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TITLE: Elevated Uracil Glycosylase Coupled to Reduced Base Excision Repair Promotes AA PCa Progression

PRINCIPAL INVESTIGATOR: Natalie R. Gassman

CONTRACTING ORGANIZATION: University of Alabama, Birmingham, AL

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14. ABSTRACT

African American (AA) males have a higher incidence of PCa, are more likely to be diagnosed at a younger age, and often present with more advanced and aggressive disease. While there are risk factors associated with the development of AA PCa, we lack detailed mechanisms about the unique tumor biology in AA PCa, which contributes to the disparity in outcomes from these patients. We have established a cross-disciplinary research team containing experts in DNA damage, PCa and health disparities, PCa clinical management and prostate pathology to address the Prostate Cancer Research Program's overarching challenges *to define the biology of lethal prostate cancer to reduce death* and *to develop treatments that improve outcomes for men with lethal prostate cancer with the long-term goal of reducing the disparity in survival outcomes for AA PCa patients*.

We are leveraging clinical data from AA and EA tumors to develop improved cell line models that recapitulate metabolic and DNA repair differences seen in patient samples. We will use these models to dissect biological features unique to AA tumors that may allow targeted therapeutic intervention in the near future. The mechanistic data generated by this proposal will support the targeted use of PARP inhibitors for AA PCa patients that show dysregulated BER from metabolic reprogramming.

15. SUBJECT TERMS

prostate cancer, base excision repair, metabolism, DNA repair, DNA damage, clinical biomarker, uracil, mitochondria, folate metabolism

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INTRODUCTION: African American (AA) men have an approximately 60% higher incidence of prostate cancer (PCa) and are at >2 times the risk of dying of PCa than their European American (EA) counterparts [1-3]. Importantly, active duty military AA men had more than two-fold greater incidence of PCa diagnosis compared to their white counterparts [4]. While the contributors to this difference are multifactorial in nature, research has demonstrated an association between West African ancestry and PCa risk [5-8]. Beyond racial comparison, we have identified critical differences in DNA repair pathways in the prostate tumors from AA and EA men, particularly changes in the base excision repair (BER) pathway[9]. Using a novel method to measure DNA damage, we observed a significant increase in uracil lesions within the genome of AA tumors. Parallel immunofluorescence analysis also revealed significantly elevated expression of Uracil-DNA glycosylase (UNG). This enzyme detects uracils within the DNA, cleaves the glycosidic bond, and primes base excision repair (BER). Subsequent recruitment of the X-ray cross complementing 1 (XRCC1) and DNA polymerase β complex completes repair to restore genomic fidelity. Interestingly, XRCC1 expression was significantly reduced in AA tumors. Low XRCC1 expression is associated with defective BER [10-13], resulting in genomic instability and, more importantly, response to poly(ADP-ribose) polymerase (PARP) inhibitors [14-16]. These data suggest unique DNA damage pathway alterations in AA PCa promoting tumor progression. This proposal will examine the biological drivers associated with changes in the DNA repair pathways, with a focus on metabolic changes that will increase the uracil nucleotide pool and incorporation of uracil lesions. Additionally, it will confirm changes in the BER pathway associated with tumor aggressiveness and explore the targeted use of PARP inhibitors to exploit these BER defects and improve cell killing.

KEYWORDS: prostate cancer, base excision repair, metabolism, DNA repair, DNA damage, clinical biomarker, uracil, mitochondria, folate metabolism

ACCOMPLISHMENTS:

1) **What were the major goals of the project?**
   a) **Aim 1: Examine the role of increased *de novo* pyrimidine biosynthesis and reduced folate cycle in elevated uracil DNA damage and uracil glycosylase expression in AA PCa.** Using innovative mass spectrometry-based metabolic imaging, we will measure metabolic intermediates of the folate cycle and the *de novo* pyrimidine synthesis and the expression of pathway enzymes in ancestry-verified AA and EA TMAs and correlate the data to the uracil DNA damage, UNG and XRCC1 expression in preliminary findings. Ancestry-verified cell models will be cultured in low folate or engineered for inducible knockdown of serine hydroxymethyltransferase 2 (SHMT2, to block the synthesis of 5,10-methylenetetrahydrofolate) or dihydroorotate dehydrogenase (DHODH, to block *de novo* pyrimidine biosynthesis) along with their respective rescues and examined for changes in uracil DNA damage and UNG expression.

      We have received IACUC and ACURO approval for the animal studies associated with this work (**Major subtask 1**). We have also conducted preliminary imaging mass spectrometry on the patient samples to examine uracil and other metabolite imbalance (Major task 2, subtask 1). We are also in the process of characterizing the genetically engineered cell lines (Major task 2, subtask 2). Altogether, we have completed 30% of Aim 1.

   b) **Aim 2: Evaluate the phenotypic and molecular consequences of elevated uracil glycosylase and reduced BER in AA PCa using *in vitro* and *in vivo* models.** Ancestry-verified AA and EA PCa cell lines will be used to study the combined effects of increased UNG and impaired BER (due to decreased XRCC1), independent of metabolic changes. Cell models will be genetically altered to recapitulate the patient findings of increased UNG and decreased XRCC1 or modified to restore UNG and XRCC1 levels and BER function. DNA damage levels and associated phenotypic consequences of altered XRCC1 and UNG expression, including tumor progression, metastasis, and sensitivity to PARP inhibitors, will be examined.

      We have received IACUC and ACURO approval for the animal studies associated with this work (**Major subtask 1**). We are also in the process of characterizing the genetically engineered cell lines for their DNA repair capacity and susceptibility to PARP inhibitors (**Major task 5 and 6**). Altogether, we have completed 40% of Aim 1.

2) **What was accomplished under these goals?**

The major activities for this reporting period were characterizing the genetically engineered cell lines to ensure they recapitulate the patient findings.

We have characterized the BER complement within the PCa patient cell lines (Figure 1). As noted in CHANGES, we have changed our EA cell model to be more representative of castration-resistant prostate cancer. We have also included a mixed-race cell line 22RV1. As shown in Figure 1, we see changes in BER protein expression across the cell line panel. For these selected cell lines, the MDA-MB-2A with a luciferase reporter incorporated, referred to as 2A-Luc, shows highly elevated XRCC1 compared to the other cell lines. This is within the range of expression we observed within the patient TMA but does not recapitulate the low XRCC1 phenotype we are looking to exploit for PARP inhibitor synergy. Additionally, we see changes in POLβ and UNG expression. For the patient TMA, we observed a significant increase in the expression of Uracil-DNA glycosylase (UNG). The *UNG* gene utilizes different promoters and alternative splicing to generate two protein isoforms, namely, UNG1 and UNG2[17]. UNG1 and UNG2 share high protein sequence identity with differences only in ~40 amino acids at the N-terminus, which dictates the isoforms' localization to the mitochondria and the nucleus, respectively[17]. The high consensus in the enzyme makes differentiating UNG1 from UNG2 in archival patient tumor samples difficult by immunohistochemistry. However, we can now see the isoform expression differences within the tumor cell lines. Surprisingly, we see increased expression of UNG1 in the AA and mixed-race cell lines compared to EA PCa cells and a non-tumorigenic EA prostate cell line.

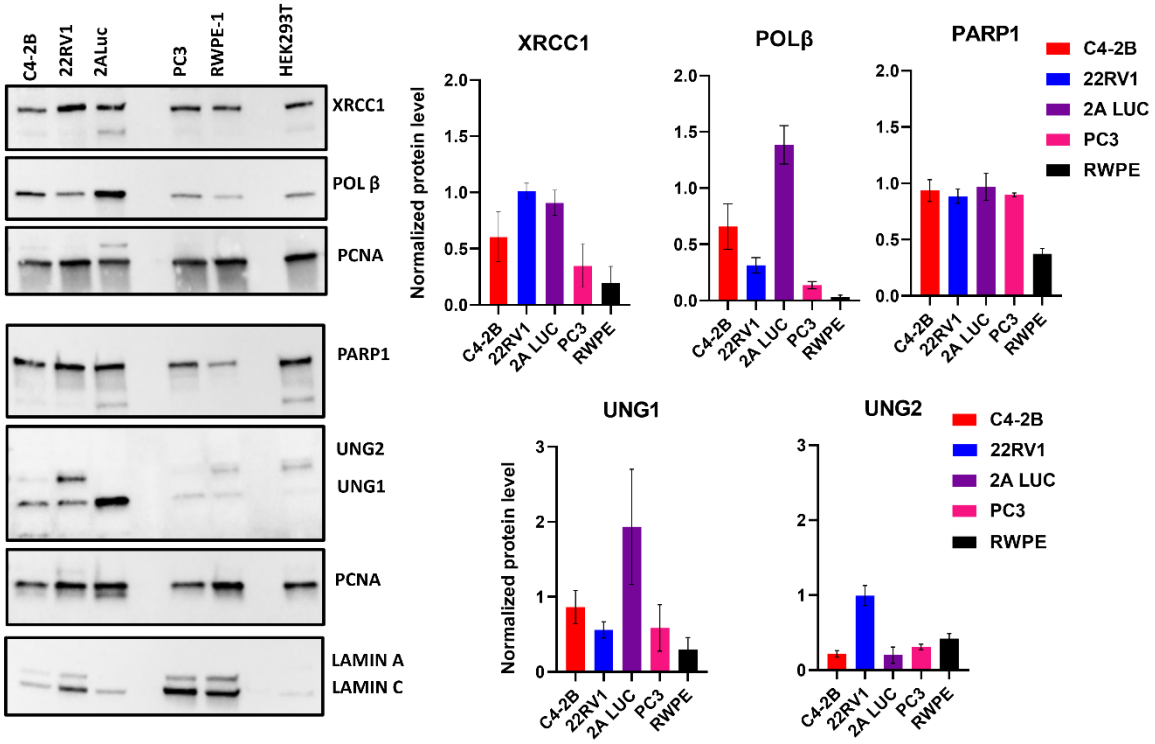

Figure 1. Immunoblot characterization of the base excision repair proteins within the PCa model cell lines.

Besides uracil, UNG1 and UNG2 recognize uracil derivatives in DNA generated from the oxidation of cytosine by hydroxyl radical attack or other oxidative processes such as isodialuric acid, alloxan and 5-hydroxyuracil[18]. Differential expression between the two protein isoforms has not been previously reported in prostate or other cancers. Elevation of the UNG1 isoform has been reported following hydrogen peroxide (H_2O_2) treatment, indicating a potential regulatory role for oxidative stress in UNG1 expression[19]. UNG1's localization to the mitochondria and its role in removing oxidation products of cytosine suggests it defends against increasing mitochondrial DNA oxidative lesions in cells. Elevated UNG1 in AA PCa tumors may offer protection against oxidative stressors improving cancer cell survival and driving prostate cancer aggressiveness in AA men compared to EA men. With the increased expression of UNG1 in AA compared to EA PCa cell models, the UNG isoform switch likely contributes to the low levels of oxidative lesions we observed in AA compared to EA cells[9].

To recapitulate the low XRCC1 expression in the AA patient samples, we used CRISPR to knockout XRCC1 in the C4-2B, 22RV1, and 2A-luc cells. We have validated knockouts and confirmed they are deficient in BER function, using the classic BER alkylating agent methyl methane sulfonate. We have also tested the sensitivity of the parental knockout cell lines to PARP inhibitors olaparib and rucaparib (Figure 2). We are continuing to screen knockout clones for the 2A-Luc cells, but we have one validated clone we are testing. Loss of XRCC1 significantly enhances sensitivity to the PARP inhibitors; however, the sensitivity differs between cell lines and is influenced by the cell background (Figure 2). We are currently evaluating known resistance mechanisms for PARP inhibitors within these models to understand other potential biological drivers.

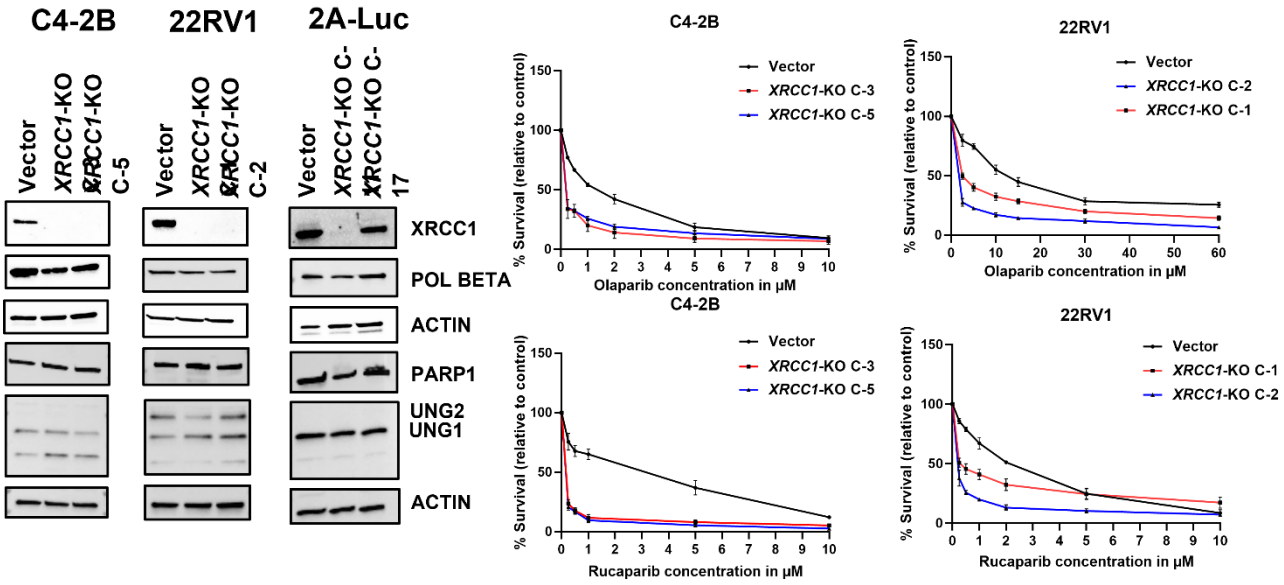

Figure 2. Immunoblot characterization of XRCC1 knockout in PCa cell lines. We are continuing to screen for 2A-luc knockouts to have two per cell model. Sensitivity of parental and XRCC1 knockout cell lines to PARP inhibitors.

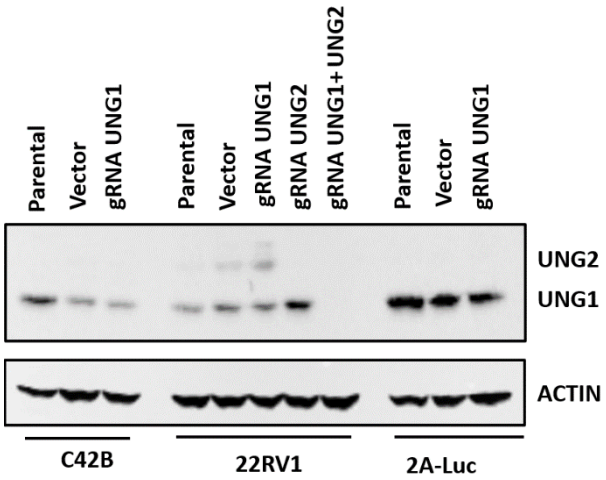

Figure 3. Immunoblot of the UNG gRNA testing for the PCa cell lines. UNG1+2 was effective in 22RV1.

Along with XRCC1, we also need to modulate UNG expression. Given the isoform switching, we redesigned our original knockout strategy for UNG to remove UNG1 and UNG2 from the cell lines. We have acquired CRISPR constructs for both UNG1 and UNG2 from Dr. Bodil Kavli, an expert in the specificity and function of UNG isoforms[20]. We are testing the gRNA for the prostate cell lines, and we have observed the gRNAs for UNG1 and UNG2 do not work as effectively in the prostate cells, as was reported for U2OS and HeLa cells in the original publication (Figure 3)[20]. We are proceeding with the double knockout to test both UNG1 and UNG2 rescue independently. We are also examining sequence and copy number changes for UNG in the cell lines to understand prostate specific differences.

We have sent the XRCC1 knockout and parental cell lines to Baylor for metabolic mass spectrometry analysis. Baylor has also received the patient data has part of Aim1 from Tempus and is working on analyzing the data. They are also working on the construction of the SHMT and DHDOH cell lines, which will be sent to the Gassman lab for DNA repair analysis.

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

We recently presented the preliminary findings from this work in a poster for AACR. The postdoctoral fellow presented the poster and interacted with key researchers in the cancer field to understand the clinical landscape for the treatment of prostate cancer and how PARP inhibitors are being

employed. Dr. Gassman is also a Health Disparities Research Education Fellow for 2022-2023 through the Minority Health Equity Research Center at UAB through a U54 partnership with Morehouse School of Medicine, Tuskegee University, and UAB. Her postdoctoral fellow will apply for the program for 2023-2024 to enhance her training, expertise, and skills in health disparities research.

4) **How were the results disseminated to communities of interest?**
Nothing to Report.

5) **What do you plan to do during the next reporting period to accomplish the goals?**
During the next reporting period, we map changes in the de novo pyrimidine biosynthesis and folate cycle for the XRCC1 and UNG1/2 altered cell lines. We are also conducting preliminary experiments to examine the invasion and migrations of these cells. For the DHODH and SHMT2 cell lines, we will map changes in DNA repair proteins and perform RADD analysis on the DNA adduct content within these constructs. We have already shared the XRCC1 cell lines with Baylor to begin the animal studies for tumor growth characteristics. The next 12 months will focus on finalizing the characterization of the cell lines and transitioning into animal experiments for evaluating the clinical use of PARP inhibitors. Our preliminary data shows significant enhancement in PARP inhibitor sensitivity, so we are also combing prostate cancer expression databases to confirm the prevalence of low XRCC1 to use as a biomarker.

IMPACT:

1) **What was the impact on the development of the principal discipline(s) of the project?**
Nothing to Report.

2) **What was the impact on other disciplines?**
Nothing to Report.

3) **What was the impact on technology transfer?**
Nothing to Report.

4) **What was the impact on society beyond science and technology?**
Nothing to Report.

CHANGES/PROBLEMS:

We originally proposed to use ancestry-verified LNCaP and VCaP cell lines as the EA cell models. Since PARP inhibitors are being explored for castration-resistant and metastatic prostate cancer, we have updated the EA models to C4-2B and 22RV1. The inclusion of these cell lines improves our clinical translational ability.

PRODUCTS:

1. **Publications, conference papers, and presentations-** We have submitted "Spatial mapping of the DNA adducts in cancer" to *DNA Repair Journal,* where it is currently under revision. We also presented "Race-associated base excision repair defects alter DNA damage landscape in prostate cancer" at the 2023 AACR annual meeting in Orlando.

2. **Website(s) or other Internet site(s)-** Nothing to report

3. **Technologies or techniques-** Nothing to report

4. **Inventions, patent applications, and/or licenses-** Nothing to report

5. **Other Products-** Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

1. **What individuals have worked on the project?**
   UAB

Name:	Natalie Gassman
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-8488-2332
Nearest person month worked:	1.8
Contribution to Project:	Dr. Gassman has coordinated and supervised the cell work, conducted RADD analysis, analyzed data and prepared publications and posters for the work.
Funding Support:	n/a

Name:	Dongquan Chen
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-5006-5342
Nearest person month worked:	0.6
Contribution to Project:	Dr. Chen is providing the TCGA and other database analysis and is continuing in those efforts. He has also overseen the data extract parameters for patient analysis.
Funding Support:	n/a

Name:	Kaveri Goel
Project Role:	Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3.6
Contribution to Project:	Dr. Goel has engineered the cell lines, conducted drug sensitivity studies, is characterizing the tumor characteristics of the cell lines. She is analyzing the data with Dr. Gassman and preparing manuscripts for the work.
Funding Support:	n/a

Name:	Manoj Sonavane
Project Role:	Scientist
Researcher Identifier (e.g. ORCID ID):	0000-0002-3215-830X
Nearest person month worked:	0.4
Contribution to Project:	Dr. Sonavane has characterized cell lines and performed RADD analysis. He also worked with the postdoctoral fellow and transferred the genetic engineering to her.
Funding Support:	n/a

Baylor

Name:	Arun Sreekumar
Project Role:	Subaward PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6
Contribution to Project:	Dr. Sreekumar will be responsible for the metabolic studies and molecular characterization studies (in vitro and in vivo) proposed in Aims 1 and 2
Funding Support:	n/a
Name:	Michael Ittmann
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.3
Contribution to Project:	Dr. Ittmann will provide pathology and biorepository support for the study.
Name:	Sai Thota Manohar
Project Role:	Postdoc Associate
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	6
Contribution to Project:	The Postdoc Associate Sai Thota will be responsible for carrying out all the metabolic and molecular (in vitro and in vivo) analysis proposed in Aim 1 and 2. He will report to Dr. Sreekumar.
Funding Support:	n/a
Name:	Arpit Rao
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.3
Contribution to Project:	Dr. Rao will develop the phase Ib/II trial of biomarker-selected prostate cancer patients to prospectively investigate the role of our proposed biomarker in inducing PARP inhibitor sensitivity. In the current application, he will provide access to datasets from AA and EA patients treated with PARP inhibitors.
Funding Support:	n/a

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

   New other support documents reflecting the active grants have been provided.

   Dr. Gassman received subaward funding through a NASA/TRISH grant.

   Dr. Sreekumar received R01 CA267090, a V-foundation award T2022-014, and R01AI165563 during the funding cycle.

   Dr. Ittman had a number of grants become inactive, not new awards are reported.

3. **What other organizations were involved as partners?** Baylor College of Medicine.

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Previous/Current/Pending Support

Natalie R. Gassman

1. Previous Support

a. R00 ES023813 (Gassman, PI) 12/01/15-11/30/18 NIH/NIEHS,

Bisphenol A modulation of DNA repair triggered by environmental genotoxic stress
This work characterized the modulation of DNA repair proteins by bisphenol A.

Aim 1: Characterize the suppression DNA repair by BPA exposure. During my mentored
Aim 2: Evaluate the effects of co-exposure of BPA with DNA damaging agents in repair-deficient cells.
Aim 3: Determine if BPA suppression of BER stimulates increased genomic instability.

Overlap: none
Effort: 9.0CM

Grant Agency Contact NIEHS
Name: Shaughnessy, Daniel

Email: shaughn1@niehs.nih.gov
Address: 111 TW Alexander Dr
Durham, NC 27709

b. R21 ES028015 (Gassman, Co-PI) 9/1/17 –11/30/19; NIH/NIEHS,

Co-detection of DNA adduct and methylation sites as predictive biomarkers for exposures
This work developed a DNA adduct detection methodology and multiplexes it with epigenetic marks to examine the role of exposure in cancer.

Overlap: none
Effort: 1.2CM

Specific Aim 1: Multiplexed detection of DNA adducts and epigenetic marks in cells and fixed tissue
Specific Aim 2: Multiplexed genomic mapping of UV-induced DNA adducts and epigenetic marks

Grant Agency Contact NIEHS
Name: Shaughnessy, Daniel

Email: shaughn1@niehs.nih.gov

Address: 111 TW Alexander Dr
Durham, NC 27709

c. R21 AT009908 (Migaud, PI) 05/01/2018-10/31/2020 NIH/NCCIH

B-vitamins and NAD metabolism, or when vitamin B3's bioavailability is not enough.
Identify physiologically relevant combinations of B-vitamins that may restore mitochondrial function through enhanced bioavailability of vitamin B1, B2 and B3 derived cofactors.

Overlap: none
Effort: 1.2CM

Aim 1: We will quantify the relative impact of vitamin B1 and B2 deficiency on the vitamin B3 metabolome and the impact of NAD^+ deficiency on the vitamin B1 and B2 metabolome in liver and kidney cells by:
Aim 2: We will establish which combination of vitamins B1, B2 and B3 deficiency contributes "first and foremost" to the collapse of mitochondrial function in mammalian cells and how NR allows for the cells to transiently delay such outcomes. Comparing NAD^+ precursors' supplementation under normal versus vitamin B1 and/or B2 partial deficiency, we will:

Grant Agency Contact NCCIH
Name: Wang, Yisong

Email: yisong.wang@nih.gov
Address: Division of Extramural Research, NCCIH
6707 Democracy Boulevard II, Suite 401
Bethesda, MD 20892
(Courier Service - 20817)

d. Celebrate Hope Developmental/Pilot Awards (Gassman, PI) 01/01/2020-12/31/2020, Mitchell Cancer Institute

DNA damage as a predictive biomarker for therapeutic response in ovarian cancer
This work is applying a novel DNA damage detection assay to tissue samples from ovarian cancer patients to validate its use as a prognostic marker for treatment response.

Overlap: none
Effort: 1.2CM

Specific Aim 1: Establish a scoring system for RADD that can be used clinically to stratify patients.

Specific Aim 2: Measure DNA damage levels in archived and fresh epithelial ovarian cancer (EOC) tumor samples, including matched pairs of pre and post neoadjuvant chemotherapy.

Grant Agency Contact MCI
Name: Pierson, Milton

Email: mpierson@southalabama.edu
Address: 1660 Springhill Ave
Mobile, AL 36604-1405

e. Innovation Award (Gassman, Co-PI) 01/01/2020-3/31/2021, Breast Cancer Research Foundation of Alabama

Blockade of CHK1 and EGFR signaling in triple negative breast cancer to enhance anti-tumor efficacy
This work is testing the combination of two small molecule inhibitors to induce cell death in triple negative breast cancer.

Overlap: none
Effort: 0.24CM

Aim 1: Combination of prexasertib and EGFR inhibition reduces tumor growth in murine xenograft models of TNBC.
Aim 2: Dual blockade of CHK1/2 and EGFR reduces cell proliferation, increases DNA damage, and promotes apoptosis in tumors.

Grant Agency Contact BCRFA
Name: Bradner, Elizabeth

Email: bbradner@uab.edu
Address: Breast Cancer Research Foundation of Alabama
PO Box 531225
Birmingham, AL 35253

f. 75715-LS-RIP (Gassman, PI) 06/1/2020-5/31/2021, Defense University Research Instrument Program

Multi-Well Extracellular Flux Analyzer for Mitochondrial Stress Arrays
This grant funds the purchase of a Seahorse Xe96 Analyzer.

Overlap: none
Effort: 0%, equipment purchase only

Project 1: Metabolic reprogramming induced by environmental exposures
Project 2: Metabolic reprogramming induced by imbalances in energy related B-vitamins
Project 3: The role of vitamin B3 in ovarian cancer recurrence

Grant Agency Contact U.S. Army Research Office
Name: Strand, Micheline

Email: micheline.k.strand.civ@mail.mil
Address: P.O. Box 12211
Research Triangle Park, NC 27709-2211

g. Pilot Award (Gassman, PI) 01/01/2021-12/31/2021, Breast Cancer Research Foundation of Alabama

Targeted nanoparticle delivery to reduce STAT3 and improve cell killing in triple negative breast cancer
This work is testing targeted nanoparticle packaging of STAT3 inhibitors and siRNA for the treatment of breast cancer.

Overlap: none
Effort: 0.24CM

Aim 1: Targeted nanoparticles improve cell killing of STAT3 siRNA and pharmacological inhibitors.
Aim 2: Targeted nanoparticles reduce tumor growth and metastases in a xenograft model.

Grant Agency Contact BCRFA
Name: Bradner, Elizabeth

Email: bbradner@uab.edu
Address: Breast Cancer Research Foundation of Alabama
PO Box 531225
Birmingham, AL 35253

2. Current Support

a. R01ES032450 (Gassman, PI) 11/19/21-10/15/2025 NIEHS

Dihydroxyacetone exposure induces metabolic reprogramming and mitochondrial dysfunction
This work is examining the exposure effects of dihydroxyacetone.

Overlap: none
Effort: 3.6CM

Aim 1: DHA incorporation into metabolic pathways alters glycolysis and induces glycosylation protein damage.

Aim 2: DHA exposure alters NAD(P)H pools to induce oxidative stress.
Aim 3: DHA exposure alters cytosolic Ca^{2+} levels and disrupts mitochondrial function.

Grant Agency Contact NIEHS
Name: Shaughnessy, Daniel

Email: shaughn1@niehs.nih.gov
Address: 111 TW Alexander Dr
Durham, NC 27709

b. W81XWH2110596 (Gassman, PI) 12/15/21-12/14/2024 DoD OCRP

DNA damage as a predictive biomarker for immunotherapy response in ovarian cancer
This work is using paralleling and immunotherapy clinical trial to determine if RADD is a predict biomarker for immunotherapy response.

Overlap: none
Effort: 3.0CM

Specific Aim 1: Measure DNA damage levels in tumor samples.
Specific Aim 2: Correlate DNA damage levels, therapeutic response, and disease outcome for the current standard of care and the immunotherapy Vigil.

Name: Neagley, Melanie
Email: melanie.a.neagley.civ@health.mil
Address: 1077 Patchel St
Fort Detrick, MD 21702

c. W81XWH2210135 (Gassman, PI) 4/15/22-4/14/2025 DoD PCRP

Elevated uracil glycosylase coupled to reduced base excision repair promotes AA PCa progression
This work is metabolomics and DNA repair capacity measurements to determine the biological determinants of PCa and develop treatment strategies tailor to these differences.

Overlap: none
Effort: 1.8CM

Specific Aim 1: Examine the role of increased *de novo* pyrimidine biosynthesis and reduced folate cycle in elevated uracil DNA damage and uracil glycosylase expression in AA PCa.
Specific Aim 2: Evaluate the phenotypic and molecular consequences of

elevated uracil glycosylase and reduced BER in AA PCa using *in vitro* and *in vivo* models.

Grant Agency Contact
Name: Mishra, Nrusingha
Email: nrusingha.mishra.civ@health.mil
Address: 1053 Patchel St, Room 114
Fort Detrick, MD 21702-5024

d. T0702 (Migaud, PI) 4/01/2023 – 3/31/2025 NASA

Controlling NAD(P) Hyper-oxidation to Regulate Repair and Maintenance Processes in Humans in Space
This work examines the biological role of ox-NAD in cells.

Aim 1. Define the impact of mimicking spaceflight-induced stress on ox-NAD(P) levels and their derivatives in human cells in a 2D and a 3D tissue context.
Aim 2. Define the impact of alterations in ox-NAD(P) levels on metabolism, ROS, proteostasis (transcription and translation), and DNA damage in human cells.
Aim 3. Evaluate the reversible and protective effect of reducing ox-NAD(P) levels with nicotinamide riboside in human cells under space stressor conditions and in a clinical trial.

Overlap: none
Effort: 0.6CM

Grant Agency Contact
Name: Donoviel, Dorit
Email: donoviel@bcm.edu
Address: Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030

e. No Number (Gassman, PI) start date: 08/15/2021 UAB (internal)

UAB Startup/Recruitment Funds
These funds are used to support the faculty research program.

Overlap: none
Effort: 0

3. Pending Support

a. TX220232 (Gassman, PI) 09/30/2023-09/29/2026 Department of Defense Toxic Exposures Research Program

Electronic cigarette use increases mitochondrial dysfunction and susceptibility to airborne exposures
The proposed work will establish the physiological effects of inhaled DHA and its co-exposure effects with BPA and PFOA.

Aim 1: Systemic DHA alters metabolic pathways and induces mitochondrial dysfunction in pulmonary and cardiac tissues.
Aim 2: Co-exposures of DHA with pervasive airborne pollutants like BPA or PFOA increase metabolic and mitochondrial dysfunction *in vitro* and *in vivo.*

Overlap: none
Effort: 1.2CM

Program officer: currently unassigned

b. R33CA278508 (Gassman, PI) 01/01/2024 – 12/31/2027 NIH/NCI

Spatial mapping of the DNA damage landscape in cancer
This work is developed a method to spatial map DNA lesions within tumor using machine learning and multiplex fluorescent probes.

Aim 1. Spatial detection of DNA adducts within clinically relevant tissue samples
Aim 2. Measurement of DNA adducts within the mitochondrial genome

Overlap: none
Effort: 1.2CM

Program officer: Rao Divi, divir@mail.nih.gov

c. RSG-23-1152800 **(Gassman, PI)** 01/01/2024-12/31/2028 American Cancer Society Research Scholar Grant

Hyperglycemia induces reprogramming of base excision repair in breast cancer
The proposed work will examine the role of obesity and diabetes in DNA reprogramming in breast cancer.

Specific Aim 1: Glucose promotes STAT3 activation and overexpression of DNA repair proteins, leading to transformation and more aggressive phenotypes
Specific Aim 2: Hyperglycemia promotes chemoresistance through the dysregulation of DNA repair proteins

Overlap: none
Effort: 0.6 CM

Program officer: currently unassigned

OTHER SUPPORT

SREEKUMAR, ARUN

Positions/Scientific Appointments:

2019- present	Co-Leader, Cell Signaling and Metabolism Program, NCI designated Dan L Duncan Comprehensive Cancer Center.
2019- present	Director Center for Translational Metabolism and Health Disparities
2023-2026	Visiting Faculty (unpaid, awaiting clearance from BCM) Department of Bioscience, Sri Sathya Sai Institute for Higher Learning, Prasanthigram, Puttaparthi, Andhra Pradesh, India
2016- present	Professor, Tenured; Baylor College of Medicine (BCM), Houston, TX
2011- present	Associate Professor, Tenured; Baylor College of Medicine (BCM), Houston, TX
2011- present	Academic Director; Metabolomics, Alkek Center for Molecular Discovery, BCM, Houston, TX

PREVIOUS

RP150451 (Sreekumar) 03/01/15 – 02/31/18 1.2 calendar
CPRIT
SRC-2 driven "metabolic switch" in metastatic prostate cancer- prognostic and therapeutic implications.
Goals: To define the metabolic alterations associated with SRC2 action in Castrate Resistant Prostate Cancer.
POC: Michael Brown / mbrown@cprit.state.tx.us

5 U01 CA167234-03 (Sreekumar) 08/01/12 – 07/31/17 1.8 calendar
NCI
Metabolomic profiling and biologic basis of racial disparity in prostate cancer
Goals: definitively define and compare the PCa metabolome of AA and EA men and uncover the biological mechanism in an ancestry-verified subset of AA and EA prostate cancers. To functionally characterize the race-associated metabolic pathways and evaluate the pathway-associated metabolites in urine specimens from AA and EA men with prostate cancer.
Grant Specialist: Rosemary Ward / wardros@mail.nih.gov

GA-2014-136 (Dacso) 05/27/14 – 05/26/19 1.2 calendar
CASIS
Goal: To develop methods to detect metabolites in biofluids with the longer term goal of applying this to studies in the International Space station.
POC: John Schubert / jschubert@iss-casis.org

1 U01 CA179674-01A1 (Sreekumar) 09/01/14 – 08/31/19 1.8 calendar
NIH
Delineating racially distinct metabolic pathways in triple negative breast cancer
Goals:
Aim 1: Validate elevated levels of unsaturated fatty acids and lipids in AA TN BCa. Aim 2: Functionally characterize the pathways leading to accumulation of 2-OHG and arachidonic acid in AA TN BCa using in vitro and in vivo models. Aim 3: Measure the serum levels of metabolites in tryptophan, unsaturated fatty acids (including arachidonic acid) and 2-HG pathway in AA TN BCa.
POC: Bryann E Benton / bentonb@mail.nih.gov

5 R01 HD076980-02 (Richards) 05/01/14 – 04/30/19 0 calendar
NIH/NICHD
Goal: To identify small molecules that bind to FSH receptors in ovarian follicles using mass spectrometry.

Grant Specialist: Teri A Pailen / pailent@mail.nih.gov

1 R01 CA184208-01A1 (Frigo) 01/27/15 – 12/31/19 0.6 calendar
NIH (Subcontract with University of Houston
Genetic and metabolic dissection of the camkk alpha signaling axis in prostate cancer
Goals: To study the metabolic pathways regulated by camkk alpha signaling axis in prostate cancer. This grant was scored at 4th percentile and is awaiting funding after the council meeting.
POC: Kelley A Smith / smithka3@mail.nih.gov

1127430-RSG-15-105-01-CNE (Putluri) 07/01/15 – 06/30/19 0.6 Calendar.
American Cancer Society (ACS)
Elucidating the Role of Xenobiotic Metabolism in Bladder Cancer Progression
Aim1: Define stage specific profiles of key xenobiotic metabolites in bladder cancer. Aim2: Define the regulation and function of AOX1 in bladder cancer. Aim 3 : Develop a prognostic panel of urinary xenobiotic metabolites.
POC: Susanna Greer /sgreer@gsu.edu

1 U01 CA179674-01A1 (Sreekumar) 09/01/14-02/29/2020 (NCE) 1.8 calendar
NIH
Delineating racially distinct metabolic pathway in triple negative breast cancer
Aim 1: To validate elevated levels of unsaturated fatty acids and lipids in AA TN BCa; Aim 2: to functionally characterize the pathways leading to accumulation of 2OHG and arachidonic acid AA TN BCa using in vitro and in vivo models; Aim 3: to measure the serum levels of metabolites in tryptophan, unsaturated fatty acids (including arachidonic acid) and 2-HG pathway in AA TN BCa
POC: Bryann E Benton / bentonb@mail.nih.gov

Metabolomics Initiative (Sreekumar) 04/01/15 – 10/30/20 0.6 calendar
Diana Helis Henry Medical Research Foundation
Goal: To establish a lipidomics facility for Cancer Research
POC: David A Kerstein, President / 228 St Charles Ave Ste 912, New Orleans LA 70130-2616

2 P30 CA125123-09 (Osborne) 07/01/15-06/30/2020 1.2 calendar
NIH/NCI
Baylor College of Medicine
The purpose of this shared resource is to provide investigators with cost effective, state-of-the-art instrumentation and specialized expertise for analysis of metabolomics with the goal to identify novel metabolic biomarkers and pathways with application in prevention, diagnosis and treatment of cancer.
POC: Shafik, Hasnaa / Shafikh@mail.nih.gov

R01CA227559 S1 CURE supplement (Sreekumar/Palapattu) 09/01/2020-08/31/2021 0.6 calendar
NIH/NCI Metabolic Rewiring
Promotes AA PCa by Regulating Stromal-Epithelial Interaction
Goal: To support training of under-represented postdoctoral trainee
POC:: Taneshia Knight Shelton Email: taneshia.shelton@nih.gov

R01CA227904 S1 (Sreekumar) 08/01/2020-07/31/2021 0.6 calendar
NIH/NCI
AADAT in Breast Cancer Health Disparity

Goal: To test if elevated AADAT promotes tumor progression by instilling a SR tumor microenvironment in AA TNBC by regulating immune infiltration and energy metabolism; and targeting AADAT has the potential to convert a "cold" tumor into a "hot," therapeutically receptive tumor.
POC: Funmi Elesinmogun / elesinmf@mail.nih.gov

Prostate Cancer Foundation (Jones and Sreekumar) 10/01/2017- 12/31/2021(NCE) 0.6 calendar
PCF
Clinico-pathological correlation & molecular signature identification & risk stratification of prostate cancer in African American U.S. Veterans, with & without exposure to battlefield chemicals.
Goals: Metabolomics of PCa in AA and EA Veterans. The subtasks include 1) To establish metabolomic profiles for distinguishing likelihood of aggressive clinical behavior of the prostate carcinoma at biopsy, 2) identifying metabolic programs affected by exposure to battle field chemicals, and 3) building metabolite-based prognostic markers to monitor castration therapy in metastatic patients
POC: Audrey Gardner / agardner@pcf.org

RP170005 (Edwards) 12/01/16-11/30/21 1.2 calendar
Cancer Prevention Research Institute of Texas (CPRIT) Tumor Metabolomics Core Facility
To establish a cancer metabolomics core facility at Baylor College of Medicine to support
POC: Michael Brown / mbrown@cprit.state.tx.us

1R01CA216426-04 (Putluri) 04/01/18-03/31/23 0.36 calendar
NIH Identify the DNA adduct and associated metabolic alterations in bladder cancer of smokers
1) Verify elevated level of DNA adducts, xenobiotic and methylated metabolites and, their pathways in smokers with BCa 2) To determine the interplay between smoke-induced alteration in methylation and DNA repair in promoting BCa 3) Quantify levels of smoke-associated DNA adducts, methylated and xenobiotic metabolites in urine of BCa patients with a longer term goal of developing a first-generation non-invasive panel of markers for BCa risk assessment among smokers.
POC: Funmi Elesinmogun / elesinmf@mail.nih.gov,

1R01CA220297-05 (Putluri) 06/05/17-05/31/22 0.6 calendar
NIH
Racial disparity in bladder cancer and identification of altered metabolism in African American compare to European bladder cancer.
1) characterize the mitochondrial associated metabolites in AA and EA BCa 2) Verify the D-2HG and associated enzymes (GLS, ADHFE1, and IDH1/2) in BCa patients and establish a therapeutically targeted deregulation pathway for glutamine metabolism in AA BCa. 3) Assess the levels of lyso PC and PC and the function of their metabolizing enzymes PLA1A and LRAT in AA BCa.
POC: Dr. Willis, Kristine Amalee; email: kristine.willis@nih.gov

P01 DK113954-05 Core B (O'Malley) 07/01/18- 04/30/23 1.08 calendar
NIDDK
Nuclear Receptors and their Coactivators as Mediators of Systems Metabolism
Goal: Serve as a metabolomics core component for the P01 grant.
CORE B (METABOLOMICS COMPONENT).
The core will provide expertise in measurement of steady state levels of metabolites and their flux in cell lines and in tissue extracts isolated from a variety of genetically engineered mouse models..
POC: Christina Coriz; Email: corizc@niddk.nih.gov;

CURRENT

RP210227 (Edwards) 08/31/21 -8/30/26 0.6 calendar Cancer Prevention Research Institute of Texas (CPRIT)
Tumor Metabolomics Core Facility
To establish a clinical cancer metabolomics core facility at Baylor College of Medicine to support analysis of clinical and patient derived xenograft samples.
Role-Co-I
POC: Michael Brown / mbrown@cprit.state.tx.us

Agilent Mass Spectrometry (Sreekumar) 08/04/17- 08/3/23 (1st yr NCE) 0 calendar Center for Excellence

This grant funds development of non-invasive metabolic markers in serum/plasma and urine for cancer detection and prognosis.
POC: Sudharshana Seshadiri /Sudharshana_Seshadiri@agilent.com

R01CA227904 (Zhang and Sreekumar) 09/01/19-08/31/24 1.8 calendar NIH/NCI
Rewired Metabolism Regulates Vessel Normalization and Immunosuppression
Goal: Aim 1: To determine the mechanisms underpinning AADAT's immunosuppressive functions in various immunocompetent breast cancer and melanoma models. Aim 2: Determine mechanism of action of AADAT by modulating intra-tumoral HIF1α signaling axis. Aim 3 Determine if genetic depletion or pharmacological inhibition of AADAT sensitizes breast cancer and melanoma to immune checkpoint blockade therapies (ICBT).
POC: Funmi Elesinmogun / elesinmf@mail.nih.gov

R01CA227559 (Sreekumar and Palapattu) 07/01/19-06/30/24 1.2 calendar NIH/NCI
Metabolic Rewiring Promotes AA PCa by Regulating Stromal-Epithelial Interaction
The major goals of this project are to determine the biochemical mechanism leading to inosine accumulation in AA PCa; evaluate the role of inosine in modulating AA tumor epithelial-stromal interactions; evaluate ratio of pre-treatment inosine to adenosine (surrogate for ADA) in plasma as a predictive marker for biochemical recurrence (BCr) in ancestry-verified AA men with PCa.
POC: Funmi Elesinmogun / elesinmf@mail.nih.gov

1R01NS110838-01A1 (Chinnaiyan) 11/01/19-10/31/24 0.6 calendar
National Institutes of Health Developing therapeutic strategies
to elicit metabolic synthetic lethality in glioblastoma The goal is to provide direction
and expertise in the metabolomics studies.
POC: Ada O'donnell / odonnella@mail.nih.gov

2 P30 CA125123-14 (Heslop) 08/14/20 – 06/30/25 0.36 calendar NIH/NCI
Baylor College of Medicine Cancer Center Program: Cell Signaling and Metabolism Program
The goal is to develop an integrated Cancer Metabolism program in the Dan L Duncan Comprehensive Cancer Center
POC: Shafik, Hasnaa / Shafikh@mail.nih.gov

W81WXH-21-1-0154 DOD Early Investigator Award (Krieger) 05/01/21-04/30/23 0 calendar
Department of Defense
The Role of ERRalpha-PGC1alpha-driven Mitochondrial Alterations Define the Biological Basis of Prostate Cancer Disparities in African Americans
This early investigator research award is to support my postdoctoral research project in relation to ERRalpha and PGC1alpha and their roles in driving alterations in mitochondria and how this affects prostate cancer disparities between African American and European American prostate cancer patients.
POC: Juan A. Rodriguez / juan.a.rodriguez236.civ@mail.mil
R01 CA267090-01 (Sreekumar/Rustveld) 04/01/22 - 03/31/27 1.2 calendar
NIH/NCI
Elevated homocysteine in African American Prostate Cancer: Association with Diet and Dietary practices, evaluating its biomarker potential, and characterizing its tumor promoting function.
Major Goals: Aim 1. Determine the mechanistic underpinnings associated with PCa progression promoted by elevated homocysteine.
Aim 2. Evaluate the biomarker potential of homocysteine, methionine and vitamin B6 for early non-invasive detection of PCa in AA men, and examine the association of elevated homocysteine with diet and dietary practices in AA men.
POC: Shakeeya Eaddy/Shakeeya.eaddy@nih.gov
W81XWH2210135 - PC210240 (Gassman/Sreekumar) 04/15/22-04/14/25 0.6
calendar Department of Defense
Elevated Uracil Glycosylase Coupled to reduced Base Excision Repair Promotes AA PCa Progression
The goal is to characterize differences in DNA Repair pathways and their metabolic regulation in AA and EA PCa.
POC: Joshua L. Disbennett, Email: joshua.l.disbennett.civ@mail.mil

S10 PAR-21-126 (Sreekumar) 02/01/22 – 01/31/23 0 calendar
NIH
ORBITRAP ID-X TRIBRID MASS SPECTROMETER FOR UNBIASED GLOBAL METABOLOMICS PROFILING
The goals is to obtain a high resolution, high speed and highly sensitive mass spectrometer for the Metabolomics Core at Baylor College of Medicine to establish unbiased in vivo metabolic flux assays.
Grant Specialist: Gavin Wilkom, NHLBI, email: gavin.wilkom@nih.gov

T2022-014 (Sreekumar) 08/01/22 - 08/01/25 0.6 calendar
V-Foundation

Development of CLIA-certified non-invasive metabolic markers for early detection of prostate cancer in African American Men
The goal is to establish a first-in-field panel of metabolic markers for early detection of PCa in AA men, addressing an unmet need in racial disparities.
POC:: Carole C. Wegner, PhD, Senior Vice President, Research and Grants Administration, the V Foundation for Cancer Research, email: grants@v.org

5R01HL152605-03 (Reddy) 5/10/20 – 4/30/24 0.6 calendar

NIH/NHLBI

COPII dependent regulation of T cell alloimmunity
The goal of this project is to gain insights in the cell biology of intracellular ER to Golgi transport mechanisms in regulation of T cell mediated alloimmunity
POC: Ronald Caulder, NHLBI, email: caulderr@nhlbi.nih.gov

7R01AI165563-02 (Reddy) 6/13/22 – 5/31/27 0.6 calendar
NIH/NIAID

Intestinal tissue intrinsic mechanisms in regulation of GI GVHD
The goal is to understand the role of ISC metabolism in regulation of GVHD severity
POC: ASHLEY COLETTE Ranellone, NIAID, email : ranelloneac@niaid.nih.gov

PENDING
None

IN-KIND

I do not have in-kind contribution related to this current grant proposal.

However, I have listed the In-Kind Contribution associated with my laboratory research which is not part of this proposal.

1) Summary of In-Kind Contribution: 6495 Triple Quadrupole Mass Spectrometer by Agilent Technologies, Santa Clara
Status of Support: Active
Primary Place of Performance: Baylor College of Medicine
Project/Proposal Start and End Date (MM/YYYY): 04/01/2022 – 10/31/23
Person Months (Calendar/Academic/Summer) per budget period: N/A
Estimated Dollar Value of In-Kind Information

3) Summary of In-Kind Contribution: Institutional support for the Center for Translational Metabolism and Health Disparities (C-TMH)
Status of Support: Active
Primary Place of Performance: Baylor College of Medicine
Project/Proposal Start and End Date (MM/YYYY): BCM-C-TMH-02/01/2022 – 06/31/23
Person Months (Calendar/Academic/Summer) per budget period: N/A
Estimated Dollar Value of In-Kind Information:

3) Summary of In-Kind Contribution: Salary Supported by Charles C Bell Jr. Endowment
Status of Support: Active
Primary Place of Performance: Baylor College of Medicine
Project/Proposal Start and End Date (MM/YYYY): 04/01/2019 – Present
Person Months (Calendar/Academic/Summer) per budget period: ~5.3 CM
Estimated Dollar Value of In-Kind Information:

***Overlap (summarized for each individual): None**

Percent efforts will be adjusted, pending funding notification so that no overlap occurs. Adjustments will be made in the event that funding is awarded on pending studies.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award and accept the obligation to comply with Section 223(a) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature: Arun Sreekumar

Digitally signed by Arun Sreekumar
Date: 2023.04.26 18:52:15 -05'00'

Date:

OTHER SUPPORT

ITTMANN, M.

PREVIOUS SUPPORT

Merit Review (Ittmann) 4/1/2019-3/31/2023 3.0 calendar
Dept of Veterans Affairs
A Novel Oncogenic Axis in African American Prostate Cancer
The goal of this project is to characterize the role of RGS12 in African American prostate cancer.
Grant specialist: Denise Naylor, 2002 Holcombe Blvd, Houston, TXdbnaylor@bcm.edu

DOD Prostate Cancer Research Program Idea (Ittmann/McGuire) 9/1/2018-8/31/2022 (NCE) 1.2 calendar
DOD Prostate Cancer Program
Enhancing outcomes of radiation therapy for prostate cancer
The goal of this proposal is to examine the impact of inhibition of RET and/or FGFR kinases on radiation therapy in prostate cancer.
Grants Specialist: Lymor R. Barnhard, Ph.D., Science Office Supporting the Congressionally Directed Medical Research Programs (CDMRP), USAMRMC Phone: 301.619.7360E-mail: Lymor.R.Barnhard.ctr@mail.mil

PC170374 (Ittmann/Ayala) 9/1/2018-8/31/2022 (NCE) 1.2 calendar
DOD Prostate Cancer Research Program HDA
Tumor microenvironment-based biomarkers in African American prostate cancer
The goal of this proposal is to evaluate reactive stroma biomarkers in African American prostate cancer.
Grants Specialist: Lymor R. Barnhard, Ph.D., Science Office Supporting the Congressionally Directed Medical Research Programs (CDMRP), USAMRMC E-mail: Lymor.R.Barnhard.ctr@mail.mil

PC181023 (Lotan) 9/1/2019-8/31/2022 0.24 calendar
DOD Prostate Cancer Research Program HDA
Epigenomic Landscape of Primary Prostate Cancer in African American Men
The goal of this proposal is to examine the epigenetic alterations in African American prostate cancer. We will provide samples for a validation cohort.
Grants specialist: Kimberly Carter, Fort Detrick, MD;Kimberly.m.carter47.civ@mail.mil

W81XWH-19-1-0410 (Frigo) 7/15/2019-7/14/2022 0.6 calendar
DOD Prostate Cancer Program
To rigorously evaluate SLC1A5's role in prostate cancer metabolism and test whether SLC1A5 represents a viable therapeutic target.
Grants specialist: Kimberly Carter, Fort Detrick, MD; Kimberly.m.carter47.civ@mail.mil

R01CA190378-02 (Xin, Li) 07/07/2015 – 06/30/2020 0.60 calendar
National Institutes of Health
The Notch Signaling in Prostate Homeostasis and Carcinogenesis
The goals of this application are to determine how Notch signaling alters prostate epithelial cell biology, and to determine whether and how Notch promotes prostate cancer metastasis.
Grant specialist: Elizabeth Snyderwine, Elizabeth snyderwine@nih.gov

MIRA RP150648-01 (PI-O'Malley,Core 1.Ldr-Ittmann) 06/01/2015 - 08/31/2020 1.2 calendar
Cancer Prevention & Research Institute of Texas (CPRIT)
Steroid Receptor Coactivator-2 (SRC-2) and Gata2 Cooperate with Androgen Receptor to Promote Prostate Cancer Progression and Androgen Resistance
Core 1 Project

The goal of this proposal is to understand the mechanism by which AR, GATA2 and SRC2 promote prostate cancer progression and develop novel methods of inhibiting this pathway. The Animal Studies and Pathology Core will provide technical support and expertise to carry out animal studies, interpret pathological changes in mouse models and carry out correlative studies in human prostate cancer specimens.
Grants Specialist: Wilfredo Ruiz, Finance Manager, email is aroyal@cprit.state.tx.us, phone: 512-305-8488

DOD Prostate Cancer Research Program Idea (Mitsiades) 10/1/2018-9/30/2021 0.6 calendar
DOD Prostate Cancer Program
Sensitization of castration resistant prostate cancer to chemotherapy via BRCA-1/BRCA-2 induced DNA replication stress
The goal of this proposal is to enhance the efficacy of chemotherapy in advanced prostate cancer by inducing DNA replication stress.
Grants Specialist: Dr Ram Arudchandran, 1053 Patchel Street, Fort Detrick, MD 21702-5012, Phone: Fax: email: ramachandran.arudchandran.civ@mail.mil

1R01 CA184208-01A1(Prime PI: Frigo; SubPI: Sreekumar)01/27/2015 - 12/31/2019 0.60 calendar
National Institutes of Health
Genetic & Metabolic Dissection of the CAMKKbeta Signaling Axis in Prostate Cancer
Dr. Sreekumar and his team at Baylor College of Medicine, will carry out the measurement of steady state metabolite levels and the associated flux in the various cell lines using mass spectrometry, analyze the data and delineate associated biochemical pathways. The results will be provided to Dr. Frigo for further analysis.
Grants Specialist: Kelley A. Smith, smithka3@mail.nih.gov, (P) 240-276-6337

Challenge Award (Jones) 12/1/2017-11/30/2019 0.12 calendar
Prostate Cancer Foundation
Clinicopathological correlation & molecular signature identification & risk stratification of prostate cancer in African American U.S. Veterans, with & without exposure to battlefield chemicals
The goal of this proposal is to define key oncogenic pathways in African American veterans
Grants Specialist: Howard Soule, PhD, Executive Vice President, Chief Science Officer, 1250 4th Street, Santa Monica, CA 90401

R21CA191009-02 (Frigo) 12/01/2015 – 01/31/2017 0.60 calendar
National Institutes of Health
Androgen Receptor-and Myc-Mediated Glutamine Metabolism in Prostate Cancer
The goal of this proposal is to use a combination of preclinical models to understand the relationship between AR signaling and glutamine metabolism to determine whether their intersection represents a viable therapeutic target.
Grants Specialist: Kelley Smith, Email: smithka2@mail.nih.gov, Phone: 240-276-6337

PC130188 W81XWH-14-1-0505 (Ittmann) 09/30/2014 – 09/29/2018 1.8 calendar
DoD Congressionally Directed Medical Research Programs
Targeting the Neural Microenvironment in Prostate Cancer
The goal of these studies is to determine the role of GDNF and RET in the interactions between prostate cancer and nerves and whether this interaction is a potential therapeutic target. On no cost extension.
Grants Specialist: Joshua McKean, 820 Chandler Street, Fort Detrick, MD 21702, (P) 301-619-4046, joshua.d.mckean3.civ@mail.mil

American Cancer Society (Li, Wenliang) 07/01/2017 – 06/30/2018 0.3 calendar
A Novel GRK3-EZH2 Regulatory Pathway in Prostate Cancer Progression
The goal of this proposal is to examine a novel pathway in prostate cancer progression.
Grants specialist: Adriana Smith, UTHSC, 7000 Fannin St, Houston, TX 77030 contracts@uth.tmc.edu

Dept of Veterans Affairs Ittmann (PI) 10/1/2014-9/30/2018 3 calendar
Merit Review
Highly specific targeting of the TMPRSS2/ERG fusion gene in prostate cancer
This project will optimize in vivo delivery of a highly specific nanoliposomal siRNA targeting the TMPRSS2/ERG fusion gene in prostate cancer.
Grant specialist: Denise Naylor, 2002 Holcombe Blvd, Houston, TX dbnaylor@bcm.edu

CURRENT

U54 (Mitisiades) 9/1/2018-8/31/2023 0.6 calendar
National Institute of Health
Minority PDX Development and Trial Center: Baylor College of Medicine and MD Anderson Cancer Center Collaboration on Mechanistic Studies to Dissect and Combat Health Disparities in Cancer
The goal of this proposal is to establish patient derived xenografts (PDXs) from African American prostate cancer and other cancer tissues from minority patients and rationally test drugs on these PDXs. I am Co-Director of the PDX Core.
Grants Specialist: Program Official: Tiffany Wallace, Ph.D. Program Director Center to Reduce Cancer Health Disparities National Cancer Institute, 9609 Medical Center Drive, West Tower, Room 6W256, Rockville, MD 20850, Email: Tiffany.Wallace@nih.gov

2 P30 CA125123-09/13 (Osborne) 07/01/2015-06/30/2025 1.2 calendar
National Institutes of Health
Baylor College of Medicine Cancer Center
Leader, Human Tissue Acquisition and Pathology Core (Ittmann)
This Core carries out tissue banking and provides pathology support for the Cancer Center.
Grants Specialist: Shafik, Hasnaa, Program Official, email: shafikh@mail.nih.gov

UM1 CA096230-10 (McGrath9/1/13-8/31/2024 0.6 calendar
NIH/NCI
AIDS and Cancer Specimen Resource (ACSR)
The BCM Regional Specimen Biorepository of the ACSR will acquire, store and distribute biospecimens and data from HIV-associated malignancies for the ACSR enterprise. We will collect both fresh tissues and parrafin-embedded tissues. We will construct tissue microarrays from the parrafin-embedded tissues. We will also collect clinical data for all specimens. These will be distributed as requested in a deidentified manner.
Grants Specialist: Jennifer Meininger, meiningerjs@mail.nih.gov,

DAMD W81XWH-20-1-0926 (Yen) 9/30/2020-9/29/2023 0.6 calendar
DOD Prostate Cancer Program
AZI1 RNA-Driven Gene Fusion in Prostate Cancer
The goal of this proposal is to evaluate the role AZI1 in prostate cancer
Grants specialist: Jason Wong, PhD. Email: jason.wong5.ctr@mail.mil

RO1CA227559 (Sreekumar/Palapattu) 05/01/2019-04/31/2024) 0.12 calendar
NIH Metabolic Rewiring Promotes AA PCa
by Regulating Stromal-Epithelial Interaction
The goal of this proposal is to examine metabolism in African American prostate cancer
Grants specialist: Neeraja Sathyamoorthy, NIH, ns61r@nih.gov

U01CA257328-01 (Haiman) 05/01/2021 – 04/30/2026 0.6 calendar
NCI
Multiethnic GWAS and TWAS to Inform Risk Prediction for Prostate Cancer
The goal of this project is to determine genetic risk factors for prostate cancer. We will be supplying specimens for analysis.
Grants specialist: Jason Gill Grants Management Officer NCI gilljas@mail.nih.gov

2U54MD007597-31 (Kwabi-Addo) 08/01/19-07/31/24 0.6 calendar NIH
Epigenetic regulated genes in African American Prostate Cancer Patients
The goal is to understand the biological basis for the more aggressive clinical behavior of prostate cancer in African American men and to begin to develop predictive tools to help manage prostate cancer in African American men.
Grants specialist: Sy Shackleford, NIH, 301-451-8542 shackleford@mail.nih.gov

W81XWH2210135 - PC210240 (Gassman/Sreekumar) 04/15/22-04/14/25 0.6 calendar
Department of Defense
Elevated Uracil Glycosylase Coupled to reduced Base Excision Repair Promotes AA PCa Progression
The goal is to characterize differences in DNA Repair pathways and their metabolic regulation in AA and EA PCa.
Grant spécialist: Joshua L. Disbennett, Email: joshua.l.disbennett.civ@mail.mil

OVERLAP

No overlap

PENDING

None

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award and accept the obligation to comply with Section 223(a) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature: Michael Ittmann
Date: Digitally signed by Michael Ittmann Date: 2023.05.11 16:18:23 -05'00'