AWARD NUMBER: W81XWH-21-1-0663

TITLE: Targeting FOXA1-Mediated Epigenetic Reprogramming in Aggressive Salivary Gland Cancer

PRINCIPAL INVESTIGATOR: Aaron M. Udager, M.D., Ph.D.

CONTRACTING ORGANIZATION: University of Michigan, Ann Arbor, MI

REPORT DATE: October 2022

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2022	Annual	01Sep2021-31Aug2022

4. TITLE AND SUBTITLE

Targeting FOXA1-Mediated Epigenetic Reprogramming in Aggressive Salivary Gland Cancer

5a. CONTRACT NUMBER
W81XWH-21-1-0663

5b. GRANT NUMBER
RA200327

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)

Regents of the University of Michigan
3003 S. State Street
Ann Arbor, MI 48109

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

Salivary duct carcinoma (SDC) is a rare, aggressive type of salivary gland cancer that has high expression of androgen receptor (AR) and AR-regulated genes. FOXA1 is a nuclear protein required for AR-regulated gene expression and tumor growth/survival. FOXA1 expression is also strongly correlated with AR expression in SDC, and subsets of these tumors harbor FOXA1 gene alterations that have previously been shown to enhance AR-regulated gene expression in prostate cancer. Taken together, these data implicate FOXA1 as a critical regulator of AR-signaling in SDC; however, FOXA1 itself is not directly targetable. Intriguingly, the nuclear protein LSD1 regulates FOXA1 activity in prostate cancer, and the LSD1 inhibitor GSK2879552 has been shown to disrupt FOXA1-dependent AR signaling and tumor growth/survival. Thus, the goal of this proposed research is to characterize the FOXA1 cistrome in salivary duct carcinoma and determine the efficacy of the LSD1 inhibitor GSK2879552 for disrupting FOXA1-mediated epigenetic reprogramming and tumor growth in ex vivo organoid cultures.

15. SUBJECT TERMS

Genomics, transcriptomics, epigenomics, next-generation sequencing, patient-derived organoids (PDO), single-cell analysis

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	28	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Salivary duct carcinoma (SDC) is a rare, aggressive type of salivary gland cancer that has high expression of androgen receptor (AR) and AR-regulated genes. FOXA1 is a nuclear protein required for AR-regulated gene expression and tumor growth/survival. FOXA1 expression is also strongly correlated with AR expression in SDC, and subsets of these tumors harbor FOXA1 gene alterations that have previously been shown to enhance AR-regulated gene expression in prostate cancer. Taken together, these data implicate FOXA1 as a critical regulator of AR-signaling in SDC; however, FOXA1 itself is not directly targetable. Intriguingly, the nuclear protein LSD1 regulates FOXA1 activity in prostate cancer, and the LSD1 inhibitor GSK2879552 has been shown to disrupt FOXA1-dependent AR signaling and tumor growth/survival. Thus, the goal of this proposed research is to characterize the FOXA1 cistrome in salivary duct carcinoma and determine the efficacy of the LSD1 inhibitor GSK2879552 for disrupting FOXA1-mediated epigenetic reprogramming and tumor growth in ex vivo organoid cultures.

2. KEYWORDS:

Genomics, transcriptomics, epigenomics, next-generation sequencing, patient-derived organoids (PDO), single-cell analysis

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Aim 1. Define the FOXA1 cistrome in salivary duct carcinoma.

Aim 2. Determine molecular and cellular responses to LSD1 inhibition in salivary duct carcinoma.

What was accomplished under these goals?

Aim 1. Define the FOXA1 cistrome in salivary duct carcinoma.

Obtain local IRB and HRPO approval (months 1-2)

Study approval from the University of Michigan Institutional Review Board (IRB) was obtained (task 100% complete).

Retrospectively collect fresh frozen salivary duct carcinoma tissue and extract DNA and RNA (n = 10) (months 3-4)

Fresh frozen salivary duct carcinoma tissue from seven unique cases has been retrospectively identified, and DNA and RNA are in the process of being extracted (task 70% complete).

Perform integrative NGS profiling of fresh frozen salivary duct carcinoma tissue (n = 10) (months 5-8)

Nothing to report.

Perform ATAC-seq and FOXA1 and AR ChIP-seq of fresh frozen salivary duct carcinoma tissue (n = 10) (months 5-8)

Nothing to report.

Integrate NGS, ATAC-seq, and ChIP-seq data from fresh frozen salivary duct carcinoma issue (months 9-10)

Nothing to report.

Aim 2. Determine molecular and cellular responses to LSD1 inhibition in salivary duct carcinoma.

Prospectively collect primary human salivary duct carcinoma samples (n = 5) (months 4-12)

Salivary duct carcinoma tissue was prospectively collected from one patient (task 20% complete).

Establish ex vivo PDO cultures from primary human salivary duct carcinoma samples and extract DNA and RNA (n = 5) (months 4-12)

Ex vivo PDO cultures were established from salivary duct carcinoma tissue prospectively obtained from one patient, and DNA and RNA were extracted (task 20% complete).

Determine responsiveness of salivary duct carcinoma PDOs to the LSD1 inhibitor GSK2879552 (n = 5) (months 4-12)

One *ex vivo* salivary duct carcinoma PDO culture was tested for responsiveness to the LSD1 inhibitor GSK2879552, but no significant effect on cellular viability was observed at the maximum dose (10 μM).

Perform bulk integrative NGS profiling of salivary duct carcinoma PDOs with and without LSD1 inhibitor treatment (n = 5) (months 4-12)

Nothing to report.

Perform single cell gene expression profiling and ATAC-seq of salivary duct carcinoma PDOs with and without LSD1 inhibitor treatment (n = 2) (months 4-12)

Nothing to report.

Integrate NGS and single cell profiling data from salivary duct carcinoma PDOs with ATAC-seq and FOXA1 and AR ChIP-seq data from fresh frozen salivary duct carcinoma tissue (months 10-12)

Nothing to report.

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

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

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

During the next reporting period, we plan to continue retrospectively identifying fresh frozen salivary duct carcinoma for molecular analyses and prospectively collecting salivary duct carcinoma tissue from patients for establishment of PDOs, drug testing, and molecular analyses.

4. IMPACT:

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

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

University of Michigan IRB and HRPO study approval took longer than expected. Since approval, we have retrospectively identified fresh frozen salivary duct carcinoma tissue for molecular analyses, and we have started to prospectively collect salivary duct carcinoma tissue from patients for establishment of PDOs, drug testing, and molecular analyses.

Changes that had a significant impact on expenditures

Due to longer than expected time for IRB and HRPO study approval and continuing impacts of the COVID-19 pandemic, we have delayed hiring a research technician to work on the study; however, we plan to hire someone for this position in the next reporting period.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

6. PRODUCTS:

Publications, conference papers, and presentations

Nothing to report.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Aaron Udager
Project Role:	Principal Investigator
Researcher Identifier (e.g., ORCID ID):	0000-0002-8254-5404
Nearest Person Month Worked:	1
Contribution to Project:	Dr. Udager has led all aspects of the study, including: obtaining approval from the local IRB and Department of Defense HRPO; and identifying study cases.
Funding Support:	N/A

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

Please see the Appendices for updated Other Support documents for Drs. Udager, Merajver, and Spector. New and ended support is indicated for each investigator.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

N/A

QUAD CHARTS:

N/A

9. APPENDICES:

Updated Other Support for Dr. Aaron Udager
Updated Other Support for Dr. Sofia Merajver
Updated Other Support for Dr. Matthew Spector

OTHER SUPPORT

UDAGER, AARON

CURRENT

W81XWH-19-1-0407 Udager (PI) 3.66 CM
Department of Defense total award amount 9/2019-8/2023
Tom Winter
Grants Management Specialist
sidney.t.winter.civ@mail.mil

Intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer
Goal(s): The goal of this project is to utilize immunohistochemistry, in situ hybridization, and next-generation sequencing to establish the frequency and pattern of intratumoral biomarker heterogeneity in lethal prostate cancer and delineate the spectrum of associated molecular alterations in these spatially-distinct areas. Specific Aims: Aim 1. Determine the incidence and pattern of spatial intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer. Aim 2. Compare the frequency and spectrum of genomic alterations across spatially-distinct areas of lethal prostate cancer with intratumoral biomarker heterogeneity. Aim 3. Evaluate transcriptomic alterations that accompany intratumoral biomarker heterogeneity in lethal prostate cancer.
No overlap with this project

W81XWH-20-1-0405 Alumkal (PI) 0.60 CM (YR3)
Department of Defense total award amount 9/2020-8/2023
Tom Winter
Grants Management Specialist
sidney.t.winter.civ@mail.mil

Targeting LSD1 in Neuroendocrine Prostate Cancer
Goal(s): The objectives of this proposal are to clarify mechanisms by which LSD1 promotes NEPC phenotypes and the anti-tumor activity of LSD1 inhibition so we may develop a new treatment strategy for NEPC patients and identify key companion biomarkers that indicate suppression of LSD1's critical function. Specific Aims: Aim 1: Identify an LSD1 inhibitor gene response signature and determine mechanisms by which LSD1 blocks gene expression in NEPC. Aim 2: Treat NEPC tumors in vivo with LSD1 inhibition and determine effect on tumor growth and differentiation. Aim 3: Determine mechanisms by which the LSD1+8a splice variant functions in NEPC.
Role: Co-Investigator
No overlap with this project

R37 CA222829 Xu (PI) 0.12 CM
NIH/NCI 1/2019-12/2023
Jennifer Meininger
Grants Management Specialist
jennifer.meininger@mail.nih.gov

Real time fine needle assessment of architectural heterogeneity in prostate cancer
Goal(s): The specific aims include: 1) examining label-free PCa aggressiveness assessments in ex vivo human tissues; and 2) examining contrast-enhanced PCa aggressiveness assessments in mouse models in vivo. Specific Aims: Aim 1. Test an all-optical fine needle PA probe for identifying aggressive PCa in biopsy cores. Aim 2. Practice and examine the PA pre-biopsy via simulated biopsy procedures with ex vivo human prostates. Aim 3.

Examine the correlation between the PA measurements and the pathology of the PCa via an observational human subjects study with 67 patients
Role: Co-Investigator
No overlap with this project

U01 CA232931 Hadjiyski/Alva (MPI) 0.24 CM
NIH/NCI 5/2019-4/2024
Jennifer Meininger
Grants Management Specialist
jennifer.meininger@mail.nih.gov

Biomarker-based tools for treatment response decision support of bladder cancer
Goal(s): The goal of this project is to validate the effectiveness of CDSS-T as an aid to the radiologists and the oncologists in assessment of bladder cancer change as a result of treatment through pilot clinical trials. Specific Aims: Aim 1. To perform a preparatory clinical trial with the clinicians at UM, which will simulate the real prospective clinical trial. Aim 2. To deploy the QIBC and CDSS-T tools at the three collaborating clinical sites. Aim 3. To use the QIBC and CDSS-T tools at the three clinical sites in the pilot clinical trial. Aim 4. To compare the clinicians' performance results with and without the QIBC and CDSST tools in the pilot clinical trial.
Role: Co-Investigator
No overlap with this project

P50 CA186786 Chinnaiyan/Palapattu/Heath (MPI) 0.60 CM
NIH/NCI 9/2019-8/2024
Jennifer Meininger
Grants Management Specialist
jennifer.meininger@mail.nih.gov

Michigan Prostate SPORE
Goal(s): The overall goal of this grant is the development of new approaches to the prevention, early detection, diagnosis and treatment of prostate cancer through translational research. Specific Aims: Project 1: Targeting Metastatic Prostate Cancer Patients with Biallelic Loss of CDK12. Project 2: Integrating a Novel MiPS-Based Next-Generation Sequencing Urine Assay for the Early Detection of Unfavorable Risk Prostate Cancer. Project 3: Exploring Ablation of the Androgen Receptor as a Therapeutic Approach for Castration-Resistant Prostate Cancer. Project 4: Targeting LSD1 in Neuroendocrine Prostate Cancer.
Role: Co-Investigator (Projects 2 and 4)
No overlap with this project

R01 CA186786 Alumkal (PI) 0.60 CM (YR2-5)
NIH/NCI 9/2020-8/2025
Elizabeth Bui
Grants Management Specialist
mimi.bui@mail.nih.gov

Targeting Prostate Cancer Lineage Plasticity with BET Bromodomain Inhibition
Goal(s): The goal of this project is to understand molecular mechanisms by which BET bromodomain proteins promote neuroendocrine prostate cancer progression so we can target those mechanisms. Specific Aims: Aim 1: Determine mechanisms by which E2F1 and BRD4 cooperate to promote expression of a t-NEPC lineage plasticity survival program. Aim 2: Treat t-NEPC patient tumors implanted in mice with BETi or BETd and measure anti-tumor activity and NEPC differentiation. Aim 3: Prevent castration-induced t-NEPC lineage switch with BETi or BETd using a patient tumor model of t-NEPC lineage switch implanted in mice.
Role: Co-Investigator
No overlap with this project

W81XWH-21-1-0238 Udager (PI) 1.20 CM
Department of Defense total award amount 6/2021-5/2024
Tom Winter
Grants Management Specialist
sidney.t.winter.civ@mail.mil

Integrative molecular profiling of whole urine in African-American men with aggressive prostate cancer
Goal(s): The goals of this project are: 1) evaluate the performance of a novel whole urine NGS assay for the detection of high-grade prostate cancer in African-American men; and, 2) validate and apply a high-throughput NGS genomic profiling method for whole urine to identify African-American men with aggressive prostate cancer. Specific Aims: Aim 1. Evaluate the performance of an established whole urine NGS assay for the detection of highgrade prostate cancer in African-American men. Aim 2. Validate a high-throughput NGS-based germline genomic profiling method for whole urine and determine its impact on the detection of high-grade prostate cancer in African-American men.
No overlap with this project

W81XWH-21-1-0663 Udager (PI) 0.9 CM
Department of Defense total award amount 9/2021-8/2022 (NCE)
Judi Sgambato
judi.a.sgambato.civ@mail.mil

Targeting FOXA1-Mediated Epigenetic Reprogramming in Aggressive Salivary Gland Cancer
Goal(s): The goal of this proposed research is to characterize the FOXA1 cistrome in salivary duct carcinoma and determine the efficacy of the LSD1 inhibitor GSK2879552 for disrupting FOXA1-mediated epigenetic reprogramming and tumor growth in ex vivo organoid cultures. Specific Aims: Aim 1. Define the FOXA1 cistrome in salivary duct carcinoma. Aim 2. Determine molecular and cellular responses to LSD1 inhibition in salivary duct carcinoma.
This project

NCCN Pfizer/Astellas Enzalutamide Alumkal (PI) 0.60 CM (YR1)
10/2021-9/2024 ***Clarifying Tumor and***
Microenvironmental Determinants of Enzalutamide Resistance
Goal(s): To provide positive impact by identifying cellular and molecular signatures of distinct cellular populations driving invasive progression. These findings could then lead to examination of candidate gene networks that will serve as the basis for biological function, potential biomarker identification and new therapeutic targets that are needed for bladder cancer patients who have been diagnosed with or have relapsed with muscle invasive disease. Specific Aims: Specific aim 1. To determine the transcriptomic signature of tumor cells and adjacent stroma isolated from the invasive interface of MIBC. Aim 2: To determine the cellular and transcriptomic signature of infiltrating immune cells in the invasive microenvironment of human bladder cancer. Aim 3: To analyze transcriptomic signatures from tumor, stromal and immune populations to identify gene regulatory programs unique to the invasive micro-environment of MIBC.
Role: Co-Investigator
No overlap with this project
****New support****

R21 CA259763 Day (PI) 0.40 CM
NIH/NCI 12/2021-11/2023
Sudhir B. Kondapaka
kondapas@mail.nih.gov
Delineation of tumor, stromal and immune transcriptomes at the infiltrating interface of muscle invasive bladder cancer

Goal(s): To provide positive impact by identifying cellular and molecular signatures of distinct cellular populations driving invasive progression. These findings could then lead to examination of candidate gene networks that will serve as the basis for biological function, potential biomarker identification and new therapeutic targets that are needed for bladder cancer patients who have been diagnosed with or have relapsed with muscle invasive disease. Specific Aims: Specific aim 1. To determine the transcriptomic signature of tumor cells and adjacent stroma isolated from the invasive interface of MIBC. Aim 2: To determine the cellular and transcriptomic signature of infiltrating immune cells in the invasive microenvironment of human bladder cancer. Aim 3: To analyze transcriptomic signatures from tumor, stromal and immune populations to identify gene regulatory programs unique to the invasive micro-environment of MIBC.
Role: Co-Investigator
No overlap with this project
****New support****

R37 CA273138 Palmbos (PI) 0.60 CM NIH/
NCI 8/2022-7/2027 Grace S. Ault
aultg@mail.nih.gov
Mechanism and Therapeutic Targeting of TRIM29-mediated Invasion in Bladder Cancer
Goal(s): The central hypothesis will be tested in the following specific aims: 1) To determine the mechanism of TRIM29 regulation of intermediate filament and focal adhesion in invasive progression. 2) To determine the genetic requirements for TRIM29-mediated invasive progression in preclinical models. 3) To develop and evaluate novel therapeutic strategies to target TRIM29-mediated invasion in bladder cancer.
Role: Co-Investigator
No overlap with this project
****New support****

PENDING

P01 Balter (PI) 0.84 CM
NIH/NCI 9/2022-8/2027
Grant Information
grantsinfo@nih.gov

Individualized Response Adaptive Radiation Therapy
Goal(s): Project 1, Individualized Response Adaptive RT for Hepatocellular Carcinoma (HCC), will use biological imaging and blood biomarkers obtained before and during the course of treatment together with advanced modeling and utility optimization to individualize RT for patients with poor prognosis HCC. Project 2, Individualized Response Adaptive RT for Oropharyngeal Squamous Cell Cancer (OPSCC), will use biological imaging and blood biomarkers obtained before and during the course of treatment together with advanced modeling to individualize RT for patients with high risk (with or without oligometastases) p16 positive OPSCC. Project 3, Advanced MRI for Individualized Response Adaptive RT, will investigate improved imaging of tissue microstructure as a biomarker of response to therapy, with the goal of applying this new imaging approach to Projects 1 and 2 in the later years of the application. Project 3 will also develop increased sampling efficiency of imaging, and motion-corrected image reconstruction and biomarker mapping for patients with HCC and OPSCC. These projects will be supported by four cores supporting: 1) Administration; 2) Quantitative Imaging (Core A); 3) In Vivo Biomarkers (Core B); and 4) Statistics and Advanced Treatment Planning (Core C).
Role: Co-Investigator
No overlap with this project

R01 Hadjiyski and Alva (MPI) 1.08 CM
NIH/NCI 4/2023-3/2028
Grant Information

grantsinfo@nih.gov

Biomarkers for Monitoring of Response to Immunotherapy for Urinary Tract Cancer
Major Goals: Urothelial carcinoma is a common type of cancer that can cause substantial morbidity and mortality among both men and women. We hypothesize that this innovative approach of integrating radiomics and other biomarkers can improve clinicians' accuracy, consistency and efficiency in assessing immunotherapy response of metastatic urothelial cancer. To test the hypotheses, we will compare the clinicians' accuracy and inter-observer variability in evaluation of metastatic urothelial tumors in MM with and without QIMUC and CDSS-IT using multiinstitutional clinical data. We will perform the following specific tasks: (1) to collect a database of multi-modality MR, CT exams of metastatic urothelial cancers undergoing immunotherapy for development, training and testing of the QIMUC and CDSS-IT tools; (2) to develop advanced computer vision techniques to quantitatively estimate metastatic carcinomas GTV and image characteristics; (3) to develop a tool to assist radiologists in the selection of target metastatic lesions on the baseline scan; and to develop predictive models using machine learning techniques to combine MM image-based, pathological and DNA/RNA biomarkers for determination of non-responders to immunotherapy; (4) to evaluate the performance of QIMUC and CDSS-IT on the independent test data sets (5) to compare the inter-clinician variability and accuracy in clinicians' estimation of GTV and treatment response with and without the QIMUC and CDSS-IT tools by observer studies. (6) To evaluate the QIMUC and CDSS-IT as clinical decision support tools for estimation of metastatic tumor treatment response in a preparatory clinical trial, which will simulate the real prospective clinical trial with high quality retrospective data at 3 collaborating clinical sites.
Role: Co-Investigator
No overlap with this project

P30 CA046592 — Fearon (PI) — 0.36 CM
NIH/NCI — 6/2023-5/2028
Grant Information
grantsinfo@nih.gov

University of Michigan Rogel Cancer Center Support Grant 2023-2028
Goal(s): The Center provides an organizational framework to promote transdisciplinary cancer research through the development of well-funded basic, translational, clinical, and prevention programs and the development of shared resources. The Cancer Center's six Research Programs includes three basic programs – Signaling and Tumor Microenvironment; Cancer Genetics, and Developmental Therapeutics; one basic/clinical/translational program - Cancer Hematopoiesis and Immunology; one clinical/translational program - Translational and Clinical Research; and Cancer Control and Population Science. Rogel supports 13 Shared Resources and two developing Shared Resources: Cancer Data Science; Cell and Tissue Imaging; Experimental Irradiation; Flow Cytometry; Health Communications; Immune Monitoring; Pharmacokinetics; Preclinical Molecular Imaging; Structure and Drug Screening; Tissue and Molecular Pathology; Transgenic Animal Models; Proteomics; Single Cell Spatial Analysis; Epigenetics and Epigenomics (developing); and Liquid Biopsy (developing).
Role: Co-Investigator
No overlap with this project

LC220436 — Udager (PI) — 0.90 CM
Department of Defense — 9/2023-8/2025
CDMRP Help Desk
help@ebrap.org

Genomic Structural Variants as Novel Therapeutic Targets in Lung Cancer Brain Metastases
Goal(s): In this proposal, we hypothesize that novel structural genomic alterations represent therapeutic targets in lung cancer with brain metastases. Aim 1. Characterize the genomic landscape of structural variation in lung cancer with brain metastases. Aim 2. Assess the potential for targeting structural variants in clinically relevant pre-clinical models of lung cancer with brain metastases.

No overlap with this project
****New Support****

PREVIOUS

None

OVERLAP FOR ALL CURRENT AND PENDING GRANTS

None

OTHER SUPPORT

MERAJVER, SOFIA D.

CURRENT

Title: Targeting RhoC in Breast Cancer: Novel Drugs, Mathematical Models and Epidemiological Studies in North Africa
Time Commitments: 3.0 CM
Supporting Agency: Breast Cancer Research Foundation (BCRF)
Address: TBD
Contracting/Grants Officer: TBD
Performance Period: 10/01/2021-09/30/2022
Level of funding: total costs
Role: PI
Project Goals: To be able to guide therapies that prevent metastases from occurring in women diagnosed with aggressive breast cancers in the US and worldwide, with an emphasis on countries in Sub-Saharan Africa where there are scarce resources for cancer health.
Specific Aims: Aim 1. Identify a transcriptomic signature of CA4 treatment using biomarker predictions. Aim 2. Identify resistance mechanisms to CA4 in TNBC cell lines using 3D organoid culture and nominate companion drugs to overcome resistance. Aim 3. Evaluate targeted inhibitors to overcome acquired CA4 resistance and synergize non-resistant cells.
Overlap: No scientific or budgetary overlap with the proposed proposal
****New support****

Title: Advanced development and validation of an in vitro platform to phenotype brain metastatic tumor cells using artificial intelligence
Time Commitments: 0.96 CM
Supporting Agency: NIH
Address: 45 Center Drive MSC 6200, Bethesda, MD 20892-6200
Contracting/Grants Officer: Elizabeth Bui, mimi.bui@nih.gov
Performance Period: 06/01/2022-05/31/2025
Level of funding: total costs
Role: Partnering PI
Project Goals: To further develop and validate the blood brain barrier on a chip platform developed in our lab, enabling comprehensive phenotyping of single tumor cells, metastatic clusters and the tumor micro-environment cultured. Further this method will enable downstream processing of patient derived tumor cells cultured for long periods.
Specific Aims: Aim1: Advanced development of a brain metastatic organ-on-a-chip platform for personalized medicine. a. Enable long term culture up to 20 days using an integrated re-usable piezo pump. b. Standardize the device with a human multi-cellular (pericytes, microglia, astrocytes) BBN tumor microenvironment (TME) system. Aim2: Demonstrate a process for recovering sub-populations of tumor cells that have extravasated through the BBN after imaging and preserve spatial information for use with downstream assays. Aim3: Refine and validate an AI based phenotyping tool. a. Optimize software and package it into a plugin for ImageJ and Cell Profiler. b. Extend confocal image phenotyping to include micro-metastases and the tumor micro-environment factors. c. Validate the software on PDXs with a high metastatic potential.

Overlap: No scientific or budgetary overlap with the proposed proposal.
****New support****

Title: Role of EZH2 in Breast Cancer Progression
Time Commitments: 0.46 Cal Months
Supporting Agency: NIH
Address: 9609 Medical Center Drive, West Tower, 2nd floor, Rockville MD 20850
Contracting/Grants Officer: Funmi Elesinmogun, elesinmf@mail.nih.gov
Performance Period: 09/26/2016-08/31/2022
Level of funding:
Role: Co-Investigator
Project Goals: To determine how EZH2 enhances ER- breast progression and translate biologic findings into clinical utility.
Specific Aims: AIM 1) To investigate the consequences of inducible mammary-specific EZH2 overexpression on breast cancer progression, and the in vivo relevance of EZH2 non-canonical mechanisms, AIM 2) To elucidate the effect of pEZH2 T367 on neoplastic functions in vivo and in vitro, AIM 3) To investigate the molecular mechanism of pEZH2 T367-mediated breast cancer progression, AIM 4) To evaluate the translational impact of EZH2 non-canonical pathways in human breast tissue samples.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: University of Michigan Breast and Ovarian Cancer Risk and Evaluation Program
Time Commitments: 0.24 CM
Supporting Agency: MDCH/NIH-CDC
Address: 201 Townsend St., 4th Floor Lansing, MI 48909
Contracting/Grants Officer: Deb Duquette; DuquetteD@michigan.gov
Performance Period: 10/01/2020 – 09/30/2022
Level of funding:
Role: PI
Project Goals: collecting and sharing data on cancer genetic visits and use of genetic testing for BRCA1/2 by board-certified genetics professionals in Michigan.
Specific Aims: The contractor will serve as one of the clinical facilities that form a network for collecting and sharing data on cancer genetic visits and use of genetic testing for BRCA1/2 by board-certified genetics professionals in Michigan.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Small-molecule degraders of BET proteins
Time Commitments: 0.48 Cal Month
Supporting Agency: NIH
Address: 9609 Medical Center Drive, West Tower, 2nd floor, Rockville MD 20850
Contracting/Grants Officer: Angela Walters, waltersar@mail.nih.gov
Performance Period: 04/01/2017-03/31/2023
Level of funding:
Role: Co-Investigator
Project Goals: This project has the goal to discover and develop highly potent small-molecule degraders of BET proteins for the treatment of human cancer.
Specific Aims: Aim 1) Design and synthesis of new analogues of our potent, promising

small-molecule BET degraders to address any issues identified from Aim 2 and Aim 3 and to further optimize their physicochemical properties, pharmacokinetics, efficacy and therapeutic index. We will focus our efforts on our orally bioavailable BET degraders, Aim 2) For new compounds synthesized in Aim 1 and a number of already identified, potent and promising BET degraders, investigation of the in vitro activity and mechanisms of action in a panel of TNBC cell lines and their selectivity over normal cells, Aim 3) For highly potent and promising BET degraders, determination of their microsomal stability, pharmacodynamics, pharmacokinetics, in vivo antitumor activity, mechanism of action and potential toxicity in animal models of TNBC, including patient- derived xenograft models of TNBC.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Imaging Metastatic Potential
Time Commitments: 0.3 CM
Supporting Agency: UCSD/NIH
Address: 9500 Gilman Dr. MC 0651, La Jolla, CA 92093-0651
Contracting/Grants Officer: Gregg Fastring, gfastring@ucsd.edu
Performance Period: 04/01/2019-3/31/2024
Level of funding:
Role: Co-Investigator
Project Goals: To Generate cells with stable expression of imaging reporter constructs and perform fluorescence lifetime imaging studies on cells in vitro and in vivo. Dr. Luker's team will be involved in all fluorescence lifetime imaging studies, mouse models of breast cancer, and mouse imaging studies.
Specific Aims: 1) Aim 1: The Luker lab will perform fluorescence lifetime imaging studies with molecular imaging probes for GIV, correlating these data with FRET measurements performed both at UM and the Ghosh lab at UCSD and biochemical validation studies in the Ghosh lab.
2) Aim 2: The Luker lab will perform flow cytometry analyses comparing established markers of breast cancer stem cells with FRET from the molecular imaging probes for GIV. The UM team will analyze mouse models of experimental metastasis with imaging studies to quantify the extent of disease and time course of disease progression. From these data, the Luker lab will quantify enrichment of metastasis-initiating cells.
3) Aim 3: The Luker lab will generate patient-derived xenograft models of human breast cancer, using established samples obtained from UCSD and UM. For this research, we will establish patient-derived breast cancer cells that stably express the molecular imaging reporter for GIV. We will perform mouse imaging studies, including intravital microscopy, to analyze active GIV as a marker of breast cancer cells with high metastatic potential.
Overlap: No scientific or budgetary overlap with the proposed proposal

Title: Therapeutic reactivation of the PP2A tumor suppressor for breast cancer treatment (BC190588P1)
Time Commitments: 0.96 CM
Supporting Agency: Department of Defense, W81XWH-19-BCRP-BTA12
Address: Congressionally Directed Medical Research Programs 1077 Patchel Street Fort Detrick, MD 21702-5024
Contracting/Grants Officer: Ashley Schneekloth, Ph.D., ashley.r.schneekloth.civ@mail.mil
Performance Period: 02/01/2020-01/31/2023

Role: Partnering PI
Level of funding:
Project Goals: To discover new clinical interventions and therapies for both the health of those dedicated to protecting our country and to our population as a whole.
Specific Aims: Aim 1) Assess germline PPP2R1B mutations in breast cancer patient samples, Aim 2) Functional Characterization of PPP2R1B germline mutations in vitro, Aim 3) In vivo characterization of PPP2R1B germline mutations.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Artificial Intelligence driven prediction of brain metastasis from primary tumor sites at diagnosis.
Time Commitments: 1.15 CM
Supporting Agency: NIH
Address: 45 Center Drive MSC 6200, Bethesda, MD 20892-6200
Contracting/Grants Officer: Jennifer S. Meininger, meiningerjs@mail.nih.gov
Performance Period: 03/01/2020-02/28/2023
Level of funding:
Role: PI
Project Goals: To develop a technology to detect cells with a high probability of metastasizing to the brain and profiling their unique signerature to identify candidates for targeted theraputics.
Specific Aims: Aim 1: Identify the primary secretome of bio-chemical interactions between the tumor and individual brain stromal components of the μmBBN. Aim 2: Develop a diagnostic platform to measure the brain metastatic potential of patient derived tumor cells.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Merajver Correlatives Agreement
Time Commitments: 0.01 CM
Supporting Agency: Dana-Farber Cancer Institute/Genetech
Address: unknown
Contracting/Grants Officer: Moira Wallgory, Moira_Wallgory@dfci.harvard.edu
Performance Period: 11/30/2016 - 10/31/2022
Level of funding:
Role: Partnering PI
Project Goals: Test efficacy of a neoadjuvant regimen in inflammatory breast cancer and develop patient-derived xenografts of IBC tumors.
Specific Aims: To test efficacy of a neoadjuvant regimen in inflammatory breast cancer and develop patient-derived xenografts of IBC tumors.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Targeting FOXA1-Mediated Epigenetic Reprogramming in Aggressive Salivary Gland Cancer
Time Commitments: 0.6 CM
Supporting Agency: Department of Defense
Address: 1077 Patchel Street, Fort Detrick, MD 21702-5024
Contracting/Grants Officer: Judi Sgambato, judi.a.sgambato.civ@mail.mil
Performance Period: 09/01/2021-08/31/2022 (NCE)

Level of funding:
Role: Co-Investigator
Project Goals: The goal of this proposed research is to characterize the FOXA1 cistrome in salivary duct carcinoma and determine the efficacy of the LSD1 inhibitor GSK2879552 for disrupting FOXA1-mediated epigenetic reprogramming and tumor growth in ex vivo organoid cultures.
Specific Aims: Aim 1. Define the FOXA1 cistrome in salivary duct carcinoma. Aim 2. Determine molecular and cellular responses to LSD1 inhibition in salivary duct carcinoma.
Overlap: This award

PENDING
Title: Targeting RhoC in Breast Cancer: Novel Drugs, Mathematical Models and Laser Spectroscopic
Time Commitments: 3.0 CM
Supporting Agency: The Breast Cancer Research Foundation
Address: 28 West 44th Street, Suite 609, New York, NY 10036
Contracting/Grants Officer: Margaret (Peg) Mastrianni, pegmast@BCRFCure.org
Performance Period: 10/01/2004 - 09/30/2023
Level of funding:
Role: PI
Project Goals: Test the molecular and biological activity of compounds directed against RhoC to decide which holds the most promise in helping patients with aggressive breast cancer.
Specific Aims: 1) Extend our mathematical non-linear dynamical model of signaling pathways with special attention to Rho-dependent pathways, to understand how multiple interacting pathways that engage in cross talk at several levels transmit information.
2) Design strategies for using the dynamical properties of interacting signaling pathways to decide how to inhibit these pathways most efficiently.
3) Test efficacy against IBC and other aggressive cancer models two novel compounds targeting the RhoC oncogene discovered by the Merajver and Wang labs. Perform molecular studies utilizing innovative methods of biological phenotype read outs in 3-dimensional in vitro and in murine models.
Study the molecular epidemiology of IBC in North Africa in collaboration with an international IBC consortium to help discern the environmental and molecular epidemiology of IBC in this region.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Targeted Nanodrug Delivery to Inhibit Myeloid Derived Suppressor Cells
Time Commitments: 0.3 CM
Supporting Agency: Michigan State University/NIH
Address: TBD
Contracting/Grants Officer: TBD
Performance Period: 09/01/2022-08/31/2027
Level of funding: total costs
Role: PI
Project Goals: To ensure that the experiments conducted at MSU are planned so that they satisfy the pre-clinical milestones to eventually proceed to larger animal studies and ultimately

clinical trials.
Specific Aims: This work requires complex levels of expertise in basic cancer biology, the natural history of cancer diseases when cancer invades the bone marrow and other sites, and the translational trajectories such a strategy may follow.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Gilteritinib for lorlatinib-resistant ALK NSCLC
Time Commitments: 0.36 CM
Supporting Agency: LUNGevity Foundation
Address: TBD
Contracting/Grants Officer: TBD
Performance Period: 09/01/2022-08/31/2023
Level of funding: total costs
Role: Co-Investigator
Project Goals: 1) Characterize mechanisms of lorlatinib resistance 2) perform drug sensitivity testing on circulating tumor cells and tissue-generated organoids and 3) develop a phase I clinical trial of gilteritinib
Specific Aims: Lorlatinib is the only approved ALK-targeted drug for patients with ALK-positive non-small cell lung cancer (ALK NSCLC) who progressed on prior ALK drugs. The duration of benefit from lorlatinib is seven months (1), before resistance develops. There are currently no approved ALK-directed therapies after lorlatinib.
One mechanism of lorlatinib resistance is that the cancer cells develop two ALK mutations which block lorlatinib. Another way is that the cancer cells activate another pathway, such that the cancer is no longer reliant on ALK. Our understanding of these mechanisms remains limited which is a main reason we do not yet have effective post-lorlatinib treatment .
This project proposes to address these issues directly with the goal of opening a clinical trial using a novel drug called gilteritinib. First, we propose to obtain tumor-containing samples from patients who are progressing on lorlatinib and perform in-depth sequencing of these cancer cells to describe the methods of resistance. Next, we will perform drug sensitivity testing on these cancer cells using new drugs and drug combinations, including gilteritinib. Finally, we will open a clinical trial using gilteritinib, which is already approved for the treatment of a blood cancer (FLT3+ acute myeloid leukemia). In multiple pre-clinical studies gilteritinib was shown to be able to kill lorlatinib-resistant cells, but this drug has not been given to patients with ALK NSCLC. Our proposal is focused on studying patients' cancer cells and bring that knowledge directly into the clinic in the form of a clinical trial with a novel drug.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Genomic Structural Variants as Novel Therapeutic Targets in Lung Cancer Brain Metastases
Time Commitments: 0.6 CM
Supporting Agency: Department of Defense
Address: TBD
Contracting/Grants Officer: TBD
Performance Period: 09/01/2023-08/31/2025
Level of funding:
Role: Co-Investigator

Project Goals: In this proposal, we hypothesize that novel structural genomic alterations represent therapeutic targets in lung cancer with brain metastases.
Specific Aims: Aim 1. Characterize the genomic landscape of structural variation in lung cancer with brain metastases. Aim 2. Assess the potential for targeting structural variants in clinically relevant pre-clinical models of lung cancer with brain metastases.
Overlap: No scientific or budgetary overlap with the proposed proposal.

PAST RESEARCH SUPPORT (in the last 5 years)
Title: Conformational Control of Protein Kinases
Time Commitments: 0.36 CM
Supporting Agency: NIH
Address: 45 Center Drive MSC 6200, Bethesda, MD 20892-6200
Contracting/Grants Officer: Christina Fleming, fleminch@mail.nih.gov
Performance Period: 09/01/2017-06/31/2022
Level of funding:
Role: Co-Investigator
Project Goals: Protein kinases (PKs) play an important role in healthy and diseased cell signaling. However, we do not fully understand the complex signaling of PKs because we lack tools to understand the full scope of kinase signaling. In this proposal, we develop a series of tools to study noncatalytic signaling of PKs.
Specific Aims: Aim 1) To identify mutations that impact c-Src global conformation, Aim 2) To develop ATP- competitive, conformation-tunable kinase inhibitors, Aim 3) To identify allosteric, conformation-selective kinase inhibitors.
Overlap: No scientific or budgetary overlap with the proposed proposal.
****Ended support****

Title: Targeting the ETV/PEA3 transcriptional circuitry with selective small molecule probes
Time Commitments: 1.0 Cal Months
Supporting Agency: NIH
Address: 9609 Medical Center Drive, West Tower, 2nd floor, Rockville MD 20850
Contracting/Grants Officer: Rogers Gross, rogers.gross@nih.gov
Performance Period: 07/01/2016-06/30/2022
Level of funding:
Role: Co-Investigator
Project Goals: In this project we will use an innovative transcriptional modulator discovery strategy to identify natural product-based inhibitors and activators of the ETV/PEA3 activators. These molecules will be used to dissect the role of the ETV/PEA3 Med25 complex in tumor growth and metastasis in vitro and in an in vivo model of breast cancer. These molecules will be broadly useful probes for chemical genetic studies of transcriptional dysregulation in human disease and serve as starting points for the development of therapeutic agents that alter ETV/PEA3 function.
Specific Aims: Aim 1) Selective small molecule modulators of ETV/PEA3---- Med25 complexes, Aim 2) Chemical genetic dissection of TV/PEA3•Med25 complex function, Aim 3) Dissecting ETV----driven transcriptional programs with small molecule modulators
Overlap: No scientific or budgetary overlap with the proposed proposal.
****Ended support****

Title: InheRET, the Inherited Risk Evaluation Tool for identifying patients at increased risk of hereditary disease.
Time Commitments: 2.0 calendar months
Supporting Agency: NIH/InheRET
Address: 3470 Greenleaf Ct, Ann Arbor, MI, 48105-3503
Contracting/Grants Officer: Amanda Cook acook@inheret.com
Performance Period: 05/01/2019-09/09/2020
Level of funding:
Role: Co-Investigator
Project Goals: Long Term Goal. Healthcare providers will use InheRET during routine check-ups to accurately identify patients with inherited cancer susceptibility enabling quality referrals and testing of high-risk patients. Phase 1 Goal. Establish feasibility of the InheRET platform to accurately detect at-risk hereditary patient variables in accordance with national best-practice guidelines for Breast, Ovarian, and Colorectal Cancer.
Specific Aims: Specific Aim 1: Confirm InheRET algorithm correctly identifies at-risk patients in accordance with national hereditary cancer guidelines. Conduct iterative testing of InheRET algorithms in silico (computer simulation) to test all combinations that could trigger referral recommendations, and of 450 enrolled patients' generated reports, comparing these results to national guidelines. Acceptance Criteria: 98.9% concordance with guideline recommendation among 530,000 in silico patient profiles and 98% among 450 enrolled patients.
Specific Aim 2. Link InheRET to an Epic EHR. Partnering with the Univ. of Michigan, InheRET will create a patient report, link the report to the corresponding patient account, and produce a system alert in the form of an "In-basket" message. A new report will be filed for each update. Acceptance Criteria: 100 patient reports with 100% occurrence of file receipts, and system auto alerts.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Quantitative Parenchyma Descriptor as an Imaging Biomarker of Breast Cancer Risk 1 U01 CA195599
Time Commitments: 0.24 Cal Months
Supporting Agency: NIH
Address: 9609 Medical Center Drive, West Tower, 2nd floor, Rockville MD 20850
Contracting/Grants Officer: Rogers Gross, rogers.gross@nih.gov
Performance Period: 08/01/2015-07/31/2020
Level of funding:
Role: Co-Investigator
Project Goals: The goal of this proposed project is to develop a new quantitative descriptor of breast parenchyma (q-BPD), which is designed to characterize the stromal and epithelial structures as well as the composition of an individual's breast, as a biomarker for breast cancer risk prediction.
Specific Aims: Aim 1) Collection of a database of patients for analysis of breast density, Aim 2) Design of quantitative breast parenchyma descriptor (q-BPD) as an image-based biomarker for cancer risk assessment, Aim 3) Validation of the effectiveness of breast cancer risk prediction with q-BP
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Exquisitely selective turn-on probes of kinase activation and localization R21CA214233
Time Commitment: 0.0 CM
Supporting Agency: NIH
Address: 9609 Medical Center Drive Bethesda, MD 20892-9760
Contracting/Grants Officer: Avery Tucker, avery.tucker@nih.gov
Performance Period: 06/01/2017-05/31/2020 **Level of Funding:** annual directs **Role:** Co-Investigator
Project Goals: In this proposal, we aim to create very specific molecules to study the activity of protein kinases. Using these molecules, we propose applications that can detect kinase amount and location in living cancer cells.
Specific Aims: Aim 1: To develop methodology that can target any kinase. Aim 2: To demonstrate utility for imaging kinase concentration and localization.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: UM-Merajver Tempus, Inc Analysis **Time Commitments:** 0.6 Cal Months **Supporting Agency:** Tempus, Inc.
Address: 733 3rd Ave 15th floor, New York, NY 10017 **Contracting/Grants Officer:** Sasha Gribov, Sasha.gribov@tempus.com
Performance Period: 05/01/2017-04/30/2020
Level of funding: (all years)
Role: PI
Project Goals: The overall goal of the Collaboration is for Tempus to produce genomic and RNA seq profiling of a select number of samples carefully curated for clinical outcomes.
Specific Aims: The University of Michigan will provide characteristics of different groups of patients from which Tempus and the University of Michigan will decide which ones to profile. Further, Tempus will analyze this select population of breast cancer patients with a longitudinal data set ("Research Cohort"), phenotypic data, therapeutic data, and outcome data to the extent it is available. An additional goal of the collaboration is to develop Organoids from a set of breast cancer research samples and to share knowledge, expertise and results from the development of the Organoids. Tempus agrees to perform RNA seq and whole exome sequencing of select organoid samples, ~ 10 samples, as part of the collaboration
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Integrative signaling to increase efficacy of targeted therapies for triple negative breast cancer
Time Commitments: 1.2 CM
Supporting Agency: NIH
Address: 9609 Medical Center Drive, West Tower, 2nd floor , Rockville MD 20850
Contracting/Grants Officer: Tracie Mcgraw, mcgrawth@mail.nih.gov
Performance Period: 08/01/2017-07/31/2019
Level of funding:
Project Goals: Using our unique collection of already characterized low-passage TNBC PDXs, we will determine by single cell analyses and bioplex signaling, biomarkers to predict patient response and resistance for future clinical trials.
Specific Aims: Aim 1) Assess the efficacy and determine biomarkers of UM-193 + trametinib using 3D in vitro assays, Aim 2) Assess the in vivo efficacy of UM-193 + trametinib with

TNBC PDXs.
Overlap: No scientific or budgetary overlap with the proposed proposal

Title: Identifying Patients at Increased Risk of Hereditary Cancer using InheRET: a Pilot Study
Time Commitments: 0.84 Cal Months
Supporting Agency: Blue Cross Blue Shields of Michigan Foundation
Address: 600 E. Lafayette Blvd., Detroit, MI 48226-2998
Contracting/Grants Officer: Jacqueline Paul, jpaul@bcbsm.com
Performance Period: 01/01/2018-12/31/2018
Level of funding:
Project Goals: The objective of this proposal is to conduct pilot studies of our online decision support tool, InheRET, designed to reduce barriers preventing patients at high risk for hereditary cancer syndromes from receiving the full benefit of available medical care.
Specific Aims: Aim 1) To Track the impact of InheRET on patient management. Method: We will deploy InheRET as a pilot at a minimum of four (4) primary care sites and one (1) oncology site and through survey of patients and providers we will quantify the clinical impact, Aim 1a) Quantify the acceptance of InheRET from the patient and provider perspectives (ease of use, completion rates, physician effort, overall satisfaction), Aim 1b) Measure the impact of InheRET on genetic counseling utilization (rate of appropriate referral for genetic counseling), genetic testing rates, and uptake of prophylactic interventions, Aim 2) To extend a health economic model of hereditary breast and ovarian cancer to include InheRET. Method: We will build upon a hybrid decision tree-Markov model to include the InheRET decision tool, Aim 2a) Use the economic model to provide context to the impact described in Aim 2 and to explore the likely effects of deploying InheRET under varying strategies in the care cascade.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: University of Michigan Comprehensive Cancer Center Support Grant 5 P30 CA046592
Time Commitments: 0.6 Cal Months
Supporting Agency: NIH
Address: 31 Center Drive, MSC 2292, Bethesda, MD 20892
Contracting/Grants Officer: Jennifer A Edwards, edwardsj@mail.nih.gov
Performance Period: 06/01/2016-05/31/2018
Level of funding:
Project Goals: The core grant supports the senior leadership, programs and shared facilities of the Cancer Center. The Center provides the organizational framework to promote interdisciplinary research through the development of defined clinical, basic science and prevention programs in cancer research, and the development and support of shared resources.
Specific Aims: The core grant supports the senior leadership, programs and shared facilities of the Cancer Center. The Center provides the organizational framework to promote interdisciplinary research through the development of defined clinical, basic science and prevention programs in cancer research, and the development and support of shared resources.
Overlap: No scientific or budgetary overlap with the proposed proposal.

Title: Low Dose Tamoxifen in Hodgkin Lymphoma Survivors for Breast Cancer Risk Reduction
Time Commitments: 0.00 CM

Supporting Agency: University of Alabama at Birmingham / NIH R01 **Address:** 1600 7th Ave South, Birmingham, AL 35233 **Contracting/Grants Officer:** Holly Simpson hsimpson@peds.uab.edu **Performance Period:** 06/01/2015 – 05/31/2017
Level of funding:
Project Goals: To determine the impact of a two-year course of low-dose tamoxifen administered at 5mg per day on surrogate endpoint biomarkers of breast cancer (BC) risk, including: • mammographic breast density (MBD), an established radiographic biomarker of BC risk, • cytomorphology and proliferative index, tissue biomarkers closely linked to BC risk, and • insulin growth factors and circulating biomarkers of BC risk. To establish safety and tolerability of this low-dose tamoxifen regimen, assessing both objective measures (lipid profiles, clotting factors and bone metabolism markers) and patient-reported outcomes. To examine the modifying effect of demographic, clinical, and molecular characteristics on the risk benefit ratio from this two- year low dose tamoxifen intervention.
Specific Aims: 1) Determine the impact of a two-year course of low-dose Tamoxifen on surrogate biomarkers of chemopreventive efficacy; 2) Establish its safety and tolerability; and 3) Examine the modifying effect of several well-defined demographic, clinical, and molecular characteristics on the risk benefit ratio from intervention.
Overlap: No scientific or budgetary overlap with the proposed proposal.

OTHER SUPPORT

SPECTOR, MATTHEW

ACTIVE

Title: Targeting FOXA1-Mediated Epigenetic Reprogramming in Aggressive Salivary Gland Cancer
Time Commitments: 0.06 calendar months
Supporting Agency: Department of Defense
Address: 1077 Patchel Street, Fort Detrick, MD 21702-5024
Contracting/Grants Officer: Judi Sgambato; judi.a.sgambato.civ@mail.mil
Performance period: 09/01/21 – 08/31/22 (NCE)
Level of funding:
Project Goals: The goal of this proposed research is to characterize the FOXA1 cistrome in salivary duct carcinoma and determine the efficacy of the LSD1 inhibitor GSK2879552 for disrupting FOXA1-mediated epigenetic reprogramming and tumor growth in ex vivo organoid cultures.
Specific Aims: Aim 1. Define the FOXA1 cistrome in salivary duct carcinoma. Aim 2. Determine molecular and cellular responses to LSD1 inhibition in salivary duct carcinoma.
Role: Co-Investigator
Overlap: This award

PENDING

None

ENDED (FROM THE LAST 5 YEARS)

Title: Evaluation of TAK-981 and TAK-981 Combinations Following Intratumoral CIVO Microdosing in Patients with Head and Neck Cancer
Time Commitments: 0.12 calendar months
Supporting Agency: Presage Biosciences
Address: 530 Fairview Avenue North, Suite 1000 Seattle, WA 98109
Contracting/Grants Officer: Kimberly Sottero; kimberly.sottero@presagebio.com
Performance period: 05/07/20 – 04/30/22
Level of funding: (DC Total)
Project Goals: To assess the highly localized pharmacodynamics (PD) in the tumor microenvironment (TME) following intratumoral administration of subtherapeutic microdoses of TAK-981 and TAK-981 combinations with cetuximab or avelumab.
Specific Aims: N/A
Role: Co-Investigator
Overlap: No scientific or budgetary overlap with the proposed proposal
****Ended support****

Title: Molecular Mechanisms of Tumor Behavior and Response to Therapy in HPV-positive Oropharyngeal Cancer (R01 CA194536)
Time Commitments: 0.18 calendar months
Supporting Agency: NIH/National Cancer Institute
Address: 31 Center Drive, Building 31, Bethesda, Maryland, 20814
Contracting/Grants Officer: Grants Management Specialist: Jennifer S Meininger, jennifer.meininger@nih.gov, 240-276-6330
Program Official: Sara Louise Hargrave
Performance Period: 02/15/16 – 01/31/21
Level of funding:

Project Goals: In this project we will investigate HPV integration site, viral oncogene expression and alternate transcripts, effects of integration on cellular gene expression, and we will characterize other genetic abnormalities that correlate with outcome.
Specific Aims: Aim 1: Determine HPV type, assess viral gene expression and the effect of alternate HPV E6 transcripts on E7 and p53 expression, malignant behavior and outcomes. Aim 2: Determine if the cellular site of HPV integration, intragenic or intergenic, alters the expression of genes with intragenic integration and correlates with clinical outcomes. Aim 3: Determine the co-dependent molecular lesions that differentiate responsive and non-responsive HPV+ oropharynx HNSCC tumors.
Role: Co-Investigator
Overlap: None

Title: Functional Imaging-Directed Adaptive Therapy of Head and Neck Cancer
Time Commitments: 0.36 calendar months
Supporting Agency: NIH / NCI
Address: 9609 Medical Center Drive
Building 9609 MSC 9760
Bethesda, MD 20892-9760
Contracting/Grants Officer:
Grants Management Specialist: Angela Walters
Email: waltersar@mail.nih.gov
Program Official: Bhadrasain Vikram
Email: vikramb@mail.nih.gov Phone: Fax: 240-276-5827
Performance Period: 03/01/15 – 02/29/20
Level of funding:
Project Goals: As DCE-MRI and DW-MRI are widely available in the community, the proposed studies will lead to future multi institutional study which will assess the improvements in LR control rates and DFS in advanced HNC promised by the proposed concepts and investigations
Specific Aims: AIM 1: Conduct a randomized phase II study of poor prognosis HNC, comparing intensification of the radiation doses to tumor sub-volumes demonstrating poor perfusion that persists after 2 weeks of chemoirradiation, vs. standard chemo-RT. We hypothesize that the intensified therapy arm will result in improved LR control and DFS, without increased toxicity, compared with the standard therapy arm, and that further improvements will be feasible once Aims 2 and 3 are evaluable in the latter years of this Aim's clinical study.
AIM 2: Incorporate tumor subvolumes derived from hypoperfusion (DCE-MRI) and high cellularity (DWMRI), as potential local therapy resistance markers for prediction of local and regional failure. We hypothesize that combining the two spatial markers will improve the identification of the resistant tumor subvolumes and improve outcome of future local dose intensification compared with relying on one modality alone. Combining the two imaging modalities will be performed using a method we have developed, global-initiated regularized local fuzzy clustering (GRELFC), for identifying subvolumes from heterogeneous functional MRI across patients and over multiple time points.
AIM 3: Develop response-induced perfusion MRI biomarker to predict toxicity related to the swallowing structures, and adapt radiotherapy planning to reduce dysphagia. Dysphagia has emerged as the main longterm toxicity of intensive chemo-irradiation for HNC. Based on our preliminary data we hypothesize that perfusion MRI early after treatment has started will improve predicting late dysphagia for the individual patient, help adapt radiotherapy, and improve the therapeutic ratio of irradiation aiming to both deliver high target doses AND avoid significant toxicity.
Role: Co-Investigator
Overlap: None

Title: Predictive Biomarkers and Targeted Therapy in Recurrent Laryngeal Cancer (Translational Innovator Award)
Time Commitments: 0.12 calendar months

Supporting Agency: American Academy of Otolaryngology - Head & Neck Surgery
Address: 1650 Diagonal Rd, Alexandria, VA 22314
Contracting/Grants Officer: Sponsor Contacts: Stephanie L. Jones: sljones@entnet.org, Cynthia Zarate: cynthia@ahns.info
Performance Period: 07/01/16 – 06/30/18
Level of funding:
Project Goals: This grant seeks to examine prognostic biomarkers and genetic drivers of recurrent laryngeal cancer by comparing patients with poor-acting versus favorable-acting recurrent laryngeal cancer. This may identify biologically unfavorable disease that is amenable to targeted therapy.
Specific Aims: Our overall strategy is to identify genetic and histologic markers in a cohort of patients with recurrent LSCC after RT/CRT that may predict outcome and may be responsive to personalized, targeted therapy. We will address this by performing IHC on a TMA consisting of recurrent LSCC, performing targeted exome sequencing on recurrent LSCCs, and evaluating recurrent LSCC response to targeted agents that are currently in early clinical trials via ex vivo models. AIM 1: To identify immunohistochemical markers independently correlated with disease free and overall survival in a recurrent LSCC cohort. AIM 2: To correlate genetic mutational signatures with survival outcomes among patients with recurrent LSCC. AIM 3: To evaluate targeted treatment strategies for recurrent LSCC using ex vivo tumor models.
Role: Co-Investigator
Overlap: None

Title: Oral HPV infection and persistence in HIV positive and HIV negative individuals with head and neck cancer
Time Commitments: 0.12 calendar months
Supporting Agency: NIH (Prime Sponsor) / Johns Hopkins University (Direct)
Address: (Direct Sponsor) Otolaryngology-HNCR Division at Johns Hopkins University
David Koch Cancer Research Building
1550 Orleans St., CRB II, Rm 505
Baltimore, MD 21231
Contracting/Grants Officer:
Johns Hopkins University (Direct)
David Sidransky,
Contact Address:
c/o Faye Mackall
Sr. Administrative Manager
Otolaryngology-HNCR Division at Johns Hopkins University
David Koch Cancer Research Building
1550 Orleans St., CRB II, Rm 505
Baltimore, MD 21231
Performance Period: 07/01/16 – 06/30/18
Level of funding:
Project Goals: The Head and Neck SPORE HIV consortium will collect frozen tumor and normal tissue samples from HNSCC patients with HIV. These samples, from multiple institutions, will be analyzed at a common site to determine the spectrum of genomic alterations that are present. This spectrum will be compared to genomics data previously generated by TCGA and the collaborating institutions.
Role: Co-Investigator
Overlap: None