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MICHAEL E. DEBAKEY VETERANS AFFAIRS MEDICAL CENTER

26 June 2021

Dear Gulf Coast Center for Precision Environmental Health (GC-CPEH) Reviewers,

Several members of the Baylor College of Medicine (BCM), Dan L Duncan Comprehensive Cancer Center (DLDCCC) and Michael E DeBakey Veteran Affairs Medical Center (MEDVAMC) Prostate Cancer Research Working Group would like to submit a Letter of Intent for submission of a proposal for the Strategic Round of Pilot Projects: Veteran's Environmental Health called: "Identifying Environmental Gene-Expression Signatures in Aviator-Associated Prostate Cancer". We propose to study a small cohort of veteran aviators, assessing epigenomic changes that may reveal environmental influences on their risk of prostate cancer and compare those findings to epigenomic changes in veterans with prostate cancer and history of exposures to the flight environment as aviators, and to agent-orange (dioxin) exposure during their military service. We propose to utilize the GC-CPEH and BCM Genomic and RNA Profiling and Multi-omics Data Analysis Cores and BCM/DLDCCC biorepository for our proposed pilot project. A young-investigator and new BCM faculty member, Dr Salma Kaochar, will lead this pilot study, with post-doctoral mentee, Dr Amit Dash.

Our team consists of:

PI- Salma Kaochar, PhD- BCM Department of Medicine, Hematology/Oncology
Post-doc- Amit Dash, PhD- BCM Department of Medicine, Hematology/Oncology
Co-I: Eli Van Allen, MD- Harvard Medical School, Computational Director for the Center for Cancer Genomics at Dana-Farber Cancer Institute, Associate Member Broad Institute
Co-I: Michael Ittmann, MD- BCM Department of Pathology, DLDCCC and Chief of Pathology (MEDVAMC)
Co-I: Jeffrey Jones, MD- BCM Department of Urology, DLDCCC, and Chief of Urology (MEDVAMC)
Collaborator: Kamlesh Yadav, PhD- BCM Dept of Urology and Texas A&M Engineering Medicine
Collaborator: Feng Yang, PhD- BCM Department of Molecular and Cellular Biology
Collaborator: Michael Scheurer, PhD BCM Biorepository Director
Clinical Research Associate: TBD

The proposal team would like to thank the GC-CPEH in advance for their time and consideration in review of our pilot proposal LOI.

With kind regards,

Salma Kaochar

S. Kaochar J Jones

Identifying Environmental Gene-Expression Signatures in Aviator-Associated Prostate Cancer

Background and Significance: Prostate cancer (PCa) was diagnosed in approximately 175,000 men in the United States in 2019 & accounts for approximately 27,000 deaths (4.4% of all cancer deaths). [1] The prevalence of disease- estimates 2.9 million men living with PCa in the United States as of 2018. [2-4] The largest US cancer health disparity exists in PC, with African American (AA) men developing PC at a younger age (64% more likely), at a more advanced stage at the time of diagnosis and has the shortest survival (2.5 times more likely to die from the disease). [1,5,6] Veterans Administration (VA) EMR analysis show PCa developed more frequently in men exposed to "Agent Orange" (AO-containing dioxins) compared to non-exposed. Many exposed to battlefield chemicals like AO, have advanced prostate cancer, often metastatic at the time of initial diagnosis. AA men exposed to AO, may have an additive risk for aggressive prostate cancer, above & beyond their pre-existing increased risk. Unfortunately, reliable biomarkers for prediction of the aggressive disease state are not yet clinically available. [7-13] A recent increase in prostate cancer, as high as 2.4 x higher, has been observed in military aviators. The causative mechanism is unclear, but postulations include the unique exposure of pilots to several sources of ionizing and non-ionizing radiation in the flight environment, to include depleted uranium, and high power/ dose radar and communication jamming pods [14-16] Other unique exposures include jet-fuel (JP-8), cadmium, and aircraft component cleaning solvents (e.g. Toluene, TCE, etc) which are known carcinogens. Aviators at Al-Asad were also exposed to burn pit effluent. All military personnel in theaters of combat received unique pre-deployment immunizations, as well. Multiple studies led by our group and others have delineated the molecular landscape of primary and advanced prostate cancer [17-19]. These efforts have demonstrated that combinations of germline (such as mutation in DNA repair genes) and somatic features (such as mutation in androgen receptor (AR)) at the single gene level contribute to prostate cancer oncogenesis and progression. [20-21]. In other cancer types, we and others have also shown that environmental exposures contribute to mutational processes, such as UV radiation for melanoma[22], smoking for non-small cell lung cancer,[23] and platinum chemotherapy in multiple chemotherapy-exposed cancers[24]. Men with prostate cancer who previously served as aviators may represent a distinct clinical entity, [25] and these men are exposed to unique environmental exposures given extended flight times in the cockpit at high altitudes. Taken together, these observations raise the hypothesis that aviators with prostate cancer harbor a unique mutational process indicative of their environmental exposures that directly contributes to oncogenesis and is a distinct class prostate cancer.

To lay the foundational work for this highly important project we propose to **(1) establish a focused database of our current aviator PCa patients along with race and age matched control cohort and (2) determine the transcriptional footprint of aviator-associated prostate cancer.** ***Hypothesis:*** Prostate cancers in aviators result from unique mutational signatures that result in enrichment for oncogenic gene expression signature. ***Preliminary Data:*** Our collaborative team has previously completed gene expression profiling of >100 prostate cancer patients (non-aviators). These gene expression profiling enabled us to identify targetable signaling axis such as lipogenesis (via metabolic inhibitors) and DNA repair deficiency (via PARP inhibitors). We also are assessing DNA methylation on a cohort of dioxin-exposed veterans with prostate cancer. We now propose to expand our expertise into establishing the gene signature of aviator-associated prostate cancer. ***Focused objectives:*** **(1)** We will first mine available VA databases to identify and assemble a selective sub-database of aviator and non-aviator prostate cancer patients (to serve as race and age matches control group). Our preliminary efforts indicate, we have identified ~450 aviators with PCa via contacts within the DOD and VA system. With the assistance of a *designated* clinical coordinator and data extractor, under IRB- approved protocol, we will perform computerized search of the pathology records from our institution for veterans with the diagnosis of prostate cancer. Next, we will identify a subset of aviator patients and collect their electronic medical record data for appropriate clinical characteristics such as exposure to agent orange, age of diagnosis, Gleason score, and PSA. We will conduct a review of the written medical records to supplement any missing information. A race and age matched control group will be established by randomly selecting patients from our Genitourinary clinic and similarly data will be obtained for comparison studies. We will perform appropriate statistical analysis, including Pearson chi-square analyses, independent samples t-test, analysis of variance, and logistic regression analyses, with statistical significance set at $P<0.05$ for a two-tailed test. Odds ratios will be calculated with 95% confidence intervals. Through this analysis, we will determine the prostate cancer prevalence and mortality in the aviator veterans compared to non-aviator men. **(2)** Next, we will identify 100 aviator veterans with prostate cancer where we have already banked frozen tissue or FFPE blocks. We will consent and obtain specimen from patients of our study interest who will undergo routine radical prostatectomy or biopsies while our study is ongoing. We will isolate RNA and perform sequencing to establish gene expression profile from these 100 aviator patients. Using established computational methods from our group, we will compare gene expression footprints of aviators to non-aviator men with PCa. For our non-aviator prostate cancer cohort, our group has already generated over 200 gene expression profiles, and we will leverage that data for our analysis. We are confident in our ability to establish unique gene signatures for aviator-associated prostate cancer. The data generated via this pilot will allow us to successfully compete for larger grant to support further deep profiling (DNA methylation status and whole exome sequencing (WES)) of our cohorts to elucidate the molecular mechanism behind altered gene expression signature. ***Anticipated results:*** We will define the molecular characteristics of this unique cancer patient population and determine the impact of aviation exposure on oncogenesis. These investigations will also reveal candidate molecular patterns specific to this patient population that may have translational relevance across tumor types in similarly exposed patients with other cancers.

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