

AWARD NUMBER: W81XWH-20-1-0264

TITLE: Evaluating Senescent Stromal Fibroblasts as a Promoter of Prostate Cancer Lethality to Inform a Paradigm Shift in Prognostic, Predictive, and Therapeutic Strategies

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14. ABSTRACT We are conducting multidisciplinary research to address the hypothesis that senescent prostate stromal fibroblasts, especially those with the senescence-associated secretory phenotype (SASP), promote lethal prostate cancer, and are more prevalent in Black men. Despite the pandemic, our research team continued non-in person lab-based aspects of the SOW, including study designing, and identifying new strategies to overcome limitations and to optimize the measurements. We received IRB approval. We developed the Prostate Cancer Case-Cohort Study using PCPT linked with Medicare claims. The study includes 151 cases and a subcohort of 378 men at risk (2.5x case N). The subcohort has a median age of 69 years and median PSA at the end-of-study biopsy of 1.5 ng/mL. We selected variables for the analysis, and requested biopsy tissue from the PCPT biorepository. SWOG and JHH are negotiating the MDUA. We requested and received test prostate tissue to use to optimize the multiplex staining and imaging protocols; had the specialized equipment we use serviced and replaced the illumination system to ensure measurement quality; identified strategies to reduce autofluorescence for our IF/imaging work; identified a possible new commercial technology. The Aim 3 question (progression to mets after salvage tx for recurrent disease) will benefit from a newly identified secondary analysis of a subset of the Aim 2 study (progression to lethal disease after prostatectomy) made possible by subsequent re-linkage extending follow up of men who experience biochemical recurrence from 2004 to 2018. Barriers to completing the Year 1 SOW included institutional restrictions on non-COVID lab research and on hiring/on-boarding during the pandemic. Year 1 was fully during the pandemic, nevertheless, we made good progress on key aspects of the SOW.						
15. SUBJECT TERMS Prostate cancer, stroma, senescent, fibroblasts, microenvironment, telomeres, epidemiology, risk, disparities						
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1. INTRODUCTION: We are conducting multidisciplinary research to address the hypothesis that senescent prostate stromal fibroblasts, especially those with the senescence-associated secretory phenotype (SASP), promote lethal prostate cancer, and are more prevalent in Black men. Specifically, we are evaluating associations of the phenotypic nature, density, and distribution of senescent stromal fibroblasts in pre-diagnostic (benign) prostate biopsy tissue with risk of prostate cancer in men (Aim 1); in benign and prostate tumor tissue with risk of progression in surgically-treated men (Aim 2); and in benign and prostate tumor tissue with risk of further progression to metastasis or prostate cancer death in surgically-treated men who received salvage radiation therapy for PSA recurrence (anti-androgen therapy) (Aim 3). In Aim 4, we will determine whether the phenotypic nature, density, and distribution of senescent stromal fibroblasts in benign and prostate tumor tissue differ between matched Black and White men. We expect our findings to be highly consequential in driving a paradigmatic shift of focus to the prostate stromal microenvironment for informing prognosis and treatment response and targeting of senescent fibroblasts (senolytics) to complement existing strategies to reduce lethal prostate cancer burden, including in Black men.

2. KEYWORDS: Prostate cancer, stroma, senescent, fibroblasts, microenvironment, telomeres, epidemiology, risk, disparities

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

In Aims 1 to 3, our goal is to document whether the phenotypic nature of senescent fibroblasts in the prostate stroma, their density, and their distribution are associated with three prostate cancer patient situations: risk, progression to lethal disease after prostatectomy, and progression to metastasis/death after salvage treatment for recurrent prostate cancer. In Aim 4, our goal is to document whether the phenotypic nature of senescent fibroblasts in the prostate stroma, their density, and their distribution differ between Black and White men to inform the racial disparity in prostate cancer and its aggressiveness.

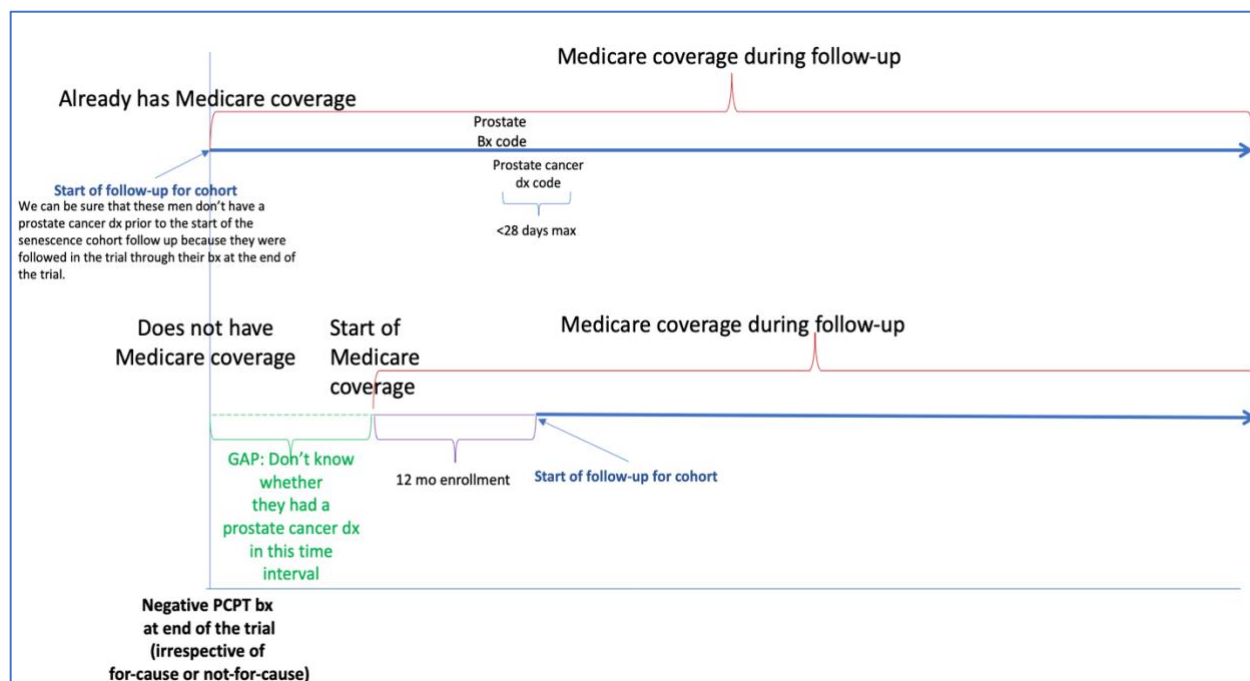
- **What was accomplished under these goals?**

The start date of this award was April 1, 2020. In the SOW, we provided tasks and subtasks by aim to achieve these goals, with aspects of each aim running concurrently - Aim 1: Months 4-36; Aim 2: Months 4-30; Aim 3: Months 4-36; Aim 4: Months 7-29. However, on March 28, 2020, Johns Hopkins University closed all non-essential research and laboratories due to COVID-19, and restricted on-boarding of new fellows (including pathology) and all faculty and staff to only COVID-related research activities onsite. Our research team was able to continue non-in person laboratory-based aspects of the SOW, including study designing (epidemiologic aspects), and the identification of new strategies to overcome limitations and to optimize the measurements (laboratory aspects). Because our specialized equipment for this study (Tissue Gnostics fluorescent slide scanner) sat idle for months during the closure, in spring 2021, we had the system serviced, including its microscope, and replaced the illumination system in preparation for this work because we previously showed that an aging illumination system increases the variability in measurements (Marrone MT et al. Clin Chem. 2019 Jan;65(1):189-198. PMID: 30518666). During Year 1, we successfully collaborated with the subcontractor (SWOG Stat Center at the Fred Hutch) while working remotely. We are very happy to report that JHU has approved the pathology fellow and the technician to being full-time in laboratory on July 1, 2021, barring renewed SARS-CoV-2 activity.

We provide here details of what we accomplished in Year 1.

Aims 1-4: All IRB approvals were received. Drs Platz and Meeker met every Friday at 10 am via Zoom to discuss these projects, barriers, and approaches to move the work forward (despite the pandemic).

Aim 1: We developed the PCPT Prostate Cancer Case-Cohort Study using PCPT linked with Medicare claims (Figure). Dr. Platz spearheaded these efforts, with Dr. Meeker providing input into the decision-making, and with the collaboration of the SWOG Statistical Center (Fred Hutch subcontract, via email and Zoom).



We used the following criteria for eligibility of PCPT men to be sampled for the subcohort. A total of 3,328 men met these criteria.

1. PCPT placebo arm.
2. Negative end-of-study biopsy.
3. Linked to Medicare with match on SSN, date-of-birth, and sex.
4. 12+ months Medicare coverage for those with a gap between PCPT end-of-study (EOS) and Medicare; for men with Medicare coverage at EOS, no minimum coverage requirement.
5. Time-at-risk begins at EOS for men with Medicare coverage at EOS, or 12 months into coverage for those with a gap between EOS and Medicare.
6. For men with a gap between EOS and Medicare, removed anyone with an ICD9 diagnosis, ICD9 procedure, CPT, or HCPCS code in the Algorithm Exclusion Codes list that we derived from Parlett LE et al. (Epidemiology 2019;30(3):466-471. PMID: 30829831), before the start of time-at-risk, to exclude possible prevalent prostate cancer cases and those not at risk for prostate cancer at the start of time-at-risk. For men with no gap, no exclusions based on Medicare claims were necessary because we were able to use SWOG's follow-up records (e.g., SELECT).
7. Adequate biopsy tissue available.

From the men eligible to be sampled from the subcohort, we identified men diagnosed with prostate cancer (cases) after the PCPT end-of-study biopsy as follows:

1. Same eligibility as the subcohort above.
2. With a PCA diagnosis code (ICD9 185 claim code), within 28 days after a biopsy CPT/HCPCS code (see Algorithm Exclusion Codes Table).
3. Diagnosis date will be defined as the biopsy date.

We identified 151 eligible cases. We then sampled from the men eligible to be in the subcohort, a stratified random sample such that the subcohort size was 2.5 times the number of cases, or 378 men, which is 11.4% of the total eligible for the subcohort. To sample, we stratified by whether the men went on to participate in SELECT (yes versus no) and Medicare coverage at EOS (had coverage at EOS versus had a gap in observation between EOS and beginning of Medicare coverage). The subcohort was sampled from all eligible men, including men already identified as cases, so that some cases will be a part of the subcohort, and some will be cases not in the subcohort, as per the case-cohort design. 83.4% of the cases, and accordingly, 83.6% of the subcohort, had Medicare coverage at the end of study biopsy at PCPT, which limits the concern about missed prostate cancer cases among eligible men post PCPT follow up, but before their enrollment in Medicare when they turned 65 years old. 13.9% of the cases and 14.0% of the subcohort participated in SELECT (SELECT interventions were subsequent to the PCPT end of study biopsy and so cannot affect the measurement of senescent stromal fibroblasts in the biopsy tissue). Per chance any of the non-case subcohort biopsy tissue cannot be located in the SWOG/PCPT biorepository, we selected an additional 5% from the eligible subcohort using the same sampling criteria as possible replacements.

We selected the clinical and other variables for the analysis, including those that may inform the findings (e.g., whether any of the selected men had any cancer type prior to their prostate end of study biopsy, information needed because any systemic therapy could affect the likelihood of senescent fibroblasts in the prostate). We made the request for biopsy tissue for the men in the case-cohort study to the PCPT biorepository (4 sequential unstained biopsy sections from one representative block). SWOG and JHU are finalizing the Materials and Data Use Agreement (was pending final counts and needed characterizing data and tissue selection).

The selected men are characterized in the Table.

Table. Newly designed prostate cancer case-cohort study (prospective design) for the study of senescent stromal fibroblasts and prostate cancer risk in the Prostate Cancer Prevention Trial

Characteristic	All Cases (N=151)	Subcohort (N=378)
	<i>Median (range)</i>	<i>Median (range)</i>
Age at baseline (years)	62 (55-75)	62 (55-79)
Age at end-of-study biopsy (years)	69 (62-82)	69 (62-86)
Closest BMI prior to end-of-study (kg/m ²)	26.4 (17.2-52.4)	27.0 (15.6-52.4)
PSA at baseline (ng/mL)	1.3 (0.3-3.0)	1.1 (0.3-3.0)
Closest PSA prior to end-of-study (ng/mL)	2.2 (0.3-79.0)	1.5 (0.3-79.0)
Hispanic	2%	1%

Race		
Black	3%	3%
Asian	1%	1%
White	96%	96%
Family history of prostate cancer	15%	18%
Attained education		
≤12 years	17%	17%
13-15 years	27%	28%
16+ years	56%	56%
Smoking status at baseline		
Never	34%	36%
Current	6%	6%
Former	60%	58%

Aims 1 to 4: With respect to the laboratory aspects of the work, during Year 1, Dr. Meeker spearheaded the following:

- Requested and received test sections of prostate tissue from the SKCCC Pathology Archives to optimize the multiplex staining and imaging protocols. This step took months because like many institutions, JHH has enhanced its protocols for providing clinical materials.
- Negotiating with Tissue Gnostics for their newly developed image analysis software. This software is more than a refinement to their current software, and is very costly. The new software is not required to successfully complete the SOW, however.
- Assessing the feasibility of the CODEX multiplexed immunostaining system (Akoyabio Biosciences: https://www.akoyabio.com/codex/?gclid=CjwKCAjw-geFBhAsEiwA2G7NI7hVHOGiG53cCJIC-jjqffmhsaenDO4DXjoc52CK4ZeOZtKGO9MfDxoCW_QQAvD_BwE) for performing repeated rounds of IF/imaging on the same tissue section after erasing prior fluorescence labeled antibodies. This technology is not yet ready for use for slide tissue sections (current configuration uses coverslips) and many of the antibodies we need for the current study have not been validated in this system. However, if both were in place, this system would overcome a currently unavoidable limitation of our approach: the need to use multiple adjacent slide sections to identify productive SASP (senescent cells identified through limited multiplexing on one slide and inflammatory cells identified through limited multiplexing on an adjacent, but not the same slide). We are discussing with Akoyabio Biosciences the possibility of an NDA for the reagents to manually test their strategy on representative whole prostate tissue section slides, and the company indicated that they realize the wider need for their method for whole slides. Alignment of the multiple individual images of the same tissue section would be done using the image analysis program HALO, which we have in house. We learned about this system because we remained highly engaged during the pandemic, including by attending scientific presentations via videoconferencing (e.g., talk by Garry Nolan from Stanford, who developed CODEX: <https://web.stanford.edu/group/nolan/nolan.html>, and who is a past DOD award recipient).
- Investigating new strategies to reduce autofluorescence. One of the challenges of IF on prostate tissue is autofluorescence. Tissues from aged individuals,

including the prostate often have lipofuscin present, which is a hydrophobic pigment that is autofluorescent. Both strategies involve a secondary light source, and one method involves immersion in hydrogen peroxide prior to IF staining and digital image capture. We also are intrigued by whether the presence and extent of lipofuscin (as measured by autofluorescence as a marker for aged prostate) could inform the likelihood of the presence of senescent stromal fibroblasts.

For Aims 2 (16 progression TMAs) and 4 (two sets of TMAs for W and B differences), we have the TMA blocks ready for sectioning. The TMAs are housed in freezers in the SKCCC's Oncology Tissues and Imaging Services Core, which is in Dr. Meeker's laboratory, as he is the Director of this shared core. The plan is to section the TMAs immediately before staining; we have found that pre-cut sections stored at room temperature do not perform as well as freshly cut for some antibodies.

For Aim 3, which involves constructing a new TMA set for salvage treatment post biochemical recurrence, we are awaiting the pathology fellow's arrival and training. The fellow will be responsible for identifying regions to core for the TMAs. As we were trying to plan for the development of this TMA set given the pandemic, we learned that our colleague Dr. Bruce Trock (former PCBN PI at JH and DOD awardee) recognized that a subset of the men TMA set from Aim 2 (which Drs. Platz and De Marzo developed under past DOD funding) could be followed to form a cohort study of metastatic progression after biochemical recurrence (the Aim 2 TMA set has as its outcome post-prostatectomy progression to biochemical, metastatic, and death (through 2004)). From these men, Dr. Trock sampled all men who experienced biochemical progression only and linked them with institutional outcomes data through December 2018. Where data were available, he characterized them with respect to salvage treatment at biochemical recurrence. The biostatistician for our DOD award worked with Dr. Trock to receive the dataset and codebook, and under Dr. Platz's supervision, she developed SAS code to analyze this cohort, which will link in senescence data once generated. The subset includes 438 men with biochemical recurrence, among whom 176 progressed to metastasis or prostate cancer death. 84 had salvage radiation, 88 had adjuvant ADT, and 73 had both salvage radiation and ADT, and the rest did not have salvage therapy. The mean (median) time from biochemical recurrence to metastasis was 10 (8) years. The great value of this subset is that we will have performed the measurement of senescent stromal fibroblasts in the Aim 2 progression set (risk of progression after prostatectomy), which can then be used to address the Aim 3 question (risk of metastasis/prostate cancer death after biochemical recurrence). However, we should note again that these men were a subset of men sampled and matched on variables for another purpose, and thus, may not reflect the full experience of men requiring salvage therapy post prostatectomy. Thus, our plan still is to develop the TMA set for salvage treatment to reflect the full experience of men with biochemical recurrence requiring salvage therapy. We will do this in collaboration with Dr. De Marzo (Co-I on this DOD award), and with a focus on contemporary cases (the cases in the progression set were from earlier in the PSA era).

Year 1 of this award was fully during the pandemic. We made good progress on key aspects of the SOW. However, we do expect that at the end of the 3-year award, we will need to request a no cost extension to complete the full SOW as proposed.

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

Nothing to Report (not intended to provide training and professional development opportunities)

- **How were the results disseminated to communities of interest?**

Nothing to Report (Year 1)

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

Dr. Meeker and Platz will continue to meet weekly to move the project forward. We assume that the CODEX approach is a longer-range possibility, so we will move forward with our proposed approach, and in parallel continue exploring whether technology will evolve to being practicable for this work.

1. On-board the pathology fellow.
2. Complete optimizing the multiplex staining and image analysis protocols using the test tissue received.
3. Select the strategy to reduce autofluorescence.
4. Section and stain the Aim 2 and Aim 4 TMAs.
5. Receive and catalog the Aim 1 biopsy sections. Stain the biopsy sections.
6. Begin image capture using the selected strategy to reduce autofluorescence.
7. Begin image analysis.
8. Begin designing the Aim 3 TMAs.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

- The value of multidisciplinary collaboration was highlighted in overcoming some of the pandemic related challenges.
- This project served as an example of research at the nexus of aging (senescence)-and cancer, and is helping to propel an aging-cancer institutional research agenda.

- **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**

No major changes in approach have been made.

- **Actual or anticipated problems or delays and actions**

COVID pandemic delays and the path forward were described under accomplishments. We have been exploring opportunities to provide master's students (JHSPH Department of

Biochemistry and Molecular Biology training program has faculty who are members of the SKCCC's Cancer Invasion and Metastasis Program) with year-long experiences and thesis projects as a win-win for the students and this project to move forward more quickly to make up for the time lost due to COVID lab closures and restrictions on hiring/on-boarding.

- **Changes that had a significant impact on expenditures**
We have delayed charging pathology fellow and lab tech time due to pandemic hiring restrictions. We expect their efforts to begin 7/1/2021 as described above.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
 - **Significant changes in use or care of human subjects**
Nothing to Report
Approved: April 13, 2020
IRB No: 00012045
Determination: NOT HUMAN SUBJECTS RESEARCH
 - **Significant changes in use or care of vertebrate animals**
Project does not involve animals.
 - **Significant changes in use of biohazards and/or select agents**
Project does not involve these.

6. PRODUCTS:

- **Publications, conference papers, and presentations**
Nothing to Report
- **Website(s) or other Internet site(s)**
Nothing to Report
- **Technologies or techniques**
Nothing to Report
- **Inventions, patent applications, and/or licenses**
Nothing to Report
- **Other Products**
Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name	Elizabeth A. Platz
Project Role	PI
Researcher Identifier	ORCID 0000-0003-3676-8954
Nearest person-month worked	2.0
Contribution to Project	Oversaw the research conducted as described in Accomplishments; directly

	collaborated with SWOG (subcontractor) to develop the case-cohort study for Aim 1
Funding Support	Only this project supports the PI for this work.

Name	Alan K. Meeker
Project Role	Co-I
Researcher Identifier	0000-0003-4601-6481
Nearest person-month worked	2.8
Contribution to Project	His efforts are detailed in Accomplishments and included the laboratory aspects of the project to optimize the measurement of senescent stromal fibroblasts.
Funding Support	Only this project supports him for this work.

Name	Jiayun Lu
Project Role	Staff Biostatistician
Researcher Identifier	0000-0002-5592-6658
Nearest person-month worked	1.0
Contribution to Project	Her efforts are detailed in Accomplishments under Aim 3: she obtained the data for and developed SAS code to extend a subset of the participants in Aim 2 to address the Aim 3 research question.
Funding Support	Only this project supports her for this work.

Note that the subcontractor (Fred Hutchinson Cancer Research Center) staff analyst contributed 0.9 calendar months during Year 1, which is <1 calendar month reporting requirement. She does not have an ORCID. She implemented the decisions made collaboratively with Drs. Platz and Meeker for the design of the Aim 1 case-cohort study.

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

Dr. Platz - Yes.
Dr. Meeker - Yes

See Appendices for updated Other Support. Changes are marked in yellow highlighting.

- **What other organizations were involved as partners?**
No other partners beyond JHU and Fred Hutchinson Cancer Research Center (subcontract)

8. SPECIAL REPORTING REQUIREMENTS

Not applicable

9. APPENDICES:

- Dr. Platz – Other Support
- Dr. Meeker – Other Support

Platz, Elizabeth A.

CURRENT

(THIS GRANT)

Award: W81XWH-20-1-0264

Title: Evaluating senescent stromal fibroblasts as a promoter of prostate cancer lethality to inform a paradigm shift in prognostic, predictive, therapeutic strategies

Effort: 2.4 calendar months (20%)

Supporting Agency: Department of Defense – Congressionally Directed Medical Research Programs

Grants Officer: Kimberly Carter

Address of Funding Agency: 820 Chandler St. Fort Detrick, MD 21702-5014

Performance Period: 05/01/2020-04/30/2023

Level of Funding:

Principal Investigator: Elizabeth Platz

Project Goals: Our goal is to determine whether senescent prostate stromal fibroblasts, especially those with the senescence-associated secretory phenotype (SASP), promote lethal prostate cancer, and are more prevalent in Black men.

Specific Aims: For Aim 1, in pre-diagnostic (benign) prostate biopsy tissue with risk of prostate cancer in men at risk. We will generate a case-cohort study (320 subcohort) sampled from a prospective cohort of 2,584 men from the PCPT placebo arm without clinical indication who underwent end-of-study biopsy per trial protocol and negative for prostate cancer by linkage with claims data up to 17 years later. Use of these biopsies as baseline provides an epidemiologically sound, temporally correct approach. For Aim 2, in benign and prostate tumor tissue with risk of progression to lethal prostate cancer in men surgically- treated for clinically localized prostate cancer. We will use a PCBN nested case-control study with TMAs developed for testing biomarkers of prostate cancer progression (426 progressors, 426 matched controls). Also, we will evaluate if prevalences of these fibroblasts and associations with lethal disease differ between the tumor microenvironment and benign tissue. For Aim 3, in benign and prostate tumor tissue with risk of further progression to metastasis or prostate cancer death in men surgically-treated and who received salvage therapy for PSA recurrence. We will design a propensity score matched cohort study of 392 men who received salvage RT ±AAT after rising PSA post-prostatectomy and construct TMAs. No such study exists in the PCBN. Also, we will evaluate if these fibroblasts are predictive of response to salvage RT ±AAT versus salvage RT only. In Aim 4, we will determine whether the phenotypic nature, density, and distribution of senescent stromal fibroblasts in benign and prostate tumor tissue differ between matched Black and White men with prostate cancer. We will use TMA sets in the PCBN for Black (N=135) and White (N=135) men matched on clinicopathologic characteristics that were designed to investigate racial differences in prostate biomarkers.

Role: PI

Scientific or financial overlap: This is the current application.

(NEW)

Award: R01 CA255349-01

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

Effort: 2.16 calendar months (18%)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: Justin Birken

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 01/01/2021-12/31/2024

Level of Funding:

Principal Investigators: Elizabeth Platz and Alan Meeker (MPI)

Project Goals: Goal 1 is to inform the pressing clinical need for identifying which men's prostate cancers are very likely to kill and, equally important, which ones are very unlikely to kill. If our hypothesis is confirmed,

information from our work could be incorporated into prognostic tools. Goal 2 is to inform use of novel therapeutics that eliminate senescent stromal fibroblasts in men at risk for progression or harboring metastases. Specific Aims: 1. Evaluate the association between senescent stromal fibroblasts, especially in the presence of stromal inflammation, in prostatectomy tissue and risk of progression to metastatic prostate cancer in men with intermediate and high-risk disease (Cohort 1). 2. Evaluate the association between senescent stromal fibroblasts, especially in the presence of stromal inflammation, in prostatectomy tissue and risk of progression to metastasis or rapidly rising PSA in a second, independent cohort of men with intermediate and high-risk disease (Cohort 2). 3. Determine whether senescent fibroblasts are present in metastases, and if so, their heterogeneity across metastatic sites of bone and soft tissues in men who died of castrate-resistant prostate cancer. We will use a castration-resistant metastatic prostate cancer rapid autopsy series and associated metastatic tissue from multiple lesions from a variety of soft tissues and bone per man.

Role: MPI

Scientific or financial overlap: None.

Award: P30 CA006973-58

Title: Regional Oncology Research Center

Effort: 0.46 calendar months (3.8%)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: Rebecca Brightful

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 05/07/1997-04/30/2022

Level of Funding:

Principal Investigator: William Nelson

Project Goals: This is the core grant that supports the Sidney Kimmel Comprehensive Cancer Center research activities.

Role: Program Co-Leader (Cancer Prevention & Control)

Scientific or financial overlap: None

Award: PR0125 (AACR prime 18-90-52-MICH)

Title: Candidate Immune Markers for Early Detection of Lung Cancer

Effort: 0.97 calendar months (8.1%)

Supporting Agency: American Association for Cancer Research

Name of Procuring Contracting/Grants Officer: via Tufts University School of Medicine – Barbara Gardner

Address of Funding Agency: via Tufts University School of Medicine

Post-Award Research Administration, 136 Harrison Avenue, Boston, MA 02111

Performance Period: 09/01/2018-08/31/2021

Level of Funding:

Principal Investigator: MPI Michaud (Tufts, contact MPI), Platz (MPI), Kelsey (Brown, MPI)

Project Goals and Specific Aims: We propose to: 1) examine whether severe periodontal disease, marked by a mounted immune response to periodontal pathogens, is associated with lung cancer risk, and can modify systemic immune profiles; 2) examine whether immune profiles measured in pre-diagnostic bloods are directly associated with lung cancer risk (even if not impacted by periodontal pathogens); and, 3) examine if immune profiles in bloods 1-4 years prior to cancer diagnosis are associated with a lower survival among those who develop lung cancer.

Role: Multiple Principal Investigator

Scientific or financial overlap: None

Award: R21 CA234436-02

Title: Circulating Antibodies to Oral Microbiota and Colon Cancer Risk

Effort: 0.12 calendar months (1%)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: via Tufts University School of Medicine – Barbara Gardner

Address of Funding Agency: via Tufts University School of Medicine

Post-Award Research Administration, 136 Harrison Avenue, Boston, MA 02111

Performance Period: 03/01/2019-02/28/2022 (NCE)

Level of Funding:

Principal Investigator: Dominique Michaud (Tufts)

Project Goals: We will evaluate if serum antibodies to 8 periodontal pathobionts are associated with colon cancer risk and will assess latency up to 25 years in a prospective study of 200 cases and 200 matched controls nested in a cohort with long follow-up. Additionally, we will optimize an existing method for measuring antibodies to periodontal microbiota in plasma, and then determine the correlation between antibody concentrations in serum and plasma from the same participants over a 15-year time period. Specific Aims: Aim 1 we propose to evaluate if serum antibodies to 8 periodontal pathobionts are associated with colon cancer risk and will assess latency up to 25 years in a prospective study of 200 cases and 200 matched controls nested in a cohort with long follow-up. In Aim 2, we will optimize an existing method for measuring antibodies to periodontal microbiota in plasma, and then determine the correlation between antibody concentrations in serum and plasma from the same participants over a 15-year time period.

Role: subcontract PI

Scientific or financial overlap: None

(NEW)

Award: P30 CA006973-57

Title: Regional Oncology Research Center (Administrative Supplement)

Effort: 0.9 calendar months (7.5%)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: Rebecca Brightful

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 10/01/2020-09/30/2021

Level of Funding:

Principal Investigator: William Nelson

Project Goals: We propose research agenda setting and engagement activities to advance interdisciplinary, population-focused intra- (Cancer Prevention and Control [CPC] Program) and inter- (CPC plus other Programs) programmatic aging and cancer research. These efforts are designed to: 1) stimulate new, innovative cancer prevention and control research at the nexus of aging and cancer and organize funding opportunities responses, 2) cultivate new population science investigators working at the aging-cancer interface, and 3) bring attention to clinical and public health needs for research and translation to practice for older adults at risk for cancer or living with or surviving cancer, including in the catchment area.

Specific Aims: 1) Generate 6 priority aging-cancer research questions that, by design, are highly relevant to the SKCCC's catchment area and are the product of interdisciplinary engagement and bi-directional patient and community engagement, 2) Offer a pilot funding opportunity to spark the prioritized aging-cancer research with an expectation of the submission of subsequent MPI interdisciplinary grant applications, 3) Develop a communications plan to promote the priority research questions and available resources to address the questions, and to bring general attention to clinical and public health needs for research and translation to practice for older adults at risk for cancer or living with or surviving cancer, including in the catchment area, and 4) Programmatically integrate aging/geroscience as theme crossing each Program aim by the time of the site visit for the SKCCC P30 competing renewal application.

Role: Project lead (PI of supplement)

Scientific or financial overlap: None

(NEW)

Award: M00P1601182

Title: Improved Understanding of Cancer Risk Factors and How They Impact the State's Unique Cancer Statistics

Effort: 0.56 calendar months (4.65%)

Supporting Agency: Maryland Department of Health and Mental Hygiene

Name of Procuring Contracting/Grants Officer: Georges C. Benjamin

Address of Funding Agency: 201 W. Preston Street, Room 500 Baltimore, MD 21201

Performance Period: 07/01/2020-06/30/2021

Level of Funding:

Principal Investigators: John Groopman

Project Goals: To provide biostatistical support to JHU investigators conducting CPC research for Developing program project (P01) and multi-principal investigator (MPI) grants pertinent to Maryland, and for addressing an array of cancer-relevant research questions pertinent to Maryland.

Specific Aim: The aim of the Cancer Prevention and Control Biostatistics Core for Research and Proposals is to serve as a needed support core to advance CPC research on cancer problems relevant to Maryland, the SKCCC's catchment area.

Role: Project lead (Cancer Prevention and Control Biostatistics Core for Research and Proposals (Year 3))

Scientific or financial overlap: None

(NEW)

Award: M00P1601182

Title: Periodontal pathogens and risk of cancer in a cohort that includes Marylanders from Washington County

Effort: 0.84 calendar months (7%)

Supporting Agency: Maryland Department of Health and Mental Hygiene

Name of Procuring Contracting/Grants Officer: Georges C. Benjamin

Address of Funding Agency: 201 W. Preston Street, Room 500 Baltimore, MD 21201

Performance Period: 07/01/2020-06/30/2021

Level of Funding:

Principal Investigators: John Groopman

Project Goals: To provide biostatistical support to JHU investigators conducting CPC research for Developing program project (P01) and multi-principal investigator (MPI) grants pertinent to Maryland, and for addressing an array of cancer-relevant research questions pertinent to Maryland.

Specific Aim: The aim of the Cancer Prevention and Control Biostatistics Core for Research and Proposals is to serve as a needed support core to advance CPC research on cancer problems relevant to Maryland, the SKCCC's catchment area.

Role: Project lead (Cancer Prevention and Control Biostatistics Core for Research and Proposals (Year 3))

Scientific or financial overlap: None

Award: T32 CA009314-38

Title: Institutional Research Cancer Epidemiology Fellowship

Effort: 0.12 calendar months (1%)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: Manda Richards

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 07/01/1988-08/31/2021

Level of Funding:

Principal Investigator: Elizabeth Platz

Project Goals: The mission of this program is to train pre-doctoral students and post-doctoral fellows to become leaders at the forefront of advancing the knowledge of a) the causes of cancer, including inherent and modifiable factors, and b) how to prevent cancer by providing a better understanding of cancer-related behaviors and identifying new markers for the early detection of cancer.

Role: Principal Investigator / Training Program Director

Scientific or financial overlap: None

(NEW)

Award: W81XWH-21-1-0295

Title: GSTP1-Positive Subset of Prostate Cancer Over-Represented in African-American Men: Systemic Treatment Implications

Effort: 0.6 calendar months (5%)

Supporting Agency: Department of Defense – Congressionally Directed Medical Research Programs

Grants Officer: Kimberly Carter

Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702

Performance Period: 5/1/2021-4/30/2024

Level of Funding:

Principal Investigator: William Nelson

Major Goals: To test the hypothesis that GSTP1-positive prostate cancers comprise a distinct disease subset, with a discrete phenotype, that is more prevalent in AA men than EA men, and that affects responses to taxane chemotherapy.

Specific Aims: Aim #1: Molecular characterization of GSTP1-positive prostate cancers, using genome, epigenome, and transcriptome sequencing. Aim #2: Ascertain the mechanistic implications of persistent GSTP1 expression, especially persistent GSTP1- I105V expression, for responses of prostate cancers to taxanes used in the treatment of life-threatening prostate cancer. Aim #3: Determine the natural history of GSTP1+ prostate cancers, including the propensity to progress to life-threatening disease.

Role: Co-investigator

Scientific or financial overlap: None

(NEW)

Award: W81XWH-20-1-0254

Title: Deciphering DDX3-mitochondrial axis in prostate cancer ethnic disparity

Effort: 0.48 calendar months (4%)

Supporting Agency: Department of Defense – Congressionally Directed Medical Research Programs

Grants Officer: Kimberly Carter

Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702

Performance Period: 09/01/20 - 08/31/2023

Level of Funding:

Principal Investigator: Venu Raman

Project Goal: The purpose of this grant is to determine if DDX3 expression can be used as a biomarker for aggressive prostate cancers in AA men and if targeting DDX3 will reduce patient morbidity and enhance the quality of life.

Specific Aims: Aim 1: To ascertain DDX3's functions in maintaining mitochondrial integrity and heterogeneity to promote aggressive prostate cancer phenotypes in the African American men. Aim 2: To determine the effect of targeting the DDX3-mitochondrial axis by RK-33 both *in vitro* and *in vivo* models generated from African American and European American prostate cancer samples. Aim 3: To compare African American and European American prostate cancer clinical samples for DDX3 expression that can be associated with aggressive cancer phenotypes.

Role: Co-Investigator

Scientific or financial overlap: None

PENDING

Award: R01CA207110

Title: Prospective immune profiling using methylation markers and pancreatic cancer risk

Effort: 1.2 calendar months (10%)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: TBD

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 09/01/2021-08/31/2025

Level of Funding:

Principal Investigator: Dominique Michaud (Tufts)

Project Goals: Project goals of this competing renewal are to examine whether DNA methylation spanning genomic regions associated with pancreatic cancer risk in a large nested case-control study is replicated in different populations and across different racial groups; whether identified genomic regions that demonstrate stability and consistency in associations over time are causally associated with pancreatic cancer risk; and develop and validate methylomic risk scores to identify high risk individuals for targeted surveillance (using risk markers) or early detection of pancreatic cancer (using early detection biomarkers), pooling data from seven cohort studies to maximize power.

Role: subcontract PI

Scientific or financial overlap: None

Award: R01CA267977-01

Title: Proteomic aging in adults before and after cancer diagnosis

Effort: 1.8 calendar months (15%)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: TBD

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 12/01/2021-11/30/2024

Level of Funding:

Principal Investigator: Anna Prizment (Minnesota)

Project Goals: Project goals are to determine with a protein-based aging clock is associated with risk of cancer in persons without a cancer diagnosis, and with premature mortality and morbidity in cancer survivors.

Role: subcontract PI

Scientific or financial overlap: None

Award: P01 (Assist 872179)

Title: Modifiable Drivers of Expansion and Malignant Transformation from Clonal Hematopoiesis

Effort: 3.0 calendar months (25%)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: TBD

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 09/01/2021-08/31/2026

Level of Funding:

Principal Investigator: Margaret Goodell (Baylor)

Project Goals: The goals of this Program project are to identify modifiable risk factors of clone expansion in clonal hematopoiesis and subsequent malignant transformation, with the ultimate purpose of developing cancer prevention strategies. Specifically, we hope to develop anticipatory guidance — in terms of lifestyle or pharmaceutical interventions — for individuals with clonal hematopoiesis. In Project 3, we will use data and samples from the Atherosclerosis Risk in Communities study to: 1) determine long-term changes in clonal composition at the single-cell level and identify inflammation and DNA damage related factors associated with those changes; 2) evaluate the association of clonal composition, variant allele frequencies (VAFs), and changes of known myeloid malignancy driver genes and novel recurrent variants with hematologic malignancy risk over the span of two decades; and 3) evaluate the association of inflammation- and DNA damage-related factors with hematologic malignancy risk in persons with detectable clonal variants.

Scientific or financial overlap: Projects in the P01 and Leukemia & Lymphoma Society have some scientific and associated effort overlap. If both were to be funded, overlapping activities would be eliminated and effort would be adjusted as aligned with those changes.

Award: SCOR-20649-20

Title: Modifiable Drivers of Expansion and Malignant Transformation from Clonal Hematopoiesis

Effort: 3.0 calendar months (25%)

Supporting Agency: Leukemia & Lymphoma Society

Name of Procuring Contracting/Grants Officer: TBD

Address of Funding Agency: 3 International Drive, Suite 200 Rye Brook, NY 10573

Performance Period: 09/01/2021-08/31/2026

Level of Funding:

Principal Investigator: Margaret Goodell (Baylor)

Project Goals: The goals of this Program project are to identify modifiable risk factors of clone expansion in clonal hematopoiesis and subsequent malignant transformation, with the ultimate purpose of developing cancer prevention strategies. Specifically, we hope to develop anticipatory guidance — in terms of lifestyle or pharmaceutical interventions — for individuals with clonal hematopoiesis. In Project 3, we will use data and samples from the Atherosclerosis Risk in Communities study to: 1) determine long-term changes in clonal composition at the single-cell level and identify inflammation and DNA damage related factors associated with those changes; 2) evaluate the association of clonal composition, variant allele frequencies (VAFs), and changes of known myeloid malignancy driver genes and novel recurrent variants with hematologic malignancy risk over the span of two decades; and 3) evaluate the association of inflammation- and DNA damage-related factors with hematologic malignancy risk in persons with detectable clonal variants.

Scientific or financial overlap: Projects in the P01 and Leukemia & Lymphoma Society have some scientific and associated effort overlap. If both were to be funded, overlapping activities would be eliminated and effort would be adjusted as aligned with those changes.

Award: R01ES033662-01

Title: The Impact of Metal Exposure on Cancer Incidence and Mortality among White and Black Adults

Effort: 1.8 calendar months (15%)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: Barbara Gittleman

Address of Funding Agency: Office of Grants Administration, National Institute of Environmental Health Science, P.O. Box 12233, Research Triangle Park, North Carolina USA 27709

Performance Period: 12/01/2021-11/30/2026

Level of Funding:

Principal Investigator: Miranda Jones

Project Goals: Project goal is to evaluate the association of exposure to metals, including arsenic, cadmium, chromium, lead and nickel, individually and as mixtures, with cancer incidence and mortality among White and Black adults.

Role: Co-investigator

Scientific or financial overlap: None

In the event that all pending grants are funded, effort would be reduced on other pending grants, such that total effort is 12 calendar months or less.

PREVIOUS

(CHANGE)

Award: U01 CA152813-10

Title: Glycoprotein Biomarkers for Early Detection of Aggressive Prostate Cancer

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: Angela Walters

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 09/01/2010-03/31/2021

Level of Funding:

Principal Investigator: Hui Zhang

Project Goals: The goal of this project is to provide a method to reliably distinguish aggressive prostate cancer from non-aggressive prostate cancer using available biomarkers. This will result in a significant decrease in unnecessary suffering among prostate cancer patients and a reduction in unnecessary health care expenditures.

Specific Aims. Aim 1, we will analyze urinary glycoproteins from patients with aggressive cancer and non-aggressive cancer using high throughput glycoproteomics and mass spectrometry to identify glycoproteins associated with aggressive prostate cancer. In Aim 2, we will validate the identified candidate urinary glycoproteins by targeted analysis of candidate glycoproteins from additional urine samples in independent testing sets of prostate cancer urine specimens from the EDRN network. In Aim 3, we will develop highly sensitive, specific, and high throughput ELISA or mass spectrometry based selective reaction monitoring assays as noninvasive urine tests using the glycoprotein biomarkers identified and validated from Aim 1 and Aim 2 and validate the performance of the tests for aggressive prostate cancer biomarkers. We will further determine the clinical utility of the validated tests to detect patients with aggressive prostate cancer in active surveillance program. In Aim 4, we will develop and optimize the immunohistochemistry assays for the glycoproteins associated aggressive prostate cancer tissues and validate these tissue glycoproteins using tissue microarrays. We will then further determine the clinical utility of the immunohistochemistry assays as biopsy based tissue tests for the early detection of patients with aggressive prostate cancer in active surveillance program. If successful, the identified and validated biomarkers will be tested by EDRN biomarker reference laboratory (BRL) and clinical validation center (CVC) in retrospective and prospective studies.

Role: Co-investigator

Award: W81XWH-12-1-0170

Title: Prospective Evaluation of Intraprostatic Inflammation and Focal Atrophy as a Predictor of Risk of High-Grade Prostate Cancer and Recurrence after Prostatectomy

Supporting Agency: Department of Defense

Name of Procuring Contracting/Grants Officer: Lance L. Nowell

Address of Funding Agency: U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702-5014

Performance Period: 07/01/2012-06/30/2016

Level of Funding:

Principal Investigator: Elizabeth Platz

Project Goals and Specific Aims: We are evaluating the following with respect to risk high-grade prostate cancer: 1) The association of a) extent of inflammatory infiltrates, and b) type of immune cells present in benign prostate tissue with subsequent risk of prostate cancer, especially high-grade disease. 2) The association of a) extent and morphologic type of focal atrophy, and b) biological characteristics in benign prostate tissue with subsequent risk of prostate cancer, especially high-grade disease. With respect to risk of prostate cancer recurrence, we are evaluating the following: 3) The association of a) extent of inflammatory infiltrates, and b) type of immune cells present in benign and malignant prostate tissue with subsequent risk of prostate cancer recurrence. 4) The association of a) extent and morphologic type of focal atrophy, and b) biological characteristics in benign prostate tissue and near cancer with subsequent risk of prostate cancer recurrence.

Role: PI

Award: W81XWH-12-1-0545

Title: Realizing the Translational Potential of Telomere Length Variation as a Tissue-based Prognostic Marker for Prostate Cancer

Supporting Agency: Department of Defense

Name of Procuring Contracting/Grants Officer: Tom Winter

Address of Funding Agency: 820 Chandler Street, Ft. Detrick, MD 21702

Performance Period: 09/30/2012-09/26/2017

Level of Funding:

Principal Investigator: Elizabeth Platz

Project Goals: The goals are to validate and optimize a novel tissue biomarker of prognosis in men with clinically localized prostate cancer that we recently identified – telomere length variability in prostate cancer cells combined with short telomere length in cancer-associated stromal cells (the telomere biomarker). Specific Aims: (1) Optimize the method for assessing telomere length by FISH using a high-throughput approach to yield a test feasible for use in the clinical setting; (2) Validate our findings in two other cohort studies on prostate cancer outcomes: a) Men surgically treated and followed for lethal prostate cancer, and b) Men surgically treated and followed for prostate cancer recurrence; (3) Determine optimal cut points for the telomere biomarker for predicting prognosis.

Role: PI

Award: U01CA164975-6

Title: Enhancing ARIC Infrastructure to Yield a New Cancer Epidemiology Cohort

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: Ashley Utter

Address of Funding Agency: Office of Grants Administration, National Cancer Institute
9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 05/15/2012-04/30/2019

Level of Funding:

Principal Investigator: Elizabeth Platz

Project Goals: The goal of the project is to enhance the infrastructure of ARIC, the Atherosclerosis Risk in Communities cohort, to yield a new Cancer Epidemiology Cohort that brings novel features to cancer epidemiology research. Specific aims: 1) Prospectively ascertain cancer incidence, recurrence/progression, and mortality beginning in 2012. 2) Retrospectively ascertain and characterize cancers and identify recurrence/progression, 1987-2011.

Role: PI

Award: P50CA058236-22

Title: SPORC in Prostate Cancer: Developing telomere length variation as a prognostic test for prostate cancer

Effort: 3.73 calendar months

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: Ashley Utter

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

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

Level of Funding:

Principal Investigator: Samuel Denmeade

Project Goals: Conduct a nested case-control study to verify the association between the telomere biomarker, assessed using automated TELL-FISH, and risk of lethal prostate cancer, determine optimal outpoints to refine the telomere biomarker for prognosis, and evaluate whether prevalence of the refined telomere biomarker differs across age, race, and other patient characteristics. Specific Aims: 1) Demonstrate the validity and reproducibility of automated “TELL-FISH”, our FISH-based telomere length measurement tool, and re-estimate the association between the telomere biomarker and prostate cancer death in the same prospective HPFS cohort study. 2) Conduct a nested case-control study to verify the association between the telomere biomarker, assessed using automated TELL-FISH, and lethal prostate cancer, including in men with Gleason 7 disease, a group for whom clinical management decisions are not always clear. 3) Determine optimal cut points to refine the telomere biomarker for prognosis using the prospective cohort and nested case-control studies of lethal prostate cancer from Aims 1 and 2. 4) Evaluate whether the prevalence of the refined telomere biomarker from Aim 3 differs by age, race, and body mass index (BMI) in cross-sectional and nested case-control studies.

Role: Project Leader

Award: JHU Provost's Discovery Award

Title: Development and characterization of a novel, statin-mediated approach to overcome immune suppression in prostate cancer

Effort: 0.12 calendar months

Supporting Agency: Johns Hopkins University

Name of Procuring Contracting/Grants Officer: Chasmine Stoddart-Osumah

Address of Funding Agency: 265 Garland Hall, 3400 North Charles Street, Baltimore, Maryland 21218

Performance Period: 07/01/2018-12/31/2019 (NCE)

Level of Funding:

Principal Investigator: Fan Pan and Elizabeth Platz, MPIs

Project Goals: We will conduct studies to determine the effects of statins on Tregs suppression, YAP localization, and prostate cancer progression; and assess anti-tumor immunity and prostate tumor growth following immunotherapy with and without a statin. Specific Aims. 1. In vitro, test the effects of statin drugs on Treg suppression of T cell response and YAP localization in Tregs. 2. In a mouse model, test the difference in anti-tumor immunity and prostate tumor growth between a commonly used immunotherapy with and without a candidate statin. 3. In human prostate cancer tissue and cancer-associated stroma, test the difference in abundance of total Tregs (FoxP3+), Tregs with nuclear YAP, T helper cells (CD4+), and T effector cells (CD8+) between statin users and non-users. 4. In men surgically treated for prostate cancer, evaluate the association between the abundance of Tregs with nuclear YAP and subsequent risk of disease progression.

Role: MPI

Meeker, Alan K.

CURRENT

(THIS GRANT)

Award: W81XWH-20-1-0264

Title: Evaluating senescent stromal fibroblasts as a promoter of prostate cancer lethality to inform a paradigm shift in prognostic, predictive, therapeutic strategies

Effort: 2.8 calendar months (23.3% effort)

Supporting Agency: Department of Defense – Congressionally Directed Medical Research Programs

Grants Officer: Kimberly Carter

Address of Funding Agency: 820 Chandler St. Fort Detrick, MD 21702-5014

Performance Period: 05/01/2020-04/30/2023

Level of Funding:

Principal Investigator: Elizabeth Platz

Project Goals: Our goal is to determine whether senescent prostate stromal fibroblasts, especially those with the senescence-associated secretory phenotype (SASP), promote lethal prostate cancer, and are more prevalent in Black men.

Specific Aims: For Aim 1, in pre-diagnostic (benign) prostate biopsy tissue with risk of prostate cancer in men at risk. We will generate a case-cohort study (320 subcohort) sampled from a prospective cohort of 2,584 men from the PCPT placebo arm without clinical indication who underwent end-of-study biopsy per trial protocol and negative for prostate cancer by linkage with claims data up to 17 years later. Use of these biopsies as baseline provides an epidemiologically sound, temporally correct approach. For Aim 2, in benign and prostate tumor tissue with risk of progression to lethal prostate cancer in men surgically- treated for clinically localized prostate cancer. We will use a PCBN nested case-control study with TMAs developed for testing biomarkers of prostate cancer progression (426 progressors, 426 matched controls). Also, we will evaluate if prevalences of these fibroblasts and associations with lethal disease differ between the tumor microenvironment and benign tissue. For Aim 3, in benign and prostate tumor tissue with risk of further progression to metastasis or prostate cancer death in men surgically-treated and who received salvage therapy for PSA recurrence. We will design a propensity score matched cohort study of 392 men who received salvage RT ±AAT after rising PSA post-prostatectomy and construct TMAs. No such study exists in the PCBN. Also, we will evaluate if these fibroblasts are predictive of response to salvage RT ±AAT versus salvage RT only. In Aim 4, we will determine whether the phenotypic nature, density, and distribution of senescent stromal fibroblasts in benign and prostate tumor tissue differ between matched Black and White men with prostate cancer. We will use TMA sets in the PCBN for Black (N=135) and White (N=135) men matched on clinicopathologic characteristics that were designed to investigate racial differences in prostate biomarkers.

Role: Co-I

Scientific or financial overlap: This is the current application.

(NEW)

Award: R01 CA255349

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

Effort: 3.0 calendar months (25.0% effort)

Supporting Agency: NIH/NCI

Performance Period: 09/01/2020-08/31/2024

Level of Funding:

Principal Investigators: Elizabeth Platz and Alan Meeker (MPI)

Project Goals: Goal 1 is to inform the pressing clinical need for identifying which men's prostate cancers are very likely to kill and, equally important, which ones are very unlikely to kill. If our hypothesis is confirmed, information from our work could be incorporated into prognostic tools. Goal 2 is to inform use of novel therapeutics that eliminate senescent stromal fibroblasts in men at risk for progression or harboring metastases.

Specific Aims: Aim 1. Evaluate the association between senescent stromal fibroblasts, especially in the

presence of stromal inflammation, in prostatectomy tissue and risk of progression to metastatic prostate cancer in men with intermediate and high-risk disease (Cohort 1). In this case-cohort study, men who received hormone, chemo-, or radiation therapy before or after surgery but before the detection of metastasis by imaging were excluded to be able to address how biomarkers are associated with outcome without interference by treatment subsequent to prostate removal during follow-up. Aim 2. Evaluate the association between senescent stromal fibroblasts, especially in the presence of stromal inflammation, in prostatectomy tissue and risk of progression to metastasis or rapidly rising PSA in a second, independent cohort of men with intermediate and high-risk disease (Cohort 2). This case-cohort study also excludes men treated before surgery, but differs from Cohort 1 by retaining men treated after surgery, but before detection of metastasis, and by including an earlier lethal event (rapidly rising PSA). If our hypothesis is confirmed, we will determine prognostic performance of senescent stromal fibroblasts, and assess whether their addition enhances performance of existing, but imperfect cancer cell-based genomic prognostic tests. We expect that this stromal biomarker (reflecting tumor microenvironment) will be complementary to cancer-based biomarkers. The Decipher test (GenomeDx) has been evaluated in Cohort 1 and the Prolaris test (Myriad Genetics) has been evaluated in Cohort 2. Aim 3. Determine whether senescent fibroblasts are present in metastases, and if so, their heterogeneity across metastatic sites of bone and soft tissues in men who died of castrate-resistant prostate cancer. We will use a castration-resistant metastatic prostate cancer rapid autopsy series and associated metastatic tissue from multiple lesions from a variety of soft tissues and bone per man.

Role: MPI

Scientific or financial overlap: None

(NEW)

Award: DOD W81XWH-18-1-0496

Title: The role of ATRX/DAXX loss in NF1-associated Solid Malignancies

Effort: 1.0 calendar months (8.3% effort)

Supporting Agency: Department of Defense – Congressionally Directed Medical Research Programs

Name and Address of Grants Officer: Jason Kuhns; 820 Chandler Street, Fort Detrick, MD 21702

Performance Period: 08/15/2018-08/14/2021

Level of Funding:

Principal Investigator: F. Rodriguez

List of Specific Aims and Project's Goal: The goal of this project is to study the effect of ATRX or DAXX loss in the context of NF1-associated tumors and identify targeted therapies. Specific Aims: (1) Understand how ATRX loss and altered telomeres facilitate tumorigenesis in the context of NF1 inactivation in human and murine glioma models; (2) Define the role of ATRX/DAXX loss and altered telomeres in NF1-associated malignant peripheral nerve sheath tumors; (3) Identify novel pharmacological approaches for NF1-associated tumors with ATRX/DAXX loss.

Role: Co-Investigator

Scientific or financial overlap: None

(NEW)

Award: U01 DA040325

Title: Effects of HIV, Cocaine, and Prolonged ART Use on Subclinical Cardiovascular Disease

Effort: 1.0 calendar months (8.3% effort)

Supporting Agency: NIH/NIDA

Name and Address of Grants Officer: Not applicable

Performance Period: 06/01/2018-05/30/2023

Level of Funding:

Principal Investigator: Shenghan Lai (University of Maryland Baltimore)

List of Specific Aims and Project's Goal: The major goal of this project is to study the effects of HIV, cocaine use, and prolonged ART use on subclinical cardiovascular disease. Specific Aim 4: To investigate whether HIV and cocaine are associated with telomere shortening.

Role: Co-Investigator; Aim 4

Scientific or financial overlap: None

Award: R01 DA044184

Title: Development & malleability from childhood to adulthood

Effort: 0.5 calendar months (4.2% effort)

Supporting Agency: NIH/NIDA

Name and Address of Grants Officer: Penny Greene penny.greene@nih.gov

Performance Period: 08/01/2018 – 05/31/2023

Level of Funding:

Principle Investigator: Nicholas Ialongo

Project Goals: The overall objectives of this proposal are to examine the phenotypic and genetic moderators and mediators of developmental and intervention outcomes in the JHU Preventive Intervention Research Center (JHU PIRC) intervention trial, a randomized controlled trial of early preventive interventions that feature follow-up from childhood into adulthood. To study whether the variation we observe in intervention and developmental outcomes is a function of genes, gene-environment interactions, and gene-environment-intervention interactions.

Specific Aims: (1). To model the extent to which adaption to the developmental challenges of young adulthood in the educational, work, romantic relationships, and family contexts varies as a function of the interplay between genetic and phenotypic factors, including the interventions and family, peer group, school, and neighborhood characteristics; (2) To model variation in the onset and course (and cessation) of substance use/abuse/dependence, antisocial behavior, psychiatric symptoms/disorders, high risk sexual behavior and sexually transmitted infections as a function of the interplay between genetic and phenotypic factors, including the interventions and family, peer group, school, and neighborhood characteristics; (3). To assess potential epigenetic effects in terms of the change in telomere length and telomerase activity over the ages of 31-35 as a function of concurrent and prior measures of accumulative stress, perceived racial discrimination, substance use, anxiety, and depression in adolescence and young adulthood (ages 11-26). To also assess whether the interventions, particularly the FSP intervention, moderate the effects of these factors on telomere length and telomerase activity in adulthood through their earlier impacts on responsive/supportive parenting in childhood and adolescence

Role: Co-investigator

Scientific or financial overlap: None

Award: P30 CA006973

Title: Regional Oncology Research Center

Effort: 1.7 calendar months (14.2% effort)

Supporting Agency: NIH/NCI

Name of Procuring Contracting/Grants Officer: Rebecca Brightful

Address of Funding Agency: Office of Grants Administration, National Cancer Institute, 9609 Medical Center Drive, West Tower, Rockville, MD 20850

Performance Period: 05/07/1997-04/30/2022

Level of Funding:

Principal Investigator: William Nelson

Project Goals: This is the core grant that supports the Sidney Kimmel Comprehensive Cancer Center research activities.

Role: Director, Oncology Tissue and Imaging Services

Scientific or financial overlap: None

COMPLETED

Award: P50 CA058236

Title: Developing Telomere Length Variation as a Prognostic Test for Prostate Cancer

Time Commitment: 1.2 calendar months

Supporting Agency: NIH/NCI

Name and Address of Grants Officer: Not applicable

Performance Period: 09/01/13-08/31/19

Level of Funding:

Principal Investigator: William Nelson

Project Goal: To validate and develop automated telomere length quantification in a high throughput manner in clinical specimens for potential translation.

Specific Aims: 1) Demonstrate the validity and reproducibility of automated "TELI-FISH", our FISH-based telomere length measurement tool, and re-estimate the association between the telomere biomarker and prostate cancer death in the same prospective HPFS cohort study. 2) Conduct a nested case-control study to verify the association between the telomere biomarker, assessed using automated TELI-FISH, and lethal prostate cancer, including in men with Gleason 7 disease, a group for whom clinical management decisions are not always clear. 3) Determine optimal cut points to refine the telomere biomarker for prognosis using the prospective cohort and nested case-control studies of lethal prostate cancer from Aims 1 and 2. 4) Evaluate whether the prevalence of the refined telomere biomarker from Aim 3 differs by age, race, and body mass index (BMI) in cross-sectional and nested case-control studies.

Role: Co-investigator.

Award: R01 CA184926

Title: Driver gene induced inflammation in pancreatic cancer development

Time Commitment: 0.6 calendar months

Supporting agency: NIH/NCI

Name and Address of Grants Officer: Shannon Silkensen, NIH, BG 6116 Rm 7003, 6116 Executive Blvd, Rockville, MD 20852

Performance Period: 05/01/2014-04/30/2018

Level of Funding:

Principal Investigator: Elizabeth Jaffee

Project Goals: To profile changes in the Tumor Inflamed Microenvironment following anti-cancer vaccine treatment targeting mutated Ras oncogene.

Specific Aims: (1) we will identify and characterize the phenotype and function of procarcinogenic inflammatory cell populations that are initiated by mutated Kras before and after vaccination with *Listeria monocytogenes* (LM) bacteria genetically engineered to express mutated Kras (LM-Kras). (2) we will perform a genetic and epigenetic analysis of suppressive cell versus anti-PanIN immune populations isolated from mouse and human PanINs. (3) we will combine the LM-Kras vaccine with the DNA hypomethylating drug 5aza- dC (DAC) and test for a synergistic anti-tumor effect.

Role: Co-Investigator

Award: R01 CA172380

Title: Determining the roles of ATRX and DAXX abnormalities in cancer telomere biology

Time Commitment: 4 calendar months

Supporting Agency: NIH/NCI

Name and Address of Grants Officer: Not applicable

Performance Period: 1/3/2013-12/31/17

Level of Funding:

Principal Investigator: Alan Meeker

Project Goals: To elucidate the roles of defective ATRX and DAXX in the ALT phenotype, with an eye towards exploiting these defects for potential therapeutic purposes.

Specific Aims: (1) Test the hypothesis that a loss of ATRX or DAXX will lead to reduced heterochromatin at the telomeres resulting in telomere instability, increased telomeric recombination and induction of the ALT telomere maintenance pathway; (2) Test the hypothesis that conditional ablation of *Daxx* in pancreatic islet cells will facilitate the development of pancreatic neuroendocrine tumors (PanNETs), and that the resulting tumors will exhibit telomere instability and engage the ALT telomere maintenance pathway; (3) Test the hypothesis

that an unbiased, in vitro cellular toxicity screen using an established chemical compound library will reveal synthetic lethality specific to ALT-positive cells, or cells in which ATRX or DAXX has been abrogated.

Role: PI.

Award: W81XWH-12-1-054S Award PC112061

Title: Realizing the Translational Potential of Telomere Length Variation as a Tissue-based Prognostic Marker for Prostate Cancer

Time Commitment: 1.2 calendar months

Supporting Agency: Department of Defense

Name and Address of Grants Officer: Not applicable

Performance Period: 09/30/2012-09/26/2017

Level of Funding:

Principal Investigator: Elizabeth Platz

Project Goals: The goals are to validate and optimize a novel tissue biomarker of prognosis in men with clinically localized prostate cancer that we recently identified – telomere length variability in prostate cancer cells combined with short telomere length in cancer-associated stromal cells (the telomere biomarker).

Specific Aims: (1) Optimize the method for assessing telomere length by FISH using a high-throughput approach to yield a test feasible for use in the clinical setting; (2) Validate our findings in two other cohort studies on prostate cancer outcomes: a) Men surgically treated and followed for lethal prostate cancer, and b) Men surgically treated and followed for prostate cancer recurrence; (3) Determine optimal cut points for the telomere biomarker for predicting prognosis.

Role: Co-Investigator

Award: CDMRP W81XWH-12-PCR-P-TIA Prostate Cancer Transformative Impact Award

Title: Toward the Practice of Precision Medicine: A Biomarker Validation Coordinating Center

Time Commitment: 1.2 calendar

Supporting Agency: Department of Defense

Name and Address of Grants Officer: Not applicable

Performance Period: 09/01/2013-08/31/16

Level of Funding:

Principal Investigator: Howard Scher

Project Goals: The central objective is to form a centralized Biomarker Development Coordinating Center that synchronizes the infrastructure of biomarker discovery platforms (i.e., NCI Prostate Cancer SPOREs, PCF and SU2C), existing pathology resources (i.e., the Prostate Cancer Biorepository Network (PCBN), Prostate SPOREs), academic and commercial assay validation efforts, and clinical trial design and management (i.e., PCCTC) will accelerate the validation and qualification of integral biomarkers, dramatically improving the effectiveness of treatments for advanced prostate cancer.

Specific Aims: 1) To cross-validate an initial set of assays for biomarkers corresponding to the AR and PI3K/PTEN axes ready for near-term filing with the FDA for use in prospective integral biomarker-driven trials in prostate cancer. 2) To use the centralized infrastructure of the Assay Validation Coordinating Center to cross-validate additional assays for biomarkers identified via established and emerging discovery platforms (i.e., NCI Prostate Cancer SPOREs, PCF, SU2C, and TCGA) for use in prospective integral biomarker-driven trials in prostate cancer.

Role: Co-investigator

Award: R01CA143299

Title: MicroRNAs in Advanced Prostate Cancer: A miR-21 Model

Time Commitment: 0.54 calendar months

Supporting Agency: NIH

Name and Address of Grants Officer: Teresa Parker Reeser

Performance Period: 07/01/10-04/30/15

Level of Funding:

Principal Investigator: Shawn Lupold

Project Goals: The goals of this project are to characterize the miR-21 signaling pathway in prostate cancer and evaluate its expression in disease progression.

Specific Aims: 1.) To identify the upstream signaling pathways which regulate the miR-21 gene locus 2.)

Identify the Downstream Pathways regulated by miR-21 in prostate cancer 3.) Quantify the Expression and

Copy number of miR-21 gene products in prostate cancer progression.

Role: Co-Investigator

Award: NIH-NCI 5R01 CA132996-03

Title: Telomere Dysfunction, Chromosome 9 Instability and Bladder Cancer Risk.

Time Commitment: 0.6 calendar months

Supporting Agency: NIH

Name and Address of Grants Officer: REID, BRITT C.

Performance Period: 09/01/09-07/31/14

Level of Funding:

Principal Investigator: Ye Zheng

Project Goals: The main goals of the project are to ascertain whether individuals with short telomeres have an increased susceptibility to bladder cancer and if short telomeres on chromosome 9p or 9q increase the likelihood of chromosome 9 alterations and risk of bladder cancer.

Specific Aims: (1) to determine the association between bladder cancer risk and overall telomere length of blood lymphocytes and determine if telomere length exerts differential effects on bladder cancer risk in non-smokers and smokers separately; (2) to determine the association between bladder cancer risk and chromosome 9 specific telomere lengths of blood lymphocytes and determine if chromosome 9 telomere lengths exert differential effects on bladder cancer risk in non-smokers and smokers separately; (3) to evaluate effects of interactions between environmental exposures (i.e., tobacco smoking or SH infection) and the telomere lengths on bladder cancer risk; (4) to determine if chromosome 9 telomere lengths are associated with chromosome 9 aberrations in bladder tumors and determine whether the association of chromosome 9 telomere length and bladder cancer risk differs by tumor chromosome 9 aberration status

Role: Collaborator