. This includes exploratory statistical and pathway analyses and interpretation of over-represented metabolic pathways.

4. IMPACT

At this early stage in the project there have been no results or methodologic advances that impact the field, other than potentially increasing awareness in the potential use of prostatic fluid as a medium for biomarker evaluation. Although we faced delays due to the COVID 19 pandemic (see next section), we are near completion of the major tasks for Year 1, as described above.

5. CHANGES/PROBLEMS

The project has experienced delays in Year 1 due to COVID 19 restrictions. In March 2021 on-site work was discontinued for non-essential Johns Hopkins employees and faculty and replaced by remote work. This severely limited opportunities for face-to-face meetings of the study team, and often made access to databases or hard copy files more cumbersome. In particular, the Research Specialist, whose job in Year 1 focused on identifying potentially eligible patients with prostatic fluid, was only on-site on a limited basis, and priority was given to her clinically-related responsibilities, so it limited the time she had to work on this project. COVID-19 restrictions began to ease in the fall-winter of 2021, and although on-site work still is not 100% for all study team members, project-related activities are now proceeding without further delay.

A major change to the project is that the P.I., Dr. Trock, will be retiring from his full-time faculty position at the end of June 2022. The Grants Management Specialist, Kimberly Carter, and the Science Officer, Dr. Nrusingha Mishra have both been made aware of this by email and formally in a letter. We have proposed, and Dr. Mishra has approved, that Dr. Srinivasan Yegnasubramanian, who is currently Co-Investigator and the lead for the epigenomic analyses, will become P.I. of the award. Dr. Angelo De Marzo, who is currently Co-Investigator, the developer of the prostatic fluid biorepository, and the expert on biomarkers and analysis of prostatic fluid, will become Co-Principal Investigator. They will submit a letter to this effect to Ms. Carter and Dr. Mishra. Both Drs. Yegnasubramanian and De Marzo internationally regarded prostate cancer research scientists, and are well-versed in the hypotheses, objectives, and methods for this project, and we anticipate no complications or delays resulting from this transition. The Sponsored Programs office at Johns Hopkins is preparing a revised budget to reflect Dr. Trock's departure, and increased effort on the project for both Drs. Yegnasubramanian and De Marzo, and possibly increased biostatistical analysis effort as well.

6. PRODUCTS

None

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

Bruce J. Trock: No change (this reflects the current reporting period; the Year 2 report will reflect his departure as described above).
Srinivasan Yegnasubramanian: No change

Angelo De Marzo: No change

Tracy Jones: No change

Yuezhou Jing: No Change

Change in Other Support

Bruce Trock

New Grant Support:
W81XWH-20-0274 The Effect of Androgen Metabolism by Gastrointestinal Microbiota on Resistance to Androgen Receptor Axis-Targeted Therapies in Metastatic Prostate Cancer

W81XWH-20-1-0353 Polyploid Giant Cancer Cells Actuate Prostate Cancer Tumor Resistance and Lethal Phenotype

R01CA255259 A First-in-Class FAP-activated Protoxin to disrupt the Tumor-Stroma Parasitic Cycle fueling lethal Prostate Cancer Progression

R01CA247959 Robot-Assisted Personalized Prostate Biopsy

W81XWH-21-1-0657 Identification of Driver Mitochondrial Genome Mutations in Urothelial Carcinoma of Bladder

R01CA255259 A First-in-Class FAP-activated Protoxin to disrupt the Tumor-Stroma Parasitic Cycle fueling lethal Prostate Cancer Progression

Grant Support Closed:
W81XWH-17-1-0425 Prospective-Retrospective Analysis of PTEN Immunohistochemistry Assay for Prediction of Outcomes in Recurrent and Metastatic Prostate Cancer

5P50CA058236: SPORE in Prostate cancer

U01CA152813 Glycoprotein biomarkers for the early detection of aggressive prostate cancer (renewal)

17053953 (Sponsor: MDxHealth, Inc.) Evaluation of ConfirmMDx and SelectMDx for Prostate Cancer Biomarkers to Assess Patient Eligibility and the Non-Invasive Monitoring of Low Risk Prostate Cancer Patients Under Active Surveillance

W81XWH-18-2-0013 PC171113-Prostate Cancer Biorepository Network (PCBN)

Srinivasan Yegnasubramanian

New Grant Support:
W81XWH-21-1-0295 GSTP1-Positive Subset of Prostate Cancer Over-Represented in African-American Men: Systemic Treatment Implications

W81XWH-21-1-0681 Role of Homeobox C Gene Cluster in Castration Resistant Prostate Cancer

U54CA260492 Johns Hopkins Excellence in Pathogenesis and Immunity Center for SARS-CoV-2 (JH-EPICS)

R37CA251447 Immunogenomic determinants of response to neoadjuvant anti-PD-1 in resectable NSCLC

P01CA247886 Transforming Human Pancreatic Cancer into an Immunologic Disease

U19AI159822 Mechanisms of spontaneous and vaccine mediated hepatitis C virus control to direct rational development of a novel HCV vaccine

19-028-ASP (Sponsor: Mark Foundation for Cancer Research) Expanding Therapeutic Options for Lung Cancer (EXTOL) in memory of Waun Ki Hong

Grant Support Closed:
5P50CA058236: SPORE in Prostate cancer

90061810 (Sponsor: Prostate Cancer Foundation) Enhancing Prostate Cancer Immunotherapy through Epigenetic Reprogramming for Optimal Activation of Specific Effector T-Cells (Erase-PCA Team Proposal)

ICD 856497 (Sponsor: Janssen Research & Development LLC) Can High Grade PIN be Distinguished from Intra-Acinar Spread of Prostatic Carcinoma? Implications for Chemoprevention Trials

P30CA006973 Regional Oncology Research Center

R01HL131812 Lung Injury Repair by Regulatory T cell LGP2

W81XWH-17-1-0581 The Role of Alternative Polyadenylation in Advanced Prostate Cancer

90077818 (Sponsor: Celgene Corporation) The Celgene Cancer Center Consortium: Targeting UHRF1 for cancer therapy

90084352 (Sponsor: Schwab Charitable Fund) Genomic studies of aggressive prostate cancer lesions

90088420 (Sponsor: Cepheid) Development of Assays for Detection of Methylated DNA to be performed on the GeneXpert platform

Angelo De Marzo

New Grant Support:
SUBK00011358 The Biology of Prostate Cancer Skeletal Metastases

R01CA255349 Stromal Senescence in Lethal Prostate Cancer: A Novel Target for Prognosis and Therapy

W81XWH-20-1-0353 Polyploid Giant Cancer Cells Actuate Prostate Cancer Tumor Resistance and Lethal Phenotype

R01CA255259 A First-in-Class FAP-activated Protoxin to disrupt the Tumor-Stroma Parasitic Cycle fueling lethal Prostate Cancer Progression

W81XWH-21-1-0295 GSTP1-Positive Subset of Prostate Cancer Over-Represented in African-American Men: Systemic Treatment Implications

21CHAS01 (Sponsor: Prostate Cancer Foundation) Artificial Intelligence for Prostate Cancer Grading, Prognosis and Molecular Subtyping

Grant Support Closed
ICD 856497 (Sponsor: Janssen Research & Development LLC) Can High Grade PIN be Distinguished from Intra-Acinar Spread of Prostatic Carcinoma? Implications for Chemoprevention Trials

90084352 (Sponsor: Schwab Charitable Fund) Genomic studies of aggressive prostate cancer lesions

5P50CA058236: SPORE in Prostate cancer

W81XWH-18-2-0013 PC171113-Prostate Cancer Biorepository Network (PCBN)

U01CA196390-03S1 Molecular and Cellular Characterization of Indolent and Aggressive Cancer

P30CA006973 Regional Oncology Research Center

90082717 (Sponsor: Janssen Research and Development LLC) Localization of T Cells and Myeloid Cells in Prostate Cancer

90082514 (Sponsor: Prostate Cancer Foundation) Concurrent Administration of Bipolar Androgen Therapy (BAT) and Nivolumab in Metstatic Castration-Resistant Prostate Cancer: The COMBAT-CRPC Trial

Other Organizations Involved as Partners:

Nothing to report

8. Special Reporting Requirements

Nothing to report

9. Appendices

None