AWARD NUMBER: W81XWH-21-1-0619

TITLE: The Role of HBP1 in Controlling Breast Cancer Dormancy Reawakening

PRINCIPAL INVESTIGATOR: Irwin Gelman

CONTRACTING ORGANIZATION: Health Research Inc.

REPORT DATE: OCTOBER 2022

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCTOBER 2022	Annual	09/01/21-08/31/22

4. TITLE AND SUBTITLE

The Role of HBP1 in Controlling Breast Cancer Dormancy Reawakening

5a. CONTRACT NUMBER
W81XWH-21-1-0619

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Health Research Inc. &
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo NY 14263

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Breast cancer (BrCa) is the most common cancer affecting women worldwide. Yet even with tumor and lymph node removal, local radiation and systemic chemotherapy, roughly 22% (60,826 estimated cases in the U.S. in 2020) develop active bone metastases after a mean period of 8.4 years, correlating with severely decreased survival rates. Indeed, at least 50% of ductal carcinoma *in situ* cases showing no evidence of macroscopic metastatic disease nonetheless harbor disseminated metastatic cells. This indicates that bone metastatic growths are likely due to the reawakening of dormant BrCa cells that disseminated early to the bone. The molecular mechanisms regulating dormancy and reawakening remain poorly understood. One guiding principle, however, is that dormancy requires activation of p38MAPK and suppression of ERK1/2-MAPK, yet little is known regarding downstream p38 mediators.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	UU	44	USAMRDC

19b. TELEPHONE NUMBER *(include area code)*

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INTRODUCTION

Objectives/Hypothesis: The transcription factor, HBP1, is a suppressor of dormancy reawakening in human estrogen receptor (ER)-positive and triple-negative BrCa cells grown in 3D microenvironments that recapitulate the bone endosteal niche (EN). Our published and preliminary data suggest that that tumor dormancy signaling is mediated through interactions between HBP1 and BRMS1or BRMSL1, metastasis suppressors known to regulate BrCa adhesion and anoikis, and with the chromatin modifier, SIN3A. Cyproheptadine (CyH), an antihistaminic drug, induces growth arrest in hepatocellular carcinoma and BrCa cells by inducing p38MAPK-mediated HBP1upregulation, suggesting that it might suppress dormancy reawakening. *We hypothesize that BrCa dormancy in the EN is facilitated by p38-mediated upregulation of HBP1/BRMS1/BRMSL1 complex formation, which, in concert with associated SIN3A, control cell cycle progression genes through chromatin landscape remodeling.* To address this experimentally, we proposed two aims: SA1- Determine how HBP1-BRMS1 interaction regulates BrCa dormancy and SA2- Determine if CyH can induce and/or maintain BrCa dormancy.

KEYWORDS

Metastasis, dormancy, reawakening, p38-MAPK, HBP1, BRMS1, SIN3A, cyproheptadine, breast cancer, bone endosteal niche, 3D growth culture.

ACCOMPLISHMENTS

Major Task 1, Subtask 1: We have produced and validated by immunoblot MCF-7, T47D, BT483, MDA-MB-231, MDA-MB-468, BT549, SUM159PT, BoM-1833, D2A1-d, -m1 or -m2 cells stably expressing shRNAs for HBP1, BRMS1 or BRMSL1 (vs. shControl). As described in the CHANGES/PROBLEMS sections, we learned that because of suppression of proliferation by the constitutive overexpression of HBP1 in some BrCa cell lines, the BrCa cells were transduced with a tetracycline/doxycycline (DOX)-inducible HBP1 lentivirus vector. Of note is that none of these clones had decreased relative 2D proliferation in the absence of DOX. MCF-7, MDA-MB-231 and the D2A1 series were also transduced with DOX-inducible H2B-GFP as a marker of dormancy *in vivo* (see **Fig. 1** for a limited validation), and as well, with pPBbsr-mKO-MK2, a marker of p38-MAPK (part of Major Task 1, Subtask 5). As part of Major Task 1, Subtask 2, MCF-7, MDA-MB231 and D2A1-d cells were transduced with pCDFDuet-MKK6-EE-p38α, whose product activates p38-MAPK (confirmed by immunoblotting with antibodies specific total p38 vs. $p38^{poT180/Y182}$; not shown).

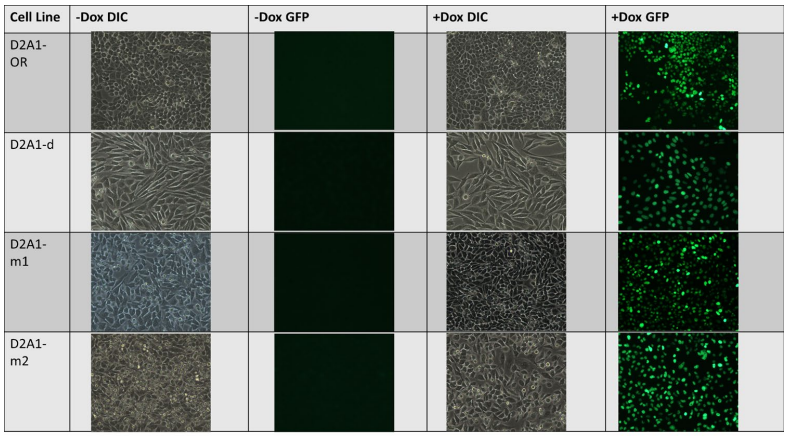

Figure 1. Validation of transduction of BrCa cell lines with DOX-inducible H2B-GFP.

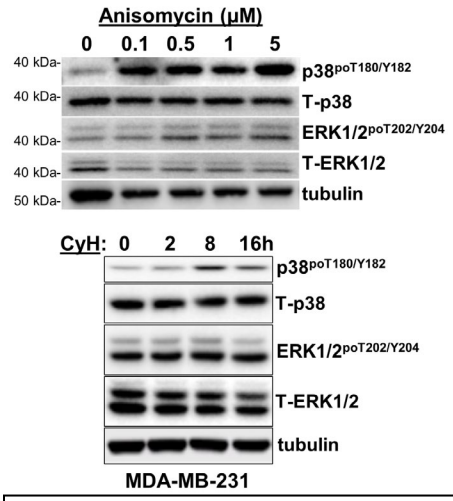

Figure 2. MDA-MB-231 cells treated with various concentrations of anisomycin (*top*) or with 0.5 μM CyH for various times (*bottom*).

Major Task 1, Subtask 5 and Major Task 2, Subtask 2/3: IACUC and Biosafety approval was obtained for all the *in vivo* experiments.

Major Task 2, Subtask 1: We confirmed that treatment of MDA-MB-231 cells treated with CyH slowed 2D proliferation (not shown), and that CyH and another p38-MAPK agonist, anisomycin, induced p38-MAPK activation, with little to no ERK1/2 activation (see **Fig. 2**).

IMPACT

In total, our molecular and drug-trial research has the promise of increasing long-term survival by BrCa patients by decreasing disease recurrence at the major metastatic site, the bone. This includes estrogen receptor-positive and so-called triple-negative (ER-, PR-, HER2-negative) cases. Importantly, because CyH has been used clinically, its repurposing would facilitate fast-track Phase I/II trials that include parameters such as recurrence frequency and time-to-recurrence as clinical readouts. Moreover, as described in the grant proposal, we already have biomarkers of CyH efficacy that could further facilitate these clinical trials.

CHANGES/PROBLEMS

An initial problem appeared in that the constitutive overexpression of HBP1 in several BrCa cell lines caused severe decreases in proliferation. This required us to clone HBP1 into a tetracycline-regulated lentivirus vector (pFUW-tetO-MCS) and then to transduce all the BrCa cell lines with this vector. This has been now accomplished and the cell lines validated for DOX-inducible HBP1 by immunoblot (not shown).

PRODUCTS

Oral Short Talk in the Aging and Metastasis session: **The Role of HBP1 in Controlling Breast Cancer Dormancy Reawakening**. American Association for Cancer Research Annual Meeting. New Orleans, LA. April 12, 2022.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Irwin Gelman, PhD- Roswell Park Comprehensive Cancer Center .6CM
Jianmin Wang, PhD- Roswell Park Comprehensive Cancer Center .12CM
QianQian Zhu, PhD- Roswell Park Comprehensive Cancer Center .12CM

Irwin Gelman, PhD

CURRENT

Title: Development Funds for Crispr Project
Supporting Agency: NIH/CCSG Development Funds
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:
Performance Period: 5/1/2019-4/30/2024
Funding:
Brief description of project's goals/Aims: The funds will be used to produce human and mouse prostate cancer cell lines with tetracycline-inducible Cas9-mediated deletion of AKT1, AKT2 or AKT3. These cell lines will be used to further characterize AKT isoform-specific and -preferred substrates, and how their phosphorylation affects metastatic progression.
Overlap: None

Title: M2 Macrophage control of breast cancer metastasis by FAK (5P30CA016056-43– PI Candace Johnson)
Time Commitment: 0 calendar months
Supporting Agency: National Cancer Institute
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, Grants Management Specialist Office of the Director, 31 Center Drive, Building 31, Bethesda, Maryland, 20814
Performance Period: 5/1/2020 – 4/30/2024
Funding:
Brief description of project's goals/Aims: The collaborative project addresses a novel role for the FAK tyrosine kinase in promoting the activation and polarization of so-called M2 tumor associated macrophages (TAM). Given that M2-TAMs are pro-metastatic in breast cancer models, we will test whether FAK kinase inhibitors can increase the efficacy of either radiation or immune checkpoint inhibitors against triple negative breast cancers.
Overlap: None

Title: Leveraging the GTP Biosynthetic Pathway for Anti-Tumor Therapies (R37CA248018 PI Bianchi)
Time Commitment: .60 calendar months
Supporting Agency: R37 National Cancer Institute
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Elizabeth Blu,
Performance Period: 12/10/2020-11/30/2025
Funding:
Brief description of project's goals/Aims: 1) To characterize a novel mechanism of G-protein activation. 2) To determine the functional significance of IMPDH2 localization in focal adhesion (FA) formation and TNBC oncogenic motility. 3) To investigate the transcriptional regulation of GTP metabolic enzymes.
Overlap: None

Title: The role of HBP1 in controlling breast cancer dormancy reawakening W81XWH-21-1-0619 (PI: Gelman)
Time Commitment: 0.5 calendar months
Supporting Agency: Department of Defense (DOD)
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Charity L. Keen,
Performance Period: 9/1/2021-8/31/2024
Funding:
Brief description of project's goals/Aims:
Specific Aims 1: Determine how HBP1-BRMS1 interaction regulates BrCa dormancy. We will use established

in vitro and in vivo bone dormancy vs. active bone metastasis models (respectively, human MDA-MB-231 vs. BoM-1833 grown in 3D-EN; intracardiac injection of BALB/c mice with dormant D2A1-d vs. proliferative

bone-tropic D2A1-m1 or -m2 mouse mammary carcinoma cells) to address how HBP1 potentiates the ability of BRMS1 to bind to and regulate the expression of cell cycle genes through SIN3A-mediated chromatin changes. Specific Aims 2: Identify and characterize the adhesion proteins on EN cells that facilitate p38MAPK/HBP1-mediated dormancy. We will use a panel of cell-cell adhesion blocking agents to identify the EN cells and cell-cell interactions that mediate p38MAPK/HBP1-dependent dormancy of ER+ and triple-negative human BrCa in our 3D-EN growth model, and then validate the requirement for these to establish BrCa dormancy in the bone. Specific Aims 3: Determine if CyH can induce and/or maintain BrCa dormancy. We will use our in vitro and in vivo dormancy models to investigate whether CyH can prevent dormancy reawakening of BrCa cell lines, and whether this requires p38MAPK activat
Overlap: None

PENDING

Title: Roswell Park Institutional Research Grant
Time Commitment: 0.0 calendar months
Supporting Agency: American Cancer Society (ACS)
Performance Period: 1/1/2023-12/31/2025
Funding:
Brief description of project's goals/Aims: Our goal for the next project period will continue focus on developing new crops of junior investigators who, by formally partnering with senior and mid-career mentors, can secure extramural funding and become productive cancer researchers.
Overlap: None

Title: AKT isoform-preferred substrates controlling prostate cancer aggressiveness
Time Commitment: 2.4 calendar months
Supporting Agency: National Institute of Health (NIH)
Performance Period: 1/1/2023-12/31/2028
Funding:
Brief description of project's goals/Aims:
1) Characterize AKT2/3-preferred substrates that mediate mPC progression. We will use in vitro kinase (IVK) assays, PC cells engineered by CRISPR for tetracycline-inducible selective AKT isoform expression or loss, and RNAi to validate the role of AKT2/3 phosphorylation of RAF1, G3BP1, GSK3α, AMOT and MYH9 in mediating parameters of mPC progression in vitro and in vivo. This aim will also dissect novel roles for PTEN in the usage or AKT isoform preference for substrates that drive mPC aggressiveness.
2) Characterize ARHGAP11A-MYH9poS1943 control of RAC1-dependent chemotaxis and invasiveness. Based on preliminary data showing that the RHO-GAP, ARHGAP11A, binds to the putative AKT3 substrate, MYH9poS1943, we will determine using cellular fractionation and confocal microscopy on engineered PC cells if enhanced oncogenic motility in vitro, and increased metastatic potential in vivo are controlled by RAC1-dependent lamellipodia formation and focal adhesion disassembly at leading edges.
3) Identify critical non-canonical MYH9 residues used by AKT3. Many of the AKT2/3 substrates we identified as potentially driving mPC aggressiveness encode non-canonical phosphorylation motifs, yet little is known of the amino acid residues that define AKT or AKT3 preference. Thus, we will identify these residues using LC-MS/MS analysis of peptide libraries phosphorylated in vitro, with a focus on identifying new substrate drivers of disease aggressiveness.
Overlap: None

Title: Suppression of metastatic prostate cancer progression by co-targeting AKT isoforms and AR
Time Commitment: 0.12 calendar months
Supporting Agency: Department of Defense
Performance Period: 4/1/2023-3/31/2025
Funding:

Brief description of project's goals/Aims: The major objective of this proposal is to determine if the selective inhibition of AKT2 and/or AKT3 increases the efficacy of ENZ in suppressing PTEN-deficient CRPC growth and cell motility parameters *in vitro* and *in vivo.*

PREVIOUS (past 5 years)

Title: Drugging gene/pathway dependencies in pancreatic cancer (development grant sub of R1227796/2UL1TR00141205A1 - PI Murphy)
Time Commitment: 1.2 calendar months
Supporting Agency: Clinical and Translational Science Institute, SUNY-Buffalo/UPENN
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Amy Lagowski, Sponsored Projects Associate The UB Commons 520 Lee Entrance, Suite 211 Amherst, NY 14228
Performance Period: 4/15/2020 – 6/30/2022
Funding:
Brief description of project's goals/Aims: The proposal seeks to identify targetable pathways in gemcitabine-resistant pancreatic cancers using functional genome-wide synthetic lethality screens.
Overlap: None

Title: Drug susceptibilities in fusion oncogene-driven pediatric sarcomas (5R21CA235092-02 – PI Gelman)
Time Commitment: 1 calendar month
Supporting Agency: National Cancer Institute
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Viviana Knowles, Grants Management Specialist Office of the Director, 31 Center Drive, Building 31, Bethesda, Maryland, 20814
Performance Period: 7/1/2019 – 6/30/2022
Funding:
Brief description of project's goals/Aims: Use genomic shRNA and CRISPRi screens to identify synovial cell and Clear cell sarcoma essential genes and pathways, and then identify and validate using bioinformatics approaches drug susceptibilities (Aim 1). Synovial cell sarcoma tissues will be then analyzed by RNA-seq for drug susceptibility gene signatures.
Aim 1 - Use synthetic lethality screens to identify ScS-/ES-specific proliferation/survival genes.
Aim 2 - Analyze human ScS tumors for pathway signatures identified by synthetic lethality screens.
Overlap: None

Title: Gene Essentialities in fusion oncogene-driven pediatric sarcomas (PI Gelman)
Time Commitment: 1.8 calendar months
Supporting Agency: Roswell Park Alliance Foundation
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14263,
Performance Period: 1/01/19 – 12/31/20
Funding:
Brief description of project's goals/Aims: The current proposal seeks to identify drug sensitivities for these undruggable cancers by combining functional genomic synthetic lethality screens with bioinformatics analyses that identify essentiality pathways and their linked drug sensitivities. The current work is envisioned to identify new therapies that will increase the survival of ScS and ES patients.
Overlap: None

Title: Strengthening knowledge for future generations: Cancer bio-banks in the landscapes of the Haudenosaunee. (PI Rodney Haring)
Time Commitment: 0.6 calendar months
Supporting Agency: Roswell Park Alliance Foundation

Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14263,
Performance Period: 2/1/18 - 12/31/19
Funding:
Brief description of project's goals/Aims: Develop IRB structures and trust-centers with local Haudenosaunee tribes in the Seneca Confederacy through surveys as a foundation to develop a biobank that includes family medical history and cancer susceptibility markers such as BRCA testing.
Overlap: None

Title: Identification of Gene Signatures that Drive Early vs. Late Prostate Cancer (Co-PI Gelman/Goodrich)
Time Commitment: 0.6 calendar months
Supporting Agency: Roswell Park Alliance Foundation
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14263,
Performance Period: 4/11/16 – 11/15/17
Funding:
Brief description of project's goals/Aims: Identify genes and signaling pathways that differ between two mouse transgenic models of prostate cancer, one producing indolent metastatic disease and the other producing aggressive cancer and systemic metastases. We will do this by performing comparative RNA-seq and signaling arrays on primary tumor and lymph node metastases between the two models and then to use bioinformatics analyses to identify differential malignancy driver pathways.
Overlap: None

Title: Breast Cancer Research Donation Fund (PI Gelman)
Time Commitment: 0 calendar months
Supporting Agency: Roswell Park Alliance Foundation
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Judith Epstein, Director Grants & Foundation Office, Elm & Carlton Streets, Research Studies Center Room 234, Buffalo, NY 14263,
Performance Period: 12/08/16 – 3/31/18
Funding:
Brief description of project's goals/Aims: To identify "dormancy-reactivation suppressor genes" (DRSG) in breast cancer models based on a 3D bone culture.
Overlap: None

I, Irwin Gelman, PhD, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with US Army Medical Research Acquisition Activity terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Irwin H. Gelman, Ph.D.

Digitally signed by Irwin H. Gelman, Ph.D.
Date: 2022.09.21 14:58:56 -04'00'

Wang, Jianmin, PhD

CURRENT SUPPORT:

Title: Replication licensing in genome stability, cancer and aging (5 R01 CA130995-15)
Time Commitment: 0.96 calendar (PI-Knudsen)
Supporting Agency: NCI/NIH
Contracting/Grants Officer: Ronald Johnson
Performance Period: 07/01/2018-06/30/2023
Level of Funding:
Projects Goals: This proposal addresses the contribution of DNA damage occurring during cellular replication to cancer initiation and progression. Studies test the hypotheses that sequence specificity in the sites at which DNA replication mechanisms fail lead to specific disease outcomes and that genetic modifiers that reduce susceptibility to replication related genetic damage or its consequences exist and can be identified.
Specific Aims:

1. High density array CGH (aCGH) has been used to define the locations and properties of genetic damage in thymic lymphomas arising in Mcm2 deficient mice on the 129Sv genetic background.
2. The effect of Mcm2 deficiency, genome-wide, on replication origin usage in thymic cells from the 129Sv, C57BL/6, C3H, BALB/c and DBA2 genetic backgrounds will be defined using congenic strains carrying the Mcm2 deficiency allele.
3. Paired-end next generation sequencing will be used to define sites of genetic damage in Mcm2 wt and deficient thymic tissue.
4. A unique mouse model of proliferation stress that reproducibly results in elevated levels of thymic lymphomas will be used to determine if tumors arising in this model exhibit genetic damage that reflects the location of mutations resulting from Mcm2 deficiency.

Overlap: None

Title: Immuno-Oncology Translation Network: Data Management and Resource-Sharing Center at Roswell Park (1 U24 CA232979-01)
Time Commitment: 0.60 calendar (MPIs- Hutson/Liu/Morgan/Odunsi)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Lillian Kuo
Performance Period: 09/30/2018-06/30/2023
Level of Funding:
Projects Goals: The goal of our Data Management and Resource-Sharing Center (DMRC) application is to serve as an administrative and analytic hub for translational studies in the NCI-supported Immuno-Oncology Translation Network (IOTN).
Specific Aims:

1. Provide a centralized administrative infrastructure to coordinate the IOTN activities.
2. Promote the IOTN and engage in the interaction with the broader scientific community.
3. Provide multidisciplinary analytic expertise to support the IOTN collaborative research.
4. Develop improved data integration methods to enhance the IOTN research capacity.

Overlap: None

Title: NOTCH signaling controls transformation to androgen independent neuroendocrine prostate cancer (5 R01 CA234162-04)
Time Commitment: 0.48 calendar (PI-Goodrich)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Ian Fingerman
Performance Period: 05/22/2019-04/30/2024
Level of Funding:

Projects Goals: Many cancers, including metastatic prostate cancer, resist molecularly targeted therapy by altering their phenotype from one that is dependent on the target to one that is not. Here we characterize genetic mutations and epigenetic mechanisms that drive transformation from androgen dependent prostate cancer to androgen independent prostate cancer. The goal is to identify new approaches for treating lethal prostate cancers.
Specific Aims:

1) Test if NOTCH signaling is sufficient to maintain an androgen dependent PADC phenotype.
2) Characterize how prostate cancer cells transition from PADC to NEPC.
3) Determine whether epigenetic modulating drugs reverse NEPC transformation and ADT resistance via NOTCH-ASCL1 signaling.

Overlap: None

Title: Targeting the Chemokine System to Sensitize Tumors to Immunotherapy – Core B (5 P01 CA234212-02)
Time Commitments: 0.60 calendar (PI-Kalinski)
Supporting Agency: NIH/NCI
Name of the Funding Agency's Grants Officer: Min-Kyung H. Song
Performance Period: 03/03/2020-12/31/2025
Level of Funding:
Brief description of project's goals: We will test widely-applicable complementary approaches to promote selective entry of therapeutic CTLs into tumors. Since intratumoral CTL numbers predict survival and therapeutic advantage of checkpoint blockers in multiple cancer types, the results are likely to benefit a broad range of cancer patients.
Specific Aims:

1. We will determine local immunologic efficacy of CKMs in reprograming the TME of cancer patients.
2. We will evaluate mechanisms underlying intratumoral efficacy of CKM and identify the most effective ways of using CKM to enhance durable antitumor activity of therapeutic vaccines and PD-1 blockade.
3. Aim 3 will evaluate the ability of CKM/PD-1 therapies to induce tumor regression in patients with microsatellite- stable (MSS)-CRC, OvCa and PD-1-refractory melanoma, and identify the most relevant TME correlates of clinical benefit and the most feasible regimens for prospective large cohort studies.

Overlap: None

Title: Long noncoding RNA regulations in breast cancer among African-American women (5 R01 CA246688-03)
Time Commitments: 0.90 calendar (PI- Gong)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Kelly Filipski
Performance Period: 07/01/2020-06/30/2025
Level of Funding:
Brief description of project's goals: In a large, well-characterized patient cohort of AA women, our proposed study will systematically characterize tumor lncRNA expression patterns and elucidate the role of aberrant expression of lncRNAs in breast cancer progression and prognosis..
Specific Aims:

1. Perform tissue lncRNA expression profiling using total RNA sequencing (1181 AA cases from WCHS and 100 AA controls from Komen Tissue Bank) to determine lncRNAs that are breast cancer- and ER subtype- specific (tumor, ER+, ER- vs. normal) and those associated with clinico-pathological factors (e.g., grade);
2. Examine associations of lncRNA expression levels with breast cancer survival, and use a machine learning approach to identify a combined panel of lncRNAs associated with breast cancer survival; and further perform computational prediction and in vitro functional assays to determine their biological relevance; and

3. Integrate paired data on lncRNA expression and DNA methylation to determine which of these cancer- and prognosis-relevant lncRNAs are regulated by DNA methylation, and explore whether diet, obesity and other lifestyle-related factors are associated with aberrant DNA methylation.

Overlap: None

Title: Functional Significance of Individual p53 Mutations In Determining the Role of Estrogen ReceptorBeta In Triple Negative Breast Cancer (5 R01 CA251545-02)
Time Commitments: 0.12 calendar (PI-Das)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Joanna Watson
Performance Period: 03/01/2021-02/28/2026
Level of Funding:
Brief description of project's goals: The long-term goal is to understand and exploit the role of ERβ-p53 crosstalk in breast cancer for the development of better therapeutic strategies.
Specific Aims:

1. Determine the interaction of different p53 mutants with p73 and ERβ in TNBC cells;
2. Analyze the differential effects of p53 mutants on tumor progression, metastasis and therapeutic response in vivo
3. Evaluate the clinical significance of the ERβ-p53-p73 signaling axis.

Overlap: None

Title: Therapeutic implication of RB1 loss in bladder cancer (5 K08 CA252161-02)
Time Commitments: 0.60 calendar (PI-Li)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Yansong Bian
Performance Period: 03/05/2021-02/28/2026
Level of Funding:
Brief description of project's goals: The role of RB1 loss in bladder cancer progression, differentiation and cancer cell plasticity remains unknown. A major obstacle in translational bladder cancer research is the lack of genetically engineered mouse models that recapitulate aggressive muscle invasive bladder cancer in humans, that makes it difficult to rigorously study in vivo responses to systemic treatment. The proposed research will utilize novel mouse models to elucidate the role of RB1 loss in tumor progression, differentiation, plasticity and resulting clinical therapeutic implications.
Specific Aims:

1. Define the function of RB1 loss in accelerating tumor progression, metastasis, and cellular plasticity in bladder cancer GEMMs
2. Dissect the impact of cell-of-origin on bladder tumorigenesis, metastasis and response to chemotherapy in TKO tumors derived from basal cells versus luminal cells. Successful completion of this proposal will allow the candidate to gain valuable technical knowledge and expertise in preclinical modeling of advanced bladder cancer and further his development as an independent physician scientist

Overlap: None

Title: Role of Type 2 Immune Response in Pancreatic Cancer Tumorigenesis (5 R01 CA262822-02)
Time Commitments: 0.60 calendar (PI-Dey)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Phillip J Daschner
Performance Period: 07/15/2021-06/30/2026
Level of Funding:
Brief description of project's goals: The overarching novel hypothesis that intratumor mycobiome in PDAC tumors enables IL33 release into the extracellular milieu which attracts and activates TH2, Treg and ILC2 cells leading to PDAC progression.
Specific Aims:

1. we will determine the molecular mechanism of mycobiome mediated IL33 release in cell and organoid models of PDAC.
2. we will analyze IL33, intratumor mycobiome and type 2 immunocytes in the PDAC patient tumor and serum samples.
3. to block the IL33-TH2/ILC2 axis we have three genetically engineered mouse models that will allow rigorous testing of the function of IL33 in PDAC tumorigenesis.

Overlap: None

Title: Hsp60 Regulation of Prostate Cancer Progression (1 R01 CA246437-01A1)
Time Commitments: 0.24 calendar (PI-Chandra)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Konstantin Salnikow
Performance Period: 09/01/2021-08/31/2026
Level of Funding:
Brief description of project's goals: This proposal will define how heat shock protein 60 (HSP60), a key component of UPRmt, promotes aggressive and resistant PCa. Using genetically-engineered triple knockout (TKO: deletion of Pten, Trp53, and Rb1) tumors, we observed that HSP60 is upregulated in aggressive tumors and castration-resistant prostate cancer (CRPC) compared to WT prostatic tissues.
Specific Aims:

1. Define the role of transcription factor ATF5 in activating mitochondrial unfolded protein response.
2. Evaluate whether HSP60 oligomerization maintains functional mitochondria and inhibits apoptosis to develop aggressive PCa.
3. Explore the clinical relevance of HSP60 inhibition using patient-derived xenografts (PDXs) and primary tumor cells.

Overlap: None

Title: STAG2 modulates environmental toxicant exposures and epigenomic heterogeneity (1 R01 ES034250-01)
Time Commitments: 0.60 calendar (PI- Ohm)
Supporting Agency: NIH/NIEHS
Contracting/Grants Officer: Frederick L Tyson
Performance Period: 03/20/2022-12/31/2026
Level of Funding:
Brief description of project's goals: In this proposal, we will focus on Ewing sarcoma due to its relatively quiet genome and clear epidemiological links to toxicant exposure.
Specific Aims:

1. To determine whether environmental toxicant exposures increase baseline levels of replication stress in iMSC and cooperate with STAG2 loss to lead to epigenomic remodeling.
2. To determine whether environmental toxicant exposures cooperate with STAG2 loss to lead increased clonal genetic and epigenetic heterogeneity.
3. To determine whether environmental toxicant exposure leads to a permissive epigenome for survival of pre-malignant cells following fusion protein expression.

Overlap: None

Title: Coordinating and Data Management Center for Acquired Resistance to Therapy Network (1 U24 CA274159-01)
Time Commitments: 0.60 calendar (PI's- Hutson/Goodrich/Morgan/Li)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Percy Ovy
Performance Period: 09/01/2022-08/31/2027
Level of Funding:

Brief description of project's goals: The goal of our proposed Coordinating and Data Management Center (CDMC) application is to coordinate the activities across the Acquired Resistance to Therapy Network (ARTNet), and to manage, integrate and disseminate the data and resources generated through the network.
Specific Aims:

1. Provide administrative and outreach support to coordinate network activities, facilitate network collaboration, and engage in interaction with the broader community
2. Coordinate the development of ARTnet resource sharing policies and build a scalable resource sharing infrastructure to facilitate cross-utilization of ArtNet resources
3. Coordinate the implementation of ARTnet data standards, develop improved data integration method, and provide multidisciplinary analytical expertise to enhance the ARTnet research capability.

Overlap: None

Title: Transcriptomic classification of non-muscle invasive bladder cancer and its clinical and prognostic implication (1 R01 CA257480-01)
Time Commitments: 1.20 calendar (PI- Tang/Kwan)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Joanne W Elena
Performance Period: 09/01/2022-08/31/2027
Level of Funding:
Brief description of project's goals: The goal of this project is to address the unmet and understudied need to define molecular subtypes of non-muscle invasive bladder cancer using data and samples from the Bladder Cancer Epidemiology, Wellness and Lifestyle Study (Be-Well), the largest prospective cohorts of newly diagnosed non-muscle invasive bladder cancer patients to date, with an ultimate goal to identify molecular signatures to refine the current pathological classification for risk stratification and treatment response prediction for non-muscle invasive bladder cancer patients.
Specific Aims:

1. Develop a risk stratification tool for NMIBC prognostic outcomes by incorporating molecular subtypes, genes, clinicopathological factors, and demographic factors
2. Develop a response prediction tool for BCG outcomes by incorporating molecular subtypes, immune signatures, genes, clinicopathological factors, and demographic factors.

Overlap: None

Title: Cancer Center Support Grant - Bioinformatics Core (5 P30 CA016056-45)
Time Commitment: 1.20 calendar (PI-Johnson)
Supporting Agency: NCI/NIH
Contracting/Grants Officer: Min He
Performance Period: 05/01/2019-04/30/2024
Level of Funding:
Projects Goals: The Bioinformatics Shared Resource ensures that Cancer Center Support Grant (CCSG) investigators have ready access to expert bioinformatics support and service to carry out basic science, translational, clinical, and population-oriented research.
Specific Aims:

1. Roswell Park Cancer Institute's Cancer Center Support Grant (CCSG) includes five programs and 15 cores resources. Support is provided for leadership, developmental funds, planning and evaluation and administration.

Overlap: None

Title: IOTN: Data Management and Resource-Sharing Center at Roswell Park (C180142)
Time Commitment: 0.60 calendar (MPIs- Hutson/Liu/Morgan/Odunsi)
Supporting Agency: NYSTAR
Contracting/Grants Officer: Judith Toll, Judith.Toll@esd.ny.gov, 518-292-5224
Performance Period: 10/01/2018-06/30/2023

Level of Funding:
Projects Goals: To establish the Data Management and Resource-sharing Center (DMRC) as the data science hub of the Cancer Moonshot Immuno-Oncology Translational Network (IOTN) of the National Cancer Institute (NCI), and to integrate the research activities of the IOTN with other Cancer Moonshot Initiative programs.
Specific Aims:

1. Provide a centralized administrative infrastructure to coordinate the IOTN activities
2. Promote the IOTN and engage in the interaction with the broader scientific community
3. Provide multidisciplinary analytic expertise to support the IOTN collaborative research.
4. Develop improved data integration methods to enhance the IOTN research capacity

Overlap: supplemental funding to NIH 1 U24 CA232979-01

Title: Modulating consumption pathways to improve follicular helper T cell and antibody responses
Time Commitments: 1.20 calendar (PI- Xue)
Supporting Agency: Veterans Administration ORD Biomedical Laboratory R&D Merit Award
Contracting/Grants Officer: Carmelen B. Chiusano
Performance Period: 05/01/2022-04/30/2024
Level of Funding:
Brief description of project's goals: Dr. Wang will apply his bioinformatics expertise to the project and perform bioinformatics and biostatistical data analysis for RNA-Seq, TATC-Seq, histone mark ChIP-Seq and transcription factor CUT&RUN data needed for this study.
Specific Aims: See above
Overlap: None

Title: Inhibiting MDSC Biogenesis to Augment Immunotherapy Efficacy in Triple-Negative Breast Cancer (W81XWH-21-1-0060)
Time Commitment: 0.60 calendar months (MPIs-Abrams/Nemeth)
Supporting Agency: Department of Defense
Contracting/Grants Officer: Ashley Schneekloth
Performance Period: 01/01/2022-12/31/2023
Level of Funding:
Project Goals: In this proposed research, we will test the hypothesis that brequinar (BRQ), a small molecule anti-metabolite, induces differentiation of early myeloid progenitors to suppress MDSC biogenesis and improves the efficacy of immune checkpoint inhibitors (ICIs) in TNBC.
Specific Aims:

1. To determine the mechanisms by which BRQ enhances responses to ICIs in preclinical models of metastatic TNBC
2. To test the hypothesis that BRQ suppresses MDSC biogenesis through the induction of early myeloid progenitor differentiation.

Overlap: None

Title: Genetic and Epigenetic Vulnerabilities in Prostate Cancer of African American Men(W81XWH-21-1-0462)
Time Commitments: 0.24 calendar (PI-Woloszynska)
Supporting Agency: Department of Defense
Contracting/Grants Officer: Department of Defense, USA Med Research ACQ Activity 820 Chandler St, Fort Detrick MD 21702-5014, Lymor Barnhard
Performance Period: 08/01/2021-07/31/2023
Level of Funding:
Brief description of project's goals: The overall objective of this proposal is to
identify how epigenetic silencing of GATA4 modifies androgen receptor (AR) signaling in prostate cancer. Our hypothesis is that epigenetically-mediated decrease in GATA4 expression and associated downregulation of AR protein expression reduce AR mediated transcriptional activity in prostate cancer from AA men.

Specific Aims: See above
Overlap: None

Title: The role of HBP1 in controlling breast cancer dormancy reawakening (W81XWH-21-1-0619)
Time Commitments: 0.12 calendar (PI-Gelman)
Supporting Agency: Department of Defense
Contracting/Grants Officer: Department of Defense, USA Med Research ACQ Activity 820 Chandler St, Fort Detrick MD 21702-5014, Lymor Barnhard
Performance Period: 09/01/2021-08/31/2024
Level of Funding:
Brief description of project's goals: we propose to determine if altering HBP1, BRMS1 or BRMS1L expression or complex formation in human and mouse BrCa cell lines affects in vitro dormancy in 3D-EN cultures or in vivo bone dormancy models, and if so, how this correlates with gene engagement by these proteins and changes to the chromatin landscape. Based on preliminary data showing that BrCa dormancy in the 3D-EN culture requires cell-cell interaction.
Specific Aims:

1. we propose to determine if altering HBP1, BRMS1 or BRMS1L expression or complex formation in human and mouse BrCa cell lines affects in vitro dormancy in 3D-EN cultures or in vivo bone dormancy models, and if so, how this correlates with gene engagement by these proteins and changes to the chromatin landscape
2. we will determine which specific adhesion proteins are involved and how they facilitate interaction between BrCa cells and specific EN cells in vitro and in vivo
3. we propose to determine whether CyH can increase BrCa quiescence in our 3D-EN and in vivo bone metastasis models, and whether this is regulated by p38MAPK and HBP1

Overlap: None

Title: The Role of Mitochondrial Unfolded Protein Responses in Resistant Prostate Cancer
Time Commitments: Effort as needed (PI-Chandra)
Supporting Agency: Roswell Park Alliance Foundation
Contracting/Grants Officer: Judith Epstein
Performance Period: 01/21/2021-01/20/2023
Level of Funding:
Brief description of project's goals: The goal of this grant is to define the mechanistic role of mitochondrial unfolded protein response in developing resistant prostate cancer.
Specific Aims: See above
Overlap: None

Title: Activation of interferon response with chromatin damaging therapy
Time Commitments: 0.53 calendar (PI- Gurova)
Supporting Agency: Roswell Park Alliance Foundation
Contracting/Grants Officer: Judith Epstein,
Performance Period: 01/21/2022-12/31/2022
Level of Funding:
Brief description of project's goals: The major goals of this project are to: 1. Establish an input of IFN-I signaling in tumor versus host cells in anti-cancer activity of CBL0137. 2. Demonstrate that the degree of IFN-I activation correlates with the degree of chromatin damage caused by different curaxins. 3. Run proof of principle study to identify candidate markers demonstrating the presence of functional IFN-I response in tumor cells.
Specific Aims: See above
Overlap: None

PENDING SUPPORT

Title: Transcriptional Control of Therapeutic Response in Pancreatic Ductal Adenocarcinoma (1 R01 CA262058-01A1)
Time Commitments: 0.60 calendar (PI- Abel)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Pending
Performance Period: 04/01/2022-03/31/2027
Level of Funding:
Brief description of project's goals: Our main hypothesis is that HNF1A is directly regulated by BRD4 and MYC, which are targeted by BETi, and that the inhibition of HNF1A by BETi nullifies HNF1A-mediated adaptive resistance to MEKi/ERKi and PCSCs. In Specific Aim 1, we will characterize the regulation of HNF1A by BETi targets BRD4 and MYC.
Specific Aims:

1. Defining regulation of HNF1A by BRD4, MYC, and BETi, and the role of HNF1A in the oncogenic activity of BRD4 PDA.
2. Establishing BETi as a means to ablate HF1A-mediated MEKi/ERKi resistance.

Overlap: None

Title: Role of CaMK1D in Breast Cancer Progression and Metastasis (1 R01 CA268506-01A1)
Time Commitments: 0.60 calendar (PI- Zhang)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Pending
Performance Period: 04/01/2022-03/31/3027
Level of Funding:
Brief description of project's goals: The overall objective of this application is to understand the underlying molecular mechanisms by which CAMK1D initiates organotrophic metastasis. The central hypothesis is that CAMK1D is a critical trigger for BC initiation and metastasis that functions through activation of the actin-binding protein cortactin signaling. The overarching goal of this research is to determine the cellular and molecular mechanisms by which CAMK1D promotes metastasis.
Specific Aims:

1. Determine the role of TAZ in the context-dependent transcriptional regulation of CAMK1D
2. Determine the role of the actin-binding protein cortacin in CAMK1D-induced cell migration and BC metastasis
3. Determine the role of CAMK1D-activated CREB1 signaling in metastatic tumor cell survival

Overlap: None

Title: Establishing a Role for STAG2 in Modulating the Replication Stress Response in Ewing Sarcoma
Time Commitments: 1.20 calendar (PI- Ohm)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Pending
Performance Period: 07/01/2022-06/30/2027
Level of Funding:
Brief description of project's goals: This proposal has been carefully crafted to test our overall hypothesis is that STAG2 plays an essential role in the DNA damage response in Ewing sarcoma, and that loss of STAG2 promotes tumor progression by inhibiting efficient repair and increasing epigenomic instability. We believe that this contributes to the ultimately poor prognosis in these patients and serves as a strong justification for pursuing a translational approach combining drugs which target the DDR pathway with epigenetic remodeling agents.
Specific Aims:

1. To determine whether STAG2 loss increases genetic and epigenetic instability in vitro
2. To determine whether STAG2 mutant Ewing sarcoma cells have increased sensitivity to therapeutics which target the replication stress response in Ewing sarcoma cells in vitro.

Overlap: None

Title: Epidemiological and mechanistic evaluation of germline mutations in SLCO transporters for prediction of aggressive prostate cancer
Time Commitments: 0.0 calendar (PI- Tang)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Pending
Performance Period: 12/01/2022-11/30/2027
Level of Funding:
Brief description of project's goals: The overarching goal of the study is to develop predictive biomarkers for differentiating aggressive from indolent prostate cancer (PCa) at the time of diagnosis considering racial genetic background.
Specific Aims:

1. Determine predictive values of germline mutations in SLCO2A1 and 5A1 for the PCa aggressive phenotypes in a validation cohort (273 AA and 2,875 EA)
2. Determine cell type-specific function of SLO2A1 and 5A1 and functional consequence of germline mutations in cell models.

Overlap: None

Title: The role of TAZ-CAMK1D-CTTN signaling axis in breast cancer progression and metastasis
Time Commitments: 0.60 calendar (PI- Zhang)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Pending
Performance Period: 09/01/2022-08/31/2027
Level of Funding:
Brief description of project's goals: The overarching goal of this research is to determine the cellular and molecular mechanisms by which CAMK1D promotes metastasis. Our long-term goal is to use this information to identify therapies which can convert disseminated disease into a stable state, leading to large improvements in long-term survival in patients with established metastases.
Specific Aims:

1. Determine the role of TAZ in the context-dependent transcriptional regulation of CAMK1D
2. Determine the rold of CTTN in CAMK1D-induced BC cell migration
3. Validate CAMK1D as a therapeutic target for the treatment of MBC

Overlap: None

Title: Exosome targeting by oncolytic virus to improve oral squamous cell carcinoma immunotherapy
Time Commitments: 0.24 calendar (PI- Kuriakose)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Pending
Performance Period: 09/01/2022-08/31/2024
Level of Funding:
Brief description of project's goals: The overall goal of this application is to design and test novel combinatorial treatments that may be clinically translated to improve therapeutic outcomes for OSCC patients.
Specific Aims:

1. To determine the impact of exosome inhibition on tumor infiltrating leukocyte populations and ICI efficacy
2. To establish whether engineered Vaccinia Virus can disrupt exosome production selectively in the TME and improve ICI efficacy

Overlap: None

Title: ANTI-ANXIETY DRUGS PROMOTE CHEMORESISTANCE IN PANCREATIC CANCER
Time Commitments: 0.24 calendar (PI- Feigin)
Supporting Agency: NIH/NCI

Contracting/Grants Officer: Pending
Performance Period: 09/01/2022-08/31/2027
Level of Funding:
Brief description of project's goals: Our central hypothesis is that BZDs that potentiate GPR68 signaling will stimulate CAF activity resulting in increased desmoplasia and chemoresistance. This hypothesis will be tested in mouse and organoid models of pancreatic cancer.
Specific Aims:

1. Directly link LOR-mediated cancer phenotypes to GPR68 activation on CAFs
2. Determine effects of BZDs and chemotherapy on TiME and therapeutic response
3. Assess clinical correlates of BZD use in PDA patients

Overlap: None

Title: Defining new roles of Galectin-3 in allogeneic hematopoietic cell transplantation
Time Commitments: 0.60 calendar (PI- Mohammadpour)
Supporting Agency: NIH
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2028
Level of Funding:
Brief description of project's goals: Our goal is to explore and define the role of Gal-3 in aGvHD.
Specific Aims:

1. Examine the cellular and molecular mechanisms by which Gal-3 signaling impacts the differentiation and function of donor T cells
2. Evaluate how Gal3 expression in recipient cells regulates GI tract repair and the microbiome after allo-HCT
3. Study the correlation of plasma levels of Gal3 with aGvHD severity in allo HCT patients as a new, independent prognostic biomarker for aGvHD

Overlap: None

Title: Targeting replication stress in FET fusion soft tissue sarcomas
Time Commitments: 1.20 calendar (PI- Ohm)
Supporting Agency: NIH
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2028
Level of Funding:
Brief description of project's goals: This study will investigate the molecular vulnerabilities associated with elevated replication stress (RS) in Ewing sarcoma and investigate the mechanisms by which RSR targeting agents disrupt the ability of Ewing sarcoma cells to compensate for elevated RS including RSR modulated HRR and fork reversal/restart. The goal is to use this increased understanding of the unique molecular vulnerabilities of both RS and the RSR in Ewing sarcoma to rationally design novel therapeutic combinations which will synergize with commonly deployed fork stalling agents used for relapsed/refractory Ewing Sarcoma.
Specific Aims:

1. To measure the extent to which chemotherapy regimens commonly deployed in the relapsed/refectory setting exacerbate RS throughout the Ewing sarcoma genome
2. To optimize synergistic cell death between chemotherapeutic agents used in the relapse/refractory setting and RSR targeting agents in vivo using Ewing sarcoma CDX and PDX models
3. To determine how Ewing sarcoma tumors evolve in response to RSR targeted therapy in vivo.

Overlap: None

Title: Epigenetic aging as a driver of racial disparities in early onset prostate cancer
Time Commitments: 0.60 calendar (PI- Woloszynska-Read)
Supporting Agency: NIH
Contracting/Grants Officer: Pending

Performance Period: 04/01/2023-03/31/2028
Level of Funding:
Brief description of project's goals: This study is designed to investigate how ancestry/race affects accelerated epigenetic aging in AA PrCa patients, and relies on previous work demonstrating that ribosomal DNA (rDNA) methylation harbors the rDNA clock, a sensitive and evolutionarily conserved determinant of biological aging4.
Specific Aims:

1. Determine whether African American (AA) prostate cancer patients have an increased rDNA methylation age at diagnosis when compared with age matched European American (EA) prostate cancer patients
2. Determine whether African American (AA) men with prostate cancer have an increased rDNA methylation age at diagnosis when compared with age and race matched non-cancer controls.
3. Assess the performance of the rDNA methylation clock in the African American (AA) prostate cancer patients age range relative to alternative metrics of epigenetic aging.

Overlap: None

Title: Immune sensitivity and initiative events in dedifferentiated human renal cell carcinoma
Time Commitments: 0.60 calendar (PI- Kauffman)
Supporting Agency: NIH
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2028
Level of Funding:
Brief description of project's goals: The goal of our research is to identify molecular initiators of sRCC and mechanisms of sensitivity to ICB.
Specific Aims:

1. To identify the transcriptional states that promote initiation and transition to sRCC
2. To examine if genomic instability underlying sRCC results in an exploitable immunogenic vulnerability during ICB
3. To prospectively validate the prognostic and predictive value of a RNA dedifferentiation biomarker signature in nephrectomy patient candidates for adjuvant ICB therapy

Overlap: None

Title: Investigating the role of GATA4 in prostate cancer initiation, progression and response to therapy
Time Commitments: 0.24 calendar (PI- Woloszynska-Read)
Supporting Agency: NIH
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2028
Level of Funding:
Brief description of project's goals: The overall objective of this proposal is to dissect the mechanisms that both regulate and are regulated by GATA4 loss which ultimately lead to prostate cancer initiation, increase in DNA repair processes upon radiation therapy, and disease progression.
Specific Aims:

1. Determine how epigenetic silencing and genetic loss of GATA4 impact prostate cancer
2. Determine biological impact of GATA4 loss on prostate cancer initiation and progression
3. Evaluate the role of GATA4 in radiation sensitivity and DNA repair response

Overlap: None

Title: The Role of Oxidative Phosphorylation Complex I in Alzheimer's Disease
Time Commitments: 0.12 calendar (PI- Chandra)
Supporting Agency: NIH
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2025

Level of Funding:
Brief description of project's goals: Using Ndufa1S55A knock-in mouse model with reduced Complex I assembly and activity, a unique mouse model that we have access to study molecular insights on AD biology, we will dissect the underlying mechanism on how inhibition of Complex I reduces the levels b-amyloid and phospho-tau as well as analyze their functional significance.
Specific Aims:

1. Characterize the role of partial Complex I deficiency on the levels and functional significance of b-amyloid and phospho-tau in mouse brain.Determine biological impact of GATA4 loss on prostate cancer initiation and progression
2. Impact of partial Complex I deficiency on mitochondrial priming and apoptosis.

Overlap: None

Title: Discovering prognostic lipid markers of metastatic prostate tumors with novel optical Omics platform
Time Commitments: 0.10 calendar (PI- Pliss)
Supporting Agency: Department of Defense
Contracting/Grants Officer: Pending
Performance Period: 07/01/2023-06/30/2026
Level of Funding:
Brief description of project's goals: Dr. Wang will provide bioinformatics expertise to complement the strengths in bioinformatics and biostatistical data analysis for mitochondrial detection needed in this study.
Specific Aims: see above
Overlap: None

Title: The Study of Apoptosome Dynamics in Prostate Cancer Racial Diversity
Time Commitments: 0.12 calendar (PI- Chandra)
Supporting Agency: Department of Defense
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2026
Level of Funding:
Brief description of project's goals: We propose to study the novel regulation of Nrf1 by c-Myc and NF-κB. The current therapeutics are not effective in AA patients with PCa due CC-deficiency, thus this project has translational potential in improving therapeutic outcome AA PCa patients. Additionally, differential expression of CC may be used as a prognostic marker for defining apparent PCa racial disparity among American men.
Specific Aims:

1. Establish that CC-deficiency contributes to therapeutic resistance in AA men with PCa
2. Characterize the molecular insights on CC-deficiency and therapeutic resistance in AA men with PCa
3. Investigate whether CC levels associate with altered cellular plasticity and differentially reinvigorate immune response in AA and CA men with PCa

Overlap: None

Title: The role of mitochondria in prostate cancer racial dispartity
Time Commitments: 0.24 calendar (PI- Chandra)
Supporting Agency: Department of Defense
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2026
Level of Funding:
Brief description of project's goals: We hypothesize that restoring mitochondrial dysfunction (OXPHOS defects) is one of the key reasons for apoptosis resistance and aggressive PCa in AA men.
Specific Aims:

1. Determine underlying mechanism(s) of mitchondrial dysfunction in AA men with PCa

2. Define how defective mitochondria modulate mitochondrial reprogramming and apoptotic machinery
3. Investigate whether mitochondrial priming in primary tumors determine chemotherapy response and whether restoration of mitochondrial function improve efficacy of current therapeutics in AA men with PCa

Overlap: None

Title: Novel approach to target therapeutic resistance in prostate cancer
Time Commitments: 0.24 calendar (PI- Chandra)
Supporting Agency: Department of Defense
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2026
Level of Funding:
Brief description of project's goals: We hypothesize that UPRmt promotes PCa progression and CRPC development, thus inhibiting of UPRmt overcome therapeutic resistance in PCa. Our objectives are to define molecular mechanisms therapy resistance and explore clinical relevance of inhibiting UPRmt using patient-derived xenografts (PDX) and primary tumor cells.
Specific Aims:

1. Define the interplay between HSP60 and ClpP in PCa. HSP60 silencing inhibited ClpP expression but not vice-versa, suggesting that HSP60 acts as an upstream regulator of ClpP expression
2. Define the importance of HSP60-ClpP axis in developing therapeutic resistance in PCa.
3. Evaluate whether disruption of HSP60-ClpP interaction by DCEM1 induces mitochondrial dysfunction and apoptosis in resistant PCa cells, primary tumor cells, and patient-derived xenografts (PDXs).

Overlap: None

Title: Arachidonic Acid-Rich Diet Provides Therapeutic Benefits to Colon Cancer Patients by Maintaining an M1 Macrophage State
Time Commitments: Effort as needed (PI- Dey)
Supporting Agency: Department of Defense
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2025
Level of Funding:
Brief description of project's goals: In this research proposal, we propose that LT signaling is an attractive therapeutic target for TAM reprogramming. Here we will define the AA pathway as a modulator of TAM state. We will test the novel hypothesis that the AA pathway maintains M1-like macrophage functional state that ameliorates CRC progression.
Specific Aims: See above
Overlap: None

Title: Exosome targeting by oncolytic virus to improve oral cancer immunotherapy
Time Commitments: 0.24 calendar (PI- Kuriakose)
Supporting Agency: Department of Defense
Contracting/Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2025
Level of Funding:
Brief description of project's goals: The overall goal of this application will be to leverage these novel data to improve clinical outcomes for OSCC patients. Therefore we have assembled a team of head and neck cancer biology experts and a collaborator with OV expertise.
Specific Aims: See above
Overlap: None

PREVIOUS SUPPORT

Title: Immuno-Oncology Translation Network: Data Management and Resource-Sharing Center at Roswell Park (3 U24 CA232979-01S5)
Time Commitment: Effort as needed (MPIs- Hutson/Liu/Morgan/Odunsi)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Lillian Kuo
Performance Period: 09/01/2021-10/31/2022
Level of Funding:
Projects Goals: The goal of our Data Management and Resource-Sharing Center (DMRC) application is to serve as an administrative and analytic hub for translational studies in the NCI-supported Immuno-Oncology Translational Network (IOTN).
Specific Aims:

1. Provide a centralized administrative infrastructure to coordinate the IOTN activities.
2. Promote the IOTN and engage in the interaction with the broader scientific community.
3. Provide multidisciplinary analytic expertise to support the IOTN collaborative research.
4. Develop improved data integration methods to enhance the IOTN research capacity.

Overlap: Supplemental funding to U24 CA232979
Dr Wang is no longer working on the project.

Title: Drugging Gene/Pathway Dependencies in Pancreatic Cancer (2 UL1 TR001412-05A1)
Time Commitment: 0.12 calendar (PI-Murphy)
Supporting Agency: UB/National Center for Advancing Translational Sciences
Contracting/Grants Officer: Jamie Mihoko Doyle
Performance Period: 4/15/2020-5/31/2024
Level of Funding:
Projects Goals: The vision for our CTSA hub is to perform innovative research across the translational spectrum to improve the health of our community and the nation. We will develop, test and share novel approaches to engage difficult-to-engage populations and reduce health disparities in our community, which represents a "population of the future".
Specific Aims:

1. Accelerate innovative translational research with teams that engage communities, regional stakeholders and the national consortium.
2. Train an excellent, diverse workforce to advance translation of discoveries.
3. Enhance inclusion of special populations across the lifespan and difficult-to-engage populations.
4. Streamline clinical research processes focusing on quality and efficiency with emphasis on multisite studies.
5. Develop, test and share biomedical informatics tools to integrate data from multiple sources to speed translation.

Overlap: None

Title: Drug susceptibilities in fusion oncogene-driven pediatric sarcomas (5 R21 CA235092-02)
Time Commitment: 0.12 calendar (PI-Gelman)
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Sudhir Kondapaka
Performance Period: 07/01/2019-06/30/2022
Level of Funding:
Projects Goals: The current proposal seeks to identify drug sensitivities for these undruggable cancers by combining functional genomic synthetic lethality screens with bioinformatics analyses that identify essentiality pathways and their linked drug sensitivities.
Specific Aims:

1) Use synthetic lethality screens to identify ScS/ES-specific essentiality genes.
2) Analyze human ScS tumors for essentiality pathway signatures.

Overlap: None
Dr Wang is no longer working on the project.

Title: Modulation of Cancer Specific Transcriptional Factors with Small Molecules (5 R01 CA197967-05)
Time Commitment: 0.60 calendar (PI-Gurova)
Supporting Agency: NCI/NIH
Contracting/Grants Officer: Sharad Kumar Verma
Performance Period: 08/01/2015-07/31/2021
Level of Funding:
Projects Goals: The goal of this study is to facilitate clinical advancement of CX through development of predictive and pharmacodynamics markers of curaxins efficacy and better understanding of selective toxicity of CX to tumor vs normal cells.
Specific Aims:

1. Explain differential effect of CX on leukemic and normal hematopoietic stem cells using a model of normal and leukemic hematopoiesis in vitro.
2. Determine whether FACT is a prognostic marker of leukemia sensitivity to CX treatment. We hypothesize that FACT can be used as a predictor of sensitivity to CX treatment.
3. Identify novel pharmacodynamic (PD) marker(s) of CX activity in vivo.

Overlap: NONE

Title: Genetic and Epigenetic Prostate Cancer Related Alterations in Early Onset Disease in African American Men (AA) (W81XWH-17-1-01-15)
Time Commitment: 0.60 calendar (PI-Woloszynska)
Supporting Agency: DOD
Contracting/Grants Officer: Lymor R. Barnhard
Performance Period: 04/01/2017-03/31/2021
Level of Funding:
Projects Goals: The objective of the proposal is to identify clinically relevant genomic and epigenomic events characteristic for prostate cancer in AAs and compare/contrast those with/to prostate cancer in European American men (EAs). These findings will be annotated with DNA methylation, gene expression, and demographic, environmental exposures, clinical, pathological and oncological outcomes.
Specific Aims:

1. Determine the relative frequency of genetic lesions found in PCa in AAs and EAs.
2. Determine novel, clinically relevant methylomic and transcriptomic differences in PCa from AAs and EAs.

Overlap: NONE

Title: Targeting the Tumor Mutanome for Personalized Vaccination Therapy in Ovarian Cancer (5 P30 CA016056-36)
Time Commitment: 0.60 calendar (PI-Johnson)
Supporting Agency: NIH
Contracting/Grants Officer: Kimery Griffin
Performance Period: 05/01/2012-04/30/2016
Level of Funding:
Project Goals: Goal is to harness the potential of cellular immune responses for improving outcome for patients with epithelial ovarian cancer (EOC).
Specific Aims:

1. To sequence the exome and transcriptome of 5 tumors and matching normal from patients with EOC to identify expressed nonsynonymous, primarily missense, mutations resulting in unique antigenic epitopes. We will focus on HLA-A2 patients and use these mutations, to predict the T cell epitopes potentially recognizable by the immune systems of the individual patients.

2. Test the ability of the predicted HLA class I epitopes to stimulate the CD8+ T cells derived from peripheral blood and tumors of the patients. Because of the critical role of CD4+ T cells in determining the outcome of CD8+ T cell responses, we will similarly test CD4+ T cells.

Overlap: NONE

Title: Pro-Oncogenic Function of Tumor Suppressor Protein Stag2 in Bladder Cancer (IRG-14-194-11)
Time Commitment: 0.12 calendar (PI-Woloszynska-Read)
Supporting Agency: American Cancer Society
Contracting/Grants Officer: Judith Epstein
Performance Period: 09/28/2016-12/31/2017
Level of Funding:
Projects Goals: A possible role of STAG2 as a tumor suppressor gene in BC and its role in tumor progression prompted us to examine STAG2 protein expression in NMIBC and MIBC. To this end, TMAs containing specimens from NMIBC and MIBC were generated at the RPCI by Pathology Resource Network (PRN). STAG2 expression was quantified via IHC staining with previously evaluated antibodies. Surprisingly, we found that loss of STAG2 protein expression is significantly correlated with increased overall survival and progression free survival in MIBC but not in NMIBC patients, suggesting that STAG2 may play different roles in the above BC subtypes.
Specific Aims:

1. To establish the functional role of novel STAG2 target genes in STAG2-dependent regulation of invasion in MIBC cells.
2. To identify prognostic significance of STAG2 alone or in combination with its downstream targets in bladder cancer progression.

Overlap: NONE

Title: PTPN14 and YAP tyrosine modification regulate YAP oncogenic functions (No grant number)
Time Commitment: 0.60 calendar (PI-Zhang)
Supporting Agency: American Cancer Society
Contracting/Grants Officer: Michael H, Melner
Performance Period: 01/01/2015-12/31/2018
Level of Funding:
Projects Goals: Our central hypothesis is that PTPN14 negatively regulates YAP oncogenic functions at two levels: 1) binding and activation of other negative upstream YAP regulators such as Kibra and Lats1/2; 2) direct binding to YAP and dephosphorylation of YAP-tyrosine 188, thus leading to cytoplasmic sequestration of YAP.
Specific Aims:

1. To investigate the mechanisms by which PTPN14, Kibra and Lats1 interactions regulate YAP.
2. The effects of YAP tyrosine modification on its oncogenic functions.
3. The effects of PTPN14 and tyrosine modification of YAP on breast tumor formation and metastasis.

Overlap: NONE

Title: Herd of Hope Core C: The RB1 Network as a Key to Understanding Cancer Etiology and Therapeutic Response (No Grant Number Assigned)
Time Commitment: 0.12 calendar (PI-Glenn)
Supporting Agency: Roswell Park Alliance Foundation
Contracting/Grants Officer: Judith Epstein
Performance Period: 03/15/2019-03/14/2020
Level of Funding:
Projects Goals: This research program includes three major projects studying different aspects of the Rb1-network, different targeted cancer therapies (e.g. osimertinib, palbociclib), and different cancers (e.g. lung, breast, pancreatic).
Specific Aims:

1. Project 1 will determine how the Rb1-network influences acquired resistance of lung cancer to osimertinib.
2. Project 2 studies mechanisms of resistance to palbociclib, a drug specifically targeting the Rb1-network, in the context of breast and pancreaticcancer.
3. Project 3 seeks to uncover unique vulnerabilities in cancer cells lacking a functional Rb1-network that can be exploited for cancer therapy. The projects are supported by 3 cores which will develop new technology customized for study of the Rb1-network, including patient derived organoid cultures which facilitate experiments with patient material.

Overlap: NONE

Title: Programing hematopoietic stem cells for long-term targeted T cell therapy of patients with relapsed ovarian cancer (C030158)
Time Commitment: 0.60 calendar (PI-Odunsi)
Supporting Agency: New York State Department of Health
Contracting/Grants Officer: Farrah M. O'Brien
Performance Period: 10/01/2015-09/30/2020
Level of Funding:
Projects Goals: The goal of our studies is to harness the immune system for improving the outcome of patients with ovarian cancer. While the majority of women with advanced stage ovarian cancer respond to surgery and first-line chemotherapy, most of these responses are not durable and more than 70% of patients die of chemoresistant disease within 5 years of diagnosis.
Specific Aims:

1. To test for TCR gene transfer into human hematopoietic stem/progenitor cells utilizing TCRs from a unique subset of tumor recognizing CD4+ Th1 cells that potently mediate tumor rejection and provide help to CD8+ T cells.
2. To develop and validate protocols for IND qualification.
3. To test in a Phase I study, the safety, in vivo persistence and anti-tumor efficacy of adoptively transferred CD4TCR transduced hHSCs, in combination with autologous mature T Cells expressing affinity enhanced CD8TCRs, in patients with chemo-resistant ovarian cancer.

Overlap: NONE

Title: Decoding the Molecular and Cellular Landscape of Meta Small Renal Tumor (No grant number)
Time Commitment: 0.30 calendar (PI-Kauffman)
Supporting Agency: Roswell Park Alliance Foundation
Contracting/Grants Officer: Judith Epstein
Performance Period: 11/03/2017-12/31/2020
Level of Funding:
Projects Goals: One of the mail goals is to survey the DNA mutation al landscape and identify those mutations specific to metastatic small renal tumors relative to nonmetastatic small renal tumors.
Specific Aims:

1. Survey the DNA mutational landscape and identify those mutations specific to metastatic small renal tumors relative to nonmetastatic small renal tumors.
2. Identify gene expression alterations at the RNA and protein levels specific to metastatic small renal tumors relative to nonmetastatic small renal tumors.
3. Identify immune cell profiles in patient blood specific to metastatic small renal tumors relative to nonmetastatic small renal tumors.

Overlap: NONE
Dr Wang is no longer working on the project.

Title: Longitudinal Genomine-Wide Transcriptome Study of PTSD Symptom Change in WTC Responders (5 U01 OH11478-03)
Time Commitment: 0.60 calendar (PI-Kuan)

Supporting Agency: NIH/SUNY Stonybrook/NIH
Contracting/Grants Officer: James Yiin
Performance Period: 07/01/2018-06/30/2021
Level of Funding:
Projects Goals: The proposed study builds on an extensive pilot study by evaluating the association between change in gene expression with changes in PTSD and LRS symptom severity across an 18-month period, using cutting edge RNA-sequencing. By characterizing the transcriptome patterns and pathways for these symptoms, our goal is to shed light on the biological mechanisms underlying this comorbidity, which can help prevent the exacerbation of physical symptoms by intervening at the level of etiological pathway.
Specific Aims:

1. We will investigate the association between changes in gene expression (gene, isoform and splice variant levels) and changes in PTSD symptoms across an 18-month period at gene as well the genetic pathways implicated by these changes; and identify the Gene Expression Signature (GES) associated with change in PTSD symptoms.
2. We will evaluate whether the GES is associated with change in each PTSD symptom dimension (re-experiencing, avoidance, numbing, hyperarousal). We expect to find both common and distinct genes/pathways regulating the change in each PTSD symptom dimension.
3. We will test the directionality of prospective associations between the GES score and PTSD symptom severity, i.e., whether the GES at the first time point predicts PTSD severity 18 months later, and vice versa.
4. We will evaluate whether the change in GES is associated with change in LRS. We hypothesize that any association observed between the GES and LRS will be mediated by change in PTSD symptom severity, indicating shared biological mechanisms underpinning PTSD-LRS comorbidity.

Overlap: NONE
Dr Wang is no longer working on the project.

IN-KIND

*Summary of In-Kind Contribution: Nothing to Report

***Overlap** (summarized for each individual): New York State award, C180142 provides supplemental funding for NIH award 1 U24 CA232979-01. This other support lists all pending projects for which funding decisions have not yet been received. Dr. Wang will ensure that his effort will not exceed 12 calendar months. Effort will be reviewed and adjusted to account for new awards and required approvals will be obtained.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with US Army Medical Research Acquisition Activity terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature: Jianmin Wang Digitally signed by Jianmin Wang Date: 2022.09.19 09:25:38 -04'00'

Date: _____

QIANQIAN ZHU, PhD

CURRENT SUPPORT

Title: The Role of TAZ in Breast Cancer Initiation and Progression (5 R01 CA207504-05)
Time Commitments: 0.60 calendar (PI-Zhang)
Supporting Agency: NIH/NCI
Grants Officer: Elizabeth G Snyderwine
Performance Period: 07/01/2017-06/30/2023
Level of Funding:
Brief Description of Project's Goals: Our long-term goal is to understand the mechanisms of TNBC relapse and thus help to improve the survival of breast cancer patients. Our overall objective here, which is the next step in pursuit of that goal, is to determine how TAZ activation induces TNBC tumor progression and metastasis. Our central hypothesis is that both TAZ-dependent cell cycle activation and expansion of transformed mammary stem cell (Ma-SC) populations are required for TAZ-initiated breast tumorigenesis. Our hypothesis has been formulated on the basis
List of Specific Aims:

1. Identify the critical downstream targets that are required for TAZ-initiated oncogene addiction.
2. Determine how TAZ induces the formation of heterogeneous mammary tumors using a unique TAZ transgenic mouse model.
3. Determine the role of TAZ in breast tumor heterogeneity and its impact on tumor metastasis.

Overlap: NONE

Title: Immuno-Oncology Translational Network: Data Management and Resource-Sharing Center at Roswell Park (1 U24 CA232979-01)
Time Commitments: 3.0 calendar (PIs-Hutson/Liu/Morgan/Odunsi)
Supporting Agency: NIH/NCI
Grants Officer: Lillian Kuo
Performance Period: 09/30/2018-06/30/2023
Level of Funding:
Brief Description of Project's Goals: The goal of our Data Management and Resource-Sharing Center (DMRC) application is to serve as an administrative and analytic hub for translational studies in the NCI-supported Immuno-Oncology Translation Network (IOTN).
List of Specific Aims:

1. Provide a centralized administrative infrastructure to coordinate the IOTN activities
2. Promote the IOTN and engage in the interaction with the broader scientific community
3. Provide multidisciplinary analytic expertise to support the IOTN collaborative research
4. Develop improved data integration methods to enhance the IOTN research capacity

Overlap: NONE

Title: Somatic Mutations and Their Etiological Determinants for Breast Cancer in African American Women (5 R01 CA228156-04)
Time Commitments: 0.60 calendar (PI-Yao)
Supporting Agency: NIH/NCI
Grants Officer: Damali Martin
Performance Period: 02/01/2019-01/31/2024
Level of Funding:
Brief Description of Project's Goals: Women of African ancestry are more likely to have highly aggressive breast cancer and die from the disease than their counterparts of European ancestry. This study will comprehensively research the genetic mutations in breast tumors in 3,000 women of African ancestry and identify possible causes of the tumor mutations. Results of the study have the potential to improve breast cancer prevention and treatment, particularly for the understudied African American populations.
List of Specific Aims:

1. We will characterize mutational landscape of TNBC in AA women by performing whole-exome sequencing and RNA-sequencing of 500 tumors. We will identify and compare significantly mutated genes and mutational signatures in AA TNBC cases with EA cases from public data sources, to test whether there are population-level differences
2. Based on data from Aim 1 and published literature, we will assemble a targeted gene panel and sequence an additional 2,500 AA tumors, inclusive of all subtypes. The design will cover all genes included in B-CAST, an ongoing breast tumor sequencing project of EA cases in Europe. Data generated in Aim 2 will be used to validate SMGs identified in Aim 1, and to further assess population-level mutational differences in comparison to EA data from B-CAST and others across all cancer subtypes.
3. We will examine etiological links between hormone-related risk factors for breast cancer and somatic mutations.
4. We will examine genetic ancestry and genetic variants with tumor mutations.

Overlap: NONE

Title: The Role of Tumor-Infiltrating Immune Cells and Estrogen Receptor Expression in Racial Disparities in Breast Cancer Biology (5 R03 CA238792-02)
Time Commitments: Effort as needed (PI- Omilian)
Supporting Agency: NIH/NCI
Grants Officer: Danielle M Carrick
Performance Period: 12/01/2019-11/30/2022
Level of Funding:
Brief description of project's goals: Our proposal involves the full implementation of a new generation of biomarker assessment techniques – multiplexed staining, multispectral imaging, automated scoring, and digital spatial analyses. A thorough comparison of the immune landscape in breast tumors in regards to race and ER expression will inform our understanding of immune escape mechanisms, and how these processes differ by ancestry.
List of Specific aims: See above
Overlap: NONE

Title: Immuno-Oncology Translation Network: Data Management and Resource-Sharing Center at Roswell Park (3 U24 CA232979-01S5)
Time Commitment: Effort as needed (PIs- Hutson/Liu/Morgan/Odunsi)
Supporting Agency: NIH/NCI
Grants Officer: Lillian Kuo
Performance Period: 09/01/2021-10/31/2022
Level of Funding:
Projects Goals: The goal of our Data Management and Resource-Sharing Center (DMRC) application is to serve as an administrative and analytic hub for translational studies in the NCI-supported Immuno-Oncology Translational Network (IOTN).
Specific Aims:

1. We will provide a centralized administration infrastructure to coordinate DRSN activities, building upon the IOTN DMRC's well-functioning infrastructure that currently coordinates network studies under the umbrella of the NCI Cancer Moonshot initiative.
2. We will actively promote the DRSN and foster trans-consortium interactions, where we will leverage the IOTN DMRC's demonstrable experience in Cross-Moonshot outreach and Bioconductor's decades-long record in community-wide engagement.
3. We will provide multidisciplinary expertise to support DRSN collaborative research, leveraging four of the Roswell Park CCSG's shared resources: Biostatistics, Bioinformatics, Data Bank and BioRepository, Bioanalytics, Metabolomics & Pharmacokinetics. Our analytic support will be armed with professional IT staff and informed by an experienced anti-cancer therapeutic researcher team.
4. We will develop innovative multi-omics data integration methods to enhance DRSN's research capacity, capitalizing on the well-respected and highly-successful Bioconductor project.

5. We will disseminate resources developed in the DRSN to the broader community, unleashing the full potential of DRSN activities. Taken together, we envision our CC, in close collaboration with the DRSN components, will allow us to conduct highly effective and innovative translational studies to address the significantly unmet needs related to anti-cancer therapeutics, and fulfill the expectations and guiding principles of NCI Cancer Moonshot initiative.

Overlap: Supplemental funding to U24 CA232979

Title: Immuno-Oncology Translation Network: Data Management and Resource-Sharing Center at Roswell Park (3 U24 CA232979-01S7)
Time Commitment: Effort as needed(PIs-Hutson/Liu/Morgan/Odunsi)
Supporting Agency: NIH/NCI
Grants Officer: Lillian Kuo
Performance Period: 07/01/2022-10/31/2022
Level of Funding:
Projects Goals: The goal of our Data Management and Resource-Sharing Center (DMRC) application is to serve as an administrative and analytic hub for translational studies in the NCI-supported Immuno-Oncology Translational Network (IOTN).This is a continuation of project U24 CA232979-01S5
Specific Aims:

1. We will provide a centralized administration infrastructure to coordinate DRSN activities, building upon the Immuno- Oncology Translational Network (IOTN) Data Management and Resource-sharing Center (DMRC)'s well- functioning infrastructure that currently coordinates network studies under the umbrella of the NCI Cancer Moonshot initiative.
2. We will actively promote the DRSN and foster trans-consortium interactions, where we will leverage the IOTN DMRC's demonstrable experience in Cross-Moonshot outreach and Bioconductor's decades-long record in community-wide engagement.
3. We will provide multidisciplinary expertise to support DRSN collaborative research, leveraging four of the Roswell Park CCSG's shared resources: Biostatistics, Bioinformatics, Data Bank and BioRepository, Bioanalytics, Metabolomics & Pharmacokinetics. Our analytic support will be armed with professional IT staff and informed by an experienced anti-cancer therapeutic researcher team.
4. We will develop innovative multi-omics data integration methods to enhance DRSN's research capacity, capitalizing on the well-respected and highly- successful Bioconductor project.
5. We will disseminate resources developed in the DRSN to the broader community, unleashing the full potential of DRSN activities.

Overlap: None

Title: Coordinating and Data Management Center for Acquired Resistance to Therapy Network (1 U24 CA274159-01)
Time Commitments: 1.20 calendar (PI- Hutson/Goodrich/Morgan/Liu)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 09/01/2022-08/31/2027
Level of Funding:
Brief description of project's goals: The goal of our proposed Coordinating and Data Management Center (CDMC) application is to coordinate the activities across the Acquired Resistance to Therapy Network (ARTNet), and to manage, integrate and disseminate the data and resources generated through the network.
List of Specific aims: See above
Overlap: NONE

Title: Multi-ethnic high-throughput study to identify novel non-HLA genetic contributors to mortality after blood and marrow transplantation (1 R01 CA262899-02)
Time Commitments: 1.80 calendar (PI-Hahn/Zhu/Clay-Gilmore)
Supporting Agency: NIH/NCI

Grants Officer: Nonniekaye F Shelburne
Performance Period: 08/01/2021-07/31/2026
Level of Funding:
Brief description of project's goals: This is the first study to use both next-generation sequencing and genome-wide association study data to analyze the contribution of non-HLA genetic variants to mortality after allogeneic blood and marrow transplantation (BMT) for life-threatening hematologic cancers.
List of Specific aims: See above
Overlap: NONE

Title: Cancer Center Support Grant-Biostatistical Core (5 P30 CA16056-45)
Time Commitments: 0.36 calendar (PI-Johnson)
Supporting Agency: NIH/NCI
Grants Officer: Min He
Performance Period: 05/01/2019-04/30/2024
Level of Funding:
Brief Description of Project's Goals: Roswell Park Cancer Institute's Cancer Support Grant (CCSG) includes five programs and 15 core resources. Support is provided for leadership, development funds, planning and evaluation and administration. The Biostatistics Shared Resource ensures that CCSG investigators have ready access to expert biostatisticians support and service to carry out basic science, translational, clinical, and population-oriented research.
List of Specific Aims:

1. Roswell Park Cancer Institute's Cancer Center Support Grant (CCSG) includes five programs and 15 cores resources. Support is provided for leadership, developmental funds, planning and evaluation and administration.

Overlap: NONE

Title: Roswell Park Cancer Center Support Grant-Bioinformatics Core (5 P30 CA16056-45)
Time Commitment: 0.30 calendar months (PI-Johnson/Liu)
Supporting Agency: NIH/NCI
Grants Officer: Min He
Performance Period: 05/01/2019-04/30/2024
Level of Funding:
Projects Goals: The Bioinformatics Shared Resource ensures that CCSG investigators have ready access to expert bioinformatics support and service to carry out basic science, translational, clinical, and population-oriented research. Roswell Park Cancer Institute's Cancer Support Grant (CCSG) includes five programs and 15 core resources. Support is provided for leadership, development funds, planning and evaluation and administration. The Biostatistics Shared Resource ensures that CCSG investigators have ready access to expert biostatisticians support and service to carry out basic science, translational, clinical, and population-oriented research.
List of Specific Aims:

1. Roswell Park Cancer Institute's Cancer Center Support Grant (CCSG) includes five programs and 15 cores resources. Support is provided for leadership, developmental funds, planning and evaluation and administration.

Overlap: None

Title: Roswell Park Ovarian Cancer SPORE: Biostatistics and Bioinformatics Core (2 P50 CA159981-08)
Time Commitments: 0.60 calendar (PI-Moysich)
Supporting Agency: NIH/NCI
Grants Officer: Viviana Knowles
Performance Period: 09/01/2021-08/31/2026
Level of Funding:

Brief description of project's goals: The overall goal of the Roswell Park Ovarian Cancer SPORE is to reduce the morbidity and mortality of ovarian cancer through innovative translational research. It includes individual research projects, supportive cores, and research and career development programs. This proposal brings together basic and applied investigators to conduct innovative and diverse translational investigations aimed at risk stratification, treatment of primary and recurrent ovarian cancer, and prevention of relapse in patients in remission.
List of Specific aims: See above
Overlap: NONE

Title: IOTN: Data Management and Resource-Sharing Center at Roswell Park (C180142)
Time Commitments: 1.56 calendar (PIs- Hutson/Liu/Morgan/Odunsi)
Supporting Agency: NYSTAR
Grants Officer: Judith Toll
Performance Period: 10/01/2018-06/30/2023
Level of Funding:
Brief Description of Project's Goals: To establish the Data Management and Resource-sharing Center (DMRC) as the data science hub of the Cancer Moonshot Immuno-Oncology Translational Network (IOTN) of the National Cancer Institute (NCI), and to integrate the research activities of the IOTN with other Cancer Moonshot Initiative programs.
List of Specific Aims:

1. Provide a centralized administrative infrastructure to coordinate the IOTN activites
2. Promote the IOTN and engage in the interaction with the broader scientific community
3. Provide multidisciplinary analytic expertise to support the IOTN collaborative research.
4. Develop improved data integration methods to enhance the IOTN research capacity.

Overlap: supplemental funding to NIH 1 U24 CA232979-01

Title: The role of HBP1 in controlling breast cancer dormancy reawakening (W81XWH-21-1-0619)
Time Commitments: 0.12 calendar (PI-Gelman)
Supporting Agency: DOD
Grants Officer: Charity L. Keen
Performance Period: 09/01/2021-08/31/2024
Level of Funding:
Brief description of project's goals: Thus, we hypothesize that BrCa dormancy in the EN is facilitated by p38-mediated upregulation of HBP1/BRMS1/BRMSL1 complex formation, which, in concert with associated SIN3A, control cell cycle progression genes through chromatin landscape remodeling.
List of Specific aims:

1. we propose to determine if altering HBP1, BRMS1 or BRMS1L expression or complex formation in human and mouse BrCa cell lines affects in vitro dormancy in 3D-EN cultures or in vivo bone dormancy models, and if so, how this correlates with gene engagement by these proteins and changes to the chromatin landscape;
2. Based on preliminary data showing that BrCa dormancy in the 3D-EN culture requires cell-cell interactions, we will determine which specific adhesion proteins are involved and how they facilitate interaction between BrCa cells and specific EN cells in vitro and in vivo;
3. we propose to determine whether CyH can increase BrCa quiescence in our 3D-EN and in vivo bone metastasis models, and whether this is regulated by p38MAPK and HBP1.

Overlap: NONE

Title: Association of the NTSE Activity with the Graft Versus Leukemia Effect
Time Commitments: Effort as needed (PI-Hahn)
Supporting Agency: Roswell Park Alliance Foundation
Grants Officer: Judith Epstein, Judith.Epstein@RoswellPark.org
Performance Period: 02/03/2022-12/31/2023

Level of Funding:
Brief description of project's goals: Our objective is to test the hypothesis that lower NT5E activity in donor immune cells results in lower adenosine levels via lower expression of CD73 which yields enhanced T- and NK- cell responses and stronger anti-leukemia effects. While we found rare *NT5E* variants in our ExWAS were associated with DRM, we expect to measure a broad range of physiologic NT5E activity in our patient population.
List of Specific aims: See above
Overlap: NONE

PENDING SUPPORT
Title: Defining the tumor immune contexture and myokine milieu as mediators of the associations of physical activity with breast cancer outcomes: Implications of using exercise to improve treatment strategy
Time Commitments: 0.60 calendar (PI- Cannioto)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 04/01/2022-03/31/2027
Level of Funding:
Brief description of project's goals: Our central hypothesis is that meeting the PAGs will be associated with improved BrCa treatment and survival outcomes which are mediated by a hot, tumor suppressive TME (i.e., increased infiltration of CD8+, NK, CD4+ cells, decreased infiltration M2-like macrophages, Tregs, and MDSCs) and increased circulating myokines.
List of Specific aims: See above
Overlap: NONE

Title: Elucidating the role of understudied kinase-CAMK1D in breast cancer progression
Time Commitments: 0.24 calendar (Zhang)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 04/01/2022-03/31/2023
Level of Funding:
Brief description of project's goals: The central hypothesis is that CAMK1D is a critical trigger for BC initiation and metastasis that functions through activation of the actin-binding protein cortactin signaling.
List of Specific aims: See above
Overlap: NONE

Title: A bilingual telemedicine-based intervention (PEDALL) for the prevention of weight gain in childhood ALL patients considering key genetic and sociodemographic risk factors
Time Commitments: 1.20 calendar (PI-Ladas)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 05/01/2022-04/30/2027
Level of Funding:
Brief description of project's goals: To determine the effect of a bilingual, multi-ethnic telemedicine diet and exercise intervention (PEDALL) for the prevention of weight gain in children and adolescents undergoing treatment for acute lymphoblastic leukemia (ALL).
List of Specific aims: See above
Overlap: NONE

Title: A bilingual telemedicine-based intervention (PEDALL) for the prevention of weight gain in childhood ALL patients considering key genetic and sociodemographic risk factors
Time Commitments: 0.60 calendar (PI-Ladas)
Supporting Agency: Department of Defense

Grants Officer: Pending
Performance Period: 09/01/2022-08/31/2026
Level of Funding:
Brief description of project's goals: We propose to examine pre-treatment variables to first determine modifiers of the efficacy of PEDALL and then synthesize this information to develop a multifactorial risk prediction score to identify participants who may benefit the greatest from the intervention.
List of Specific aims: See above
Overlap: NONE

Title: Homologous recombination repair capacity in peripheral blood lymphocytes as a breast cancer risk factor
Time Commitments: 1.80 calendar (PI- Zhao/Liu/Zhu)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 07/01/2022-06/30/2027
Level of Funding:
Brief description of project's goals: Dr. Liu will lead the proposed tumor whole-exome sequencing efforts and further assess the correlation between HRR capacity in PBLs and mutational signatures in breast tumor tissues in Aim 2. He will also collaborate with Drs. Zhao and Zhu on the data analysis of Aim 1 and Aim 3.
List of Specific aims: See above
Overlap: NONE

Title: Impact of germline mutations on the development of breast-implant associated anaplastic large cell lymphoma in women with textured breast implants
Time Commitments: 0.24 calendar (PI- Ghione)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 07/01/2022-06/30/2024
Level of Funding:
Brief description of project's goals: This unusual and absolutely unique combination of studies conducted on this population may allow us to determine if BRCA and other germline mutations are related to lymphomagenesis in people with breast implants, and the relative risk of women with germline mutations to develop BIA-ALCL.
List of Specific aims: See above
Overlap: NONE

Title: Identifying the role of physical activity and immune pathways in breast cancer survival disparities: Implications for using exercise to improve treatment outcomes
Time Commitments: 0.60 calendar (PI- Cannioto)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 07/01/2022-06/30/2027
Level of Funding:
Brief description of project's goals: Our central hypothesis is that the association of RPA with BC survival is mediated by the TME and myokine milieu.
List of Specific aims: See above
Overlap: NONE

Title: Regulation of the immune-tumor interaction in triple-negative breast cancer
Time Commitments: 0.60 calendar (PI- Zhang)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 07/01/2022-06/30/2027

Level of Funding:
Brief description of project's goals: In this study, we will use integrative biology approaches to investigate the cellular and molecular mechanisms behind the TAZ regulation in TME in xenograft and transgenic mouse models we have developed as well as clinical BC tumor samples. Our central hypothesis is that TAZ regulates BC TME by conferring immune evasion, survival, and growth properties to tumor cells.
List of Specific aims: See above
Overlap: NONE

Title: Identifying the role of physical activity and immunity in breast cancer disparities: Implications for using exercise to improve outcomes
Time Commitments: 0.60 calendar (PI- Cannioto)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2028
Level of Funding:
Brief description of project's goals: We will examine how the association of RPA and these potential mediators vary according to BMI, race, ethnicity, BC subtype and tumor stage in a diverse population of women by using the Pathways Study, a large multiethnic cohort of 4,505 BC patients.
List of Specific aims: See above
Overlap: NONE

Title: Dissecting molecular mechanisms of breast cancer metastasis
Time Commitments: 0.36 calendar (PI- Zhang)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 04/01/2023-03/31/2028
Level of Funding:
Brief description of project's goals: The overall objective of this application is to understand the underlying molecular mechanisms by which CAMK1D initiates organotrophic metastasis. The central hypothesis is that CAMK1D is a novel candidate of metastatic BC driver gene that promotes metastatic tumor colonization by activating the signaling of cortactin (CTTN), an actin-binding protein. The overarching goal of this research is to determine the cellular and molecular mechanisms by which CAMK1D promotes metastasis. Our long-term goal is to use this information to identify therapies which can convert disseminated disease into a stable state, leading to large improvements in long-term survival in patients with established metastases.
List of Specific aims: See above
Overlap: NONE

Title: Regulation of the Immune-Tumor Interaction in Triple-Negative Breast Cancer
Time Commitments: 0.60 calendar (PI- Zhang)
Supporting Agency: NIH/NCI
Grants Officer: Pending
Performance Period: 07/01/2022-06/30/2027
Level of Funding:
Brief description of project's goals: In this study, we will use integrative biology approaches to investigate the cellular and molecular mechanisms behind the TAZ regulation in TME in xenograft and transgenic mouse models we have developed as well as clinical BC tumor samples. Our central hypothesis is that TAZ regulates BC TME by conferring immune evasion, survival, and growth properties to tumor cells.
List of Specific aims: See above
Overlap: NONE

PREVIOUS SUPPORT
Title: NRG Oncology Statistical and Data Management Center (5 U10 CA180822-08)

Time Commitment: 0.36 calendar (PI-Dignam)
Supporting Agency: NIH/NCI
Grants Officer: Margaret Marian Mooney
Performance Period: 03/28/19-02/28/25
Level of Funding: *Dr. Zhu is no longer working on this project*
Project Goals: The major goal of this project is to staff and operate the Statistical and Data Center of the NRG, a cooperative research group. It is the function of this office to collect, abstract, code, update, process, analyze and present the data submitted by member institutions. The principal objective is to manage patient data resulting in timely analyses, and logical and appropriate interpretation of data.
Specific Aims: The integrated resources, organizational structure, disease expertise, noteworthy experience, and focused dedication of the Statistics and Data Management Center provide the infrastructure essential for data collection, abstraction, quality control, analysis, and publication of NRG Oncology research.
Overlap: NONE

Title: Multi-ethnic high-throughput study to identify novel non-HLA genetic contributors to mortality after blood and marrow transplantation (1 R01 CA262899-01)
Time Commitments: 1.80 calendar (PI-Hahn/Zhu/Clay-Gilmore)
Supporting Agency: NIH/NCI
Grants Officer: Nonniekaye F Shelburne
Performance Period: 08/01/2021-07/31/2026
Level of Funding: *Dr. Zhu is no longer working on this project*
Brief description of project's goals: This is the first study to use both next-generation sequencing and genome-wide association study data to analyze the contribution of non-HLA genetic variants to mortality after allogeneic blood and marrow transplantation (BMT) for life-threatening hematologic cancers.
List of Specific aims: See above
Overlap: NONE

Title: Infrastructure for Pathways, A Prospective Study of Breast Cancer Survivorship (5 U01 CA195565-05)
Time Commitments: 0.60 calendar (PIs-Kushi/Ambrosone)
Supporting Agency: NIH/NCI
Grants Officer: Joanne W Elena
Performance Period: 06/01/16-05/31/21
Level of Funding:
Brief Description of Project's Goals: In this infrastructure application, we plan to enhance the Pathways Study resource by continuing to follow study participants and documenting outcomes; enhancing biospecimen resources with a follow-up blood sample and tumor biobank; and by adding new data from KPNC medical records, genome-wide assays, and neighborhood characteristics. These activities will make the Pathways Study an outstanding and unique resource for research on breast cancer survivorship and prognosis.
List of Specific Aims:

1. This grant will support the infrastructure of the Pathways study, a prospective cohort of breast cancer patients. It will support collection of data biospecimens and tumor tissues, and follow-up of participants for cancer outcomes.

Overlap: NONE

Title: Genetic underpinnings of ethnic disparities in bone toxicities between Hispanic and non-Hispanic children treated for acute Lymphoblastic leukemia (5 R03 CA223730-02)
Time Commitments: 0.60 calendar (PIs-Yao/Kelly/Zhu)
Supporting Agency: NIH/NCI
Grants Officer: Kelly Filipski, Kelly.filipski@nih.gov
Performance Period: 12/05/17-11/30/20

Level of Funding:
Brief Description of Project's Goals: This R03 grant seeks to perform a novel pharmacogenomic study based on 05-001 and its successor trial DFCI 11-001 to identify genetic underpinnings of ethnic disparities in bone toxicities. We plan to first test global genetic ancestry with bone toxicities, followed by a bivariate genome-wide association study (GWAS) to jointly analyze osteonecrosis and fracture as two related traits.
List of Specific Aims:

1. Determine whether the composition of genetic ancestry in Hispanic children is an underlying cause for the ethnic disparities in therapy-related bone toxicities, namely osteonecrosis and fracture, in children with ALL in the DFCI 05-001 and 11-001 trials.
2. a). Investigate single variants and polygenic risk scores from previous GWAS of bone-related phenotypes with bone toxicities in children treated for ALL.
   b). Identify genetic loci associated with therapy-related bone toxicities by performing bivariate GWAS analyses with directional alignment and meta-analysis in the DFCI 05-001 and 11-001 trials
   c). Investigate whether genetic variants and polygenic scores significant in 2a and 2b explain disparities in bone toxicities between Hispanic and non-Hispanic children with ALL.

Overlap: NONE

Title: Targeting the Methionine Salvage Pathway as a Metabolic Point of Leverage in Novel Therapeutic Approaches for Prostate Cancer (W81-XWH-5-1-0665)
Time Commitments: 0.30 calendar (PI-Smiraglia)
Supporting Agency: DOD
Performance Period: 09/30/15-04/30/16
Level of Funding:
Brief description of project's goals: Our proposal, if successful, will provide the necessary preclinical data needed to open up an entirely new line of clinical investigation for treatment of, or prevention of, advanced prostate cancer. If this novel antimetabolite therapy can collaborate with androgen deprivation to greatly reduce risk of recurrence, then this would be an ideal and highly impactful outcome.
List of Specific aims:

1. We propose to test MTAP inhibition and pharmacological enhancement of SSAT activity in a panel of androgen sensitive and androgen independent CaP cell lines to test for synergy both with and without androgen.
2. We propose to identify individual and combined therapeutic approaches to treat androgen independent CWR22Rv1 and LNCaP C4-2 s.q. xenografts grown in castrate nude mice.
3. We propose to test if these approaches can prevent recurrence during ADT using the LuCaP and CWR22 xenograft models of castration recurrence.

Overlap: NONE

Title: Pharmacoepigenetics of Noncoding RNAs in Breast Cancer (CCR-12225973)
Time Commitments: 0.60 calendar (PI- Yao)
Supporting Agency: Susan Komen Foundation
Grants Officer: Anna Cabanes
Performance Period: 07/01/12-11/26/16
Level of Funding:
Brief Description of Project's Goals: The goal of this study is to investigate genetic variations in noncoding RNAs and target genes in predicting the efficacy of breast cancer adjuvant chemotherapy based on the cooperative group trial SWOG S8897 and a population-based Pathways Study.
List of Specific Aims:

1. To identify germline variants in epigenetic ncRNAs associated with risk of recurrence in a group of 528 women treated with cyclophosphamide-based adjuvant chemotherapy in a prospective trial for early stage breast cancer. To determine if the associations are of prognostic or predictive value, similar analyses will be performed in 1,079 women followed-up without adjuvant treatment.

2. To validate the initial findings in a group of 800 early stage breast cancer patients selected from a prospective cohort and matched on cancer characteristics and treatment with patients from Aim 1.
3. To investigate the functional significance of identified variants in epigenetic ncRNAs using laboratory approaches.

Overlap: NONE

Title: AntiRetroviral PharmacoGenomics, PharmacoKinetics and Toxicity in NEUROAIDS (K08 MH098794)
Time Commitments: 0.99 calendar (PI- Ma)
Supporting Agency: NIH/NIMH
Grants Officer: Deborah Colosi
Performance Period: 07/01/12-06/30/17
Level of Funding:
Brief Description of Project's Goals: The research plan focuses on the development of a model system to improve risk and intervention assessments by integrating genetic data, pharmacokinetics and toxicity to establish an individualized risk profile of HIV-associated neurocognitive disorders, one of the prevalent co-morbidities in treated individuals.
List of Specific Aims:

1. To determine the association between AntiRetroviral PharmacoKinetics and neurocognitive function among treated patients from CHARTER and Chinese studies.
2. To identify genes and genetic polymorphisms that are associated with AntiRetroviral exposure, particularly genes that are linked to drug metabolism and drug distribution into the central nervous system.
3. To identify neurotoxicity and inflammation-associated genes that are linked to neurocognitive abnormalities using gene Expression Profiling and Bioinformatics techniques.
4. To develop a disease progression model that integrates PharmacoKinetics and the genetic data generated from aims 1 to 3 to predict HAND development.

Overlap: NONE

Title: Hippo Signaling Pathway in Breast Cancer Disparities: A Translational Approach (R21CA179693)
Time Commitments: 0.36 calendar (PI-Zhang)
Supporting Agency: NCI
Grants Officer: Joanna Watson
Performance Period: 08/01/14-07/31/17
Level of Funding:
Brief Description of Project's Goals: African-American (AA) women in compare to European-American (EA) women are more likely to be diagnosed breast cancer at a younger age and to have more aggressive tumors, characterized by higher grade, higher proliferative indices, and lack of expression of estrogen (ER) and progesterone receptors (PR). Down-regulation of Hippo pathway components LATS1/2 by DNA hypermethylation has been associated with large tumor size, lymph node metastasis and ER/PR negativity. We hypothesize that dysfunction of the Hippo signaling pathway leads the more aggressive breast cancer, which occurs more frequently in AA than EA women.
List of Specific Aims:

1. Determine whether YAP/TAZ-activated EGFR signaling pathway contributes to TNBC tumorigenesis.
2. Investigate differential EGFR activation by YAP/TAZ between AA and EA women using breast cancer tumor collections.

Overlap: NONE

Title: Epidemiology of Breast Cancer Subtypes in African American Women: A Consortium (P01CA151135)
Time Commitments: 1.20 calendar (PI- Ambrosone/Palmer/Millkan)
Supporting Agency: NCI
Grants Officer: Elizabeth Gillanders; lgilland@mail.nih.gov
Performance Period: 08/01/11-05/31/17

Level of Funding:
Brief Description of Project's Goals: In this Program Project, we will pool data and samples from the Carolina Breast Cancer Study, the Black Women's Health Study, the Women's Circle of Health Study and the Multi-ethnic Cohort and continue to accrue cases for a final sample size of more than 5500 cases and 5500 controls.
List of Specific Aims:

1. Genetic loci identified in recent GWAS findings, using fine-mapping to identify potential causal alleles.
2. Pregnancy history and lactation, and potential modification by genetic variants in related pathways.
3. Body size, early life and adult physical activity, and gene/environment interactions.
4. Risk factors that may have been adaptive in Africa to endemic infectious disease (robust immune response) and intense sunlight (high skin pigmentation), but that in later life and western society may result in hyper-inflammatory milieu and vitamin D deficiency.

Overlap: NONE

Title: Genomic markers predicting tumor response to cytotoxic chemotherapy (R01 CA202354)
Time Commitments: 0.00 calendar (PI-Demant)
Supporting Agency: NIH
Grants Officer: Sudhir B. Kondapaka
Performance Period: 12/01/15-11/30/17
Level of Funding:
Brief Description of Project's Goals: We propose to develop a novel way to determine in advance whether individual cancer patients will benefit from a therapy with a certain anti-cancer drug, or whether they should receive another drug, because their tumor is not likely to be suppressed by the drug considered as the first. The specific advantage of the method we propose is that it is based not only on the current knowledge of pharmacology of anti-cancer drugs but can discover also reliable predictive factors that are based on novel mechanisms.
List of Specific Aims:

1. Determination of linkage of Tctr genes polymorphic between CcS-2 and CcS-9 will be performed by standard linkage methods in F2 hybrids using a whole polymorphic genome coverage.
2. The linkages detected in the previous experiment will be confirmed in subsequent backcrosses that will serve as starting points for production of congenic lines, each carrying a single Tctr gene, so the functions of each such gene could be investigated separately. However, these congenic lines cannot be completed within the time frame of this project.

Overlap: NONE

Title: Exome Array Analysis of Reproductive Aging and Breast Cancer in African Americans (R03 CA192205)
Time Commitments: 0.72 calendar (PI-Yao)
Supporting Agency: NCI
Grants Officer: Damali Martin
Performance Period: 07/01/15-06/30/18
Level of Funding:
Brief Description of Project's Goals: By leveraging the existing exome array genotype data from a total of 8,350 AA breast cancer cases and healthy controls in the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium, we propose to identify rare and low-frequency coding variants associated with reproductive aging.
List of Specific Aims:

1. To evaluate rare and low-frequency coding variants in the regions identified by previous genome-wide association studies for age at menarche and age at natural menopause.
2. To identify rare and low-frequency coding variants across the genome associated with reproductive aging phenotypes.

Overlap: NONE

Title: Impact of HIV, Oral Microbiome and Mycobiome on Oral HPV (Impact of HIV, Oral Microbiome and Mycobiome on Oral HPV)
Time Commitments: 0.60 calendar
Supporting Agency: NIH
Grants Officer: Neeraja Sathyamoorthy
Performance Period: 9/18/18 - 9/17/19
Level of Funding:
Brief Description of Project's Goals: The overall goal of this application is to understand the role and mechanisms of functioning of KLF9-TXNRD2 axis in melanomagenesis and characterize TXNRD2 inhibitor auranofin as a potential anti-melanoma agent.
List of Specific Aims: The proposed study will investigate the natural history of oral HPV in HIV-positive individuals and assess the risk effects of oral bacterial infections (microbiome) and fungal infections (mycobiome) on oral HPV persistence, an intermediate biomarker HPV-associated oral papilloma and oropharyngeal cancer risks.
Overlap: NONE

Title: Genetic variations in SLCO transporter and racial disparity in aggressiveness of PCa (W81XWH-14-0453)
Time Commitments: 0.60 calendar (PI-Wu)
Supporting Agency: DOD
Grants Officer: Mirlene Desir
Performance Period: 04/01/14-3/14/19
Level of Funding: annual direct
Brief Description of Project's Goals: The objective seeks to address how transporter-regulated androgen availability to cancer cells may contribute to the difference in prostate cancer aggressiveness between African-American (AA) and European –American (EA) men. The hypothesis is: Genetic variations in solute carrier family of organic anion transporting peptides (SLCO) androgen transporter genes and expression profiles of SLCO androgen transporters in prostate tissue are associated with aggressiveness of prostate cancer and contribute to racial differences in prostate.
List of Specific Aims:

1. Aim 1 is to examine genetic variations in SLCO transporters genes and to investigate the associations of the variations with prostate cancer aggressiveness in AA and EA.
2. Aim 2 is to examine in situ expression profiles of SLCO transporters in prostate tissue and to investigate the associations of the expression profiles with prostate cancer aggressiveness in AA and EA.
3. Aim 3 is to characterize the functions of candidate SLCO transporters in androgen uptake and to evaluate the biological effects on androgen receptor signaling in human prostate cancer cell lines.

Overlap: NONE

Title: b-catenin in vaccine-induced anti-tumor CD8 cell immunity (5 R01 CA198105-04)
Time Commitments: 0.30 calendar (PI-Jiang)
Supporting Agency: NCI
Grants Officer: Anthony Welch
Performance Period: 07/01/15-06/30/20
Level of Funding:
Brief Description of Project's Goals: The long-term goal is to develop strategies to block tumor-induced immunosuppression to augment CD8+ T cell immunity and improve cancer vaccine efficacy. The objectives in this application is to elucidate the underlying mechanisms of how tumors inhibit cross-priming through b-catenin in DCs, and validate blocking b-catenin signaling as a novel strategy to improve cancer vaccine efficacy.
List of Specific Aims:

1. To determine whether activation of ß-catenin in DCs suppresses anti- tumor CD8+ T cell immunity under diverse cancer vaccinations.
2. To elucidate the molecular mechanisms of how tumors inhibit cross-priming through ß-catenin in DCs.
3. To determine whether blocking ß-catenin pharmacologically improves cancer vaccine efficacy.

Overlap: NONE

Title: KLF9-TXNRD2 axis in melanoma progression and therapy (7 R01 CA190533-05)
Time Commitments: 0.41 calendar (PI-Nikiforov)
Supporting Agency: NIH/NCI
Grants Officer: Neeraja Sathyamoorthy
Performance Period: 11/12/18-06/30/20
Level of Funding:
Brief Description of Project's Goals: The overall goal of this application is to understand the role and mechanisms of functioning of KLF9-TXNRD2 axis in melanomagenesis and characterize TXNRD2 inhibitor auranofin as a potential anti-melanoma agent.
List of Specific Aims:

1. To characterize the mechanism of RAC1 activation via GME recruitment.
2. To functionally characterize novel EphR-GMPR-RAC1-invasion axis.
3. To establish moderate depletion of GTP as effective anti-melanoma strategy.

Overlap: NONE

Title: GMPS-GMPR Axis Melanoma Progression and Therapy (1 R01 CA224434-01A1)
Time Commitments: 0.32 calendar (PI-Nikiforov)
Supporting Agency: NIH
Grants Officer: Neeraja Sathyamoorthy
Performance Period: 5/15/18-4/30/23 *Dr Zhu is no longer working on this project*
Level of Funding:
Brief Description of Project's Goals: The goal of this project will be to test the hypothesis that recruitment of GMEs and physiological modulation of their activity regulate GTP loading on RAC1 and therefore can be exploited therapeutically.
List of Specific Aims:

1. To characterize the mechanism of RAC1 activation via GME recruitment.
2. To functionally characterize novel EphR-GMPR-RAC1-invasion axis.
3. To establish moderate depletion of GTP as effective anti-melanoma strategy.

Overlap: NONE

Title: Genetic Basis for Ethnic Disparities of Bone Toxicities in Pediatrics ALL (No Grant Number)
Time Commitments: 5.00 calendar (PI-Yao)
Supporting Agency: Rally Foundation
Performance Period: 7/1/2020-6/30/2022
Level of Funding:
Brief description of project's goals: The goal of this study is to investigate genetic underpinnings of ethnic differences in bone toxicities after treatment for pediatric ALL based on three DFCI ALL Consortium trials.
List of Specific aims:

1. Perform genome-wide genotyping assays on approximately 600 patients from the DFCI 11-001 and the 16-001 trial cohorts and combine with existing data from the 05-001 cohort, to confirm the protective effects of African ancestry against bone toxicities following ALL treatment.
2. Based on the genome-wide genotype data from 1,050 patients from the three pediatric ALL cohorts:
    a. Validate the 20p11.21 locus in association with bone toxicities;
    b. Identify new risk loci using a GWAS meta-analysis framework.

c. Develop multi-marker and genome-wide polygenic scores for risk stratification of bone toxicities;
d. Examine whether the identified genetic variants and polygenic scores drive the bone-protecting effects of African ancestry among Hispanic children.

Overlap: NONE

IN-KIND

*Summary of In-Kind Contribution: dbGAP Database access

*Status of Support: ACTIVE

*Primary Place of Performance: Roswell Park Comprehensive Cancer Center

Project/Proposal Start and End Date (MM/YYYY) (if available): 01/01/2015 – 12/31/2022

*Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
7. 2021 - 2022	Effort as needed

*Summary of In-Kind Contribution: Wellcome Sanger Institute databases

*Status of Support: ACTIVE

*Primary Place of Performance: Roswell Park Comprehensive Cancer Center

Project/Proposal Start and End Date (MM/YYYY) (if available): 06/23/2021 – 06/22/2022

*Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##.##)
1. 2021 - 2022	Effort as needed

***Overlap** (summarized for each individual): New York State award, C180142 provides supplemental funding for NIH award 1 U24 CA232979-01. This other support lists all pending projects for which funding decisions have not yet been received. NIH awards, 3 U24 CA232979-01S5 and 3 U24 CA232979-01S7 are for the same project. The S5 funds are on no cost extension. Dr. Zhu will ensure that his effort will not exceed 12 calendar months.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with US Army Medical Research Acquisition Activity terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature: Qianqian Zhu Digitally signed by Qianqian Zhu Date: 2022.09.15 13:34:58 -04'00'

Date: _____