AWARD NUMBER: W81XWH-17-1-0141

TITLE: Epigenomic Priming as an Immunotherapy Enhancer in Ovarian Cancer

PRINCIPAL INVESTIGATOR: Daniela Matei, MD

RECIPIENT: Northwestern University

REPORT DATE: MAY 2020

TYPE OF REPORT: ANNUAL

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
MAY 2020	Annual Technical	05/01/2019-04/30/2020

4. TITLE AND SUBTITLE

Epigenomic Priming as an Immunotherapy Enhancer in Ovarian Cancer

5a. CONTRACT NUMBER
W81XWH-17-1-0141

5b. GRANT NUMBER
OC160260

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Daniela Matei, MD
Bin Zhang, MD, PhD

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
NORTHWESTERN UNIVERSITY
633 CLARK STEVANSTON IL 60208

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Rosalind Franklin University of Medicine and Science North
Chicago, IL 60064-3095

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
New immunologic approaches targeting immune checkpoint pathways, such as the programmed cell death protein-1 (PD-1) are under clinical development for solid tumors,including ovarian cancer (OC). Anti-PD1 strategies prevent T-cell exhaustion, augmenting immune anti-tumor responses. The focus of this application is to develop a combination regimen that enhances the activity of PD1-targeted immunotherapy in a clinical trial designed for women with recurrent ovarian cancer. We speculate that an important mechanism of immune evasion in OC is represented by epigenetic silencing of tumor antigens. One of the mechanisms of transcriptional repression of tumor antigens.

15. SUBJECT TERMS
Ovarian cancer, DNA methylation, immune checkpoint inhibitors, tumor neoantigen

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	30	19b. TELEPHONE NUMBER *(Include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The purpose of the project is to analyze tumor biopsies and PBMCs collected as part of a clinical trial for women with platinum resistant ovarian cancer treated with epigenetic priming (guadecitabine) and pembrolizumab. The hypothesis is that epigenomic priming will enhance anti-tumor immunity and synergize with immune checkpoint inhibitors.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Ovarian cancer, DNA methylation, immune checkpoint inhibitors, tumor neoantigen

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Major Task 1: Measure tumor antigens in specimens collected from clinical trial

Subtask 1: Clinical trial enrollment and treatment	Completed; 48 patients enrolled, 43 patients treated and 33 patients evaluable. Clinical trial analysis is completed.
Subtask 2: Tumor biopsies, PBMC and plasma collection and storage	samples from 35 patients collected (325 PBMC specimens and 48 tumor biopsies and 8 ascites specimens)
Subtask 3: Extract DNA and RNA from tumor biopsies	100% completed for the patients enrolled
Subtask 4: Extract DNA from PBMC	100% completed for all patients enrolled
Subtask 5: LINE 1 and tumor antigen pyrosequencing	Completed for all specimens
Subtask 6: Tumor neoantigen measurement	3 paired samples completed
Subtask 8: Q-RT-PCR in tumor biopsies—tumor antigens	Completed in samples where RNA was sufficient
Subtask 9: Erv transcript assessment via PCR	Completed on existing specimens

Major Task 2: Measure immune response in specimens collected from clinical trial:

Subtask 11: FFPE tissue sections — Completed for all core biopsies collected to date

Subtask 12: IHC for CD3, CD8, CD4, granzyme B — Because the technology advanced since the time of the grant submission and the scant material available from the biopsies had to be prioritized, we developed multiplex IHC that allows evaluation of 7 markers on the same tissue (cytokeratin, CD3, CD8, CD20, CD68, FoxP3 and DAPI). The conditions for mIHC were optimized and slides were stained. Analysis is ongoing.

Subtask 13: Flow cytometry ascites and PBMC — Flow cytometry was performed on few ascites specimens. Additionally, because the technology advanced, we had access to CyTOF which permits much deeper characterization of immune cell subsets and performed CyTOF on several paired PBMC and ascites specimens, with very important results.

Subtask 14: Double IHC for TA and CD8 — Done on several specimens

Subtask 15: IHC interpretation — In process

Subtask 16: Measure NY-ESO-1–specific $CD8^+$ response. — This was done on 3 ascites specimens collected that were HLA2 positive.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

George Hutchins, undergraduate student, CURE Program, summer 2017
Natalia Rombell, high school student, spring 2018
Guangyuan Zhao, PhD student, fall 2017, spring 2018
Yakqi Zhang, PdD student, spring 2018
Azza Mohamed, Master student, spring-fall 2018
Nikita Lavanya Mani PhD student, fall 2017
Renqiang Ma, MD Visiting Scholar, spring 2018
Gaoxiang Wang MD Visiting Scholar, spring 2018
George Hutchins, undergraduate student, CURE Program, summer 2018
Natalia Rombell, undergraduate student, spring 2018
Hanna Kubo, PhD student, fall 2018
Matthew Cowan, DO, fall-winter 2018, spring 2019
Sonal Khare, PhD Postdoc, spring 2019
Ping Xie, Post doc fall 2019, winter, spring 2020

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Survive and Thrive, Chicago, September 2017 –Dr. Matei presented the clinical trial to a group of patients at Northwestern University
Stop Cancer, Bucharest April 2017—Dr. Matei presented design of the study to a group of physicians and scientists in Romania
MDACC, March 2018: Research Seminar, Houston Texas
Cleveland Clinic, December 2017: Research Seminar, Cleveland OH
Ohio State University, September 2018: Research Seminar including preliminary results from the trial
Oklahoma University, March 2019: Research Seminar including preliminary results from the trial
Stop Cancer, Bucharest, May 2019—Research seminar to physicians and scientists in Romania
Gynecology Oncology Showcase, Northwestern University May 2019—results presented to physicians from the Department of Obstetrics and Gynecology
ASCO 2020; poster presentation of clinical endpoints
AACR 2020; part of oral presentation in Educational Symposia

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We are working on completing the analysis of multiplex IHC and the processing and analysis of methylomic and transcriptomic comparison of specimens before and after treatment.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*

- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Because the tissue obtained through biopsies is scant, nucleic acids extracted for some specimens are in low amount and will have to be prioritized for use. To gain most knowledge from the specimens obtained, we will use RNA sequencing (instead of RT-PCR for multiple genes) for the specimens yielding sufficient amount of RNA. This will allow getting information on many genes, rather than on a small set of genes. Validation will be limited by the amount of RNA available for the specific specimens.
Likewise, for the IHC analyses proposed in Aim 2, we developed multi-channel IHC to allow examining multiple markers on the same specimen and maximize use of tissue. Additionally, we have used CyTOF to characterize PBMC populations, as this technology allows for higher resolution definition of immune cell populations. This is in line with the **advancement of technology** during the past 2 years and represents the current state of the art and **does not change the scope of the research objectives proposed**. The costs for these analyses are higher than what is originally proposed and we supplemented with additional internal sources of funding.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Several patients were enrolled, but were not evaluable due to early disease progression. These patients were replaced in order to have sufficient numbers to reach the clinical objectives of the trial. The regulatory approvals slightly delayed completion of enrollment. However, the trial completed enrollment in late fall 2019 and now the analysis is ongoing. All specimens were received and processed.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

There is a slight lag in expenditures, as collection and processing of specimens is ongoing.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

None

Significant changes in use or care of vertebrate animals

None

Significant changes in use of biohazards and/or select agents

None

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation);*

status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Poster presentation at ASCO 2020 and Oral Presentation at AACR 2020. A manuscript is in preparation.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*

- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name: Daniela Matei
Project Role: PD/PI
Nearest person month worked: 1
Contribution: oversees clinical trial activities, oversees research activities, organizes monthly meeting with co-Is, meets individually with co-Is at least quarterly, meets with research coordinators weekly, reviews results, organizes plan for analyses

Name: Bin Zhang
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution: responsible for completion of Aim 2, oversees one postdoctoral fellow, reviews results, organizes plan for analyses

Name: Hao Huang
Project Role: Co-Investigator
Nearest person month worked: 5
Contribution: RT-PCR, library preparation and sequencing, methylomic analysis, data analysis

Name: Horacio Cardenas
Project Role: Co-Investigator
Nearest person month worked: 3
Contribution: specimen collection and logging, sequencing analysis, data analysis, pyrosequencing

Name: Siqi Chen
Project Role: Co-Investigator
Nearest person month worked: 12
Contribution: postdoctoral fellow, IHC, flow cytometry, data analysis

Name: Azza Mohammad
Project Role: Technician
Nearest person month worked: 7
Contribution: nucleic acid extraction, specimen collection and logging.

Name: Mathew Cowan, MD
Project Role: Fellow
Nearest person month worked: 7
Contribution: multi-plex IHC and analysis.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

MATEI, DANIELA E.

CHANGES
*Indicates New Award since last report
**All Pending new since last report
***Completed since last report
Active

R01CA224275 (Matei) 08/01/2018 – 07/31/2023 1.80
Calendar Months
NIH/NCI
Targeting Lipid Unsaturation in Ovarian Cancer Stem Cells

Objective: To analyze whether the balance between saturated and unsaturated lipids enhance the survival of drug-tolerant cells after chemotherapy. We will use SCD1 knock down and chemical inhibitors to eradicate drug-tolerant cells persisting after treatment with platinum in ovarian xenografts and patient derived xenografts (PDX).
Role: PI
Agency Contact: Arya Suresh Email: aryas@mail.nih.gov

Aim 1: Determine the mechanisms by which lipid unsaturation mediated by SCD1 promotes stemness. Aim 2: Use label free chemical imaging to identify and characterize ovarian CSCs within the tumor microenvironment (TME).
Aim 3: Define anti-tumor and metabolic effects of SCD1 inhibition or knock down in vivo.

W81XWH-17-0141 (Matei) 05/01/17 – 04/30/21 0.60
Calendar USAMRMC/CDMRP NCE)
Epigenomic Priming as an Immunotherapy Enhancer in Ovarian Cancer
Objective: To propose a clinical trial testing a novel strategy to enhance efficacy of immunotherapy in OC by using epigenetic priming. The ultimate goal of the project is to develop a new treatment that extends the lives of women with OC, while preserving the quality of life of the survivors.
Aim 1: Measure the antigen burden induced bytreatment with guadecitabine in human tumors in relationship to clinical response.
Aim 2: Determine the anti-tumor activity of CD8+ effector T cells induced by treatment with guadecitabine and pembrolizumab in relationship to clinical response.
Role: PI
Contact: Lisa Wells Roark, lisa.l.wellsroark.civ@mail.mil

I01 BX000792 (Matei) 10/01/10 – 09/30/23 3.00
Calendar Months*
NIH/VA Merit Review Award
The Tissue Transglutaminase-Fibronectin Interaction in Ovarian Cancer Metastasis
We propose to elucidate the mechanism by which TG2/FN complex initiates oncogenic signaling leading to metastasis and to characterize pre-clinically the top hit identified during the screening process.
Role: PI

Aims: 1: Characterize the mechanisms by which formation of the TG2/FN/integrin complex activates EMT. 2: Define mechanisms engaged by TG2/FN/integrin complexes to promote stem cell signaling.
3: Characterize the effects of the lead TG2/FN inhibitor in an OC metastasis model. Agency Contact: Kenute Myrie, kenute.myrie@va.gov

**Dr. Matei's appointment includes a Northwestern University appointment (62%) and a 5/8ths (38%) VA-appointment with the Jesse Brown VA, Chicago. The effort she devotes to this VA Merit Review Grant is part of her VA appointment only. Salary recovery and effort commitments in the other active grants listed here reflect percentages of her Northwestern University-based effort and salary.*

1UG1CA233320-01 (Benson, Matei) 04/01/19 - 02/28/25 1.20 Calendar
NIH/NCI

Northwestern University Lead Academic Participating Site (NCI National Clinical Trials Network)
The goal of this grant is to allow the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (LCC) to continue leadership of and participation in Network Group trials as a high performing LAPS. This grant will enable expanded participation of LCC members in NCTN trials, scientific leadership of key network activities, increased inter-institutional collaborations, and access to unique scientific resources to advance cancer interventions.
Role: Co-PI
Aims 1: Provide scientific leadership and mentorship for the development, conduct, and reporting of multi-center late phase clinical trials. 2: Contribute patients, imaging and tissue resources to Network Group trials. 3: Collaborate with other NCTN sites and NCI-supported clinical research programs.
Agency Contact: WLODEK LOPACZYNSKI, lopacw@mail.nih.gov

Completed

#T2013-003B (Matei) 01/01/16-01/01/18 N/A
The V Foundation for Cancer Research An Epigenetic Strategy for Restoring Carboplatin Sensitivity in Ovarian Cancer
This study will bring epigenetic interventions to the forefront of therapy for ovarian cancer impacting treatment strategies and outcomes for this deadly cancer. Successful completion of this study will move forward the field of epigenome-targeted therapy for solid tumors and will provide key information for biologically- directed future design of phase III trials
Aims:
1. To measure DNMTI (SGI-110)-induced changes in the OC methylome by performing MethylCap-seq.
2: To determine if DNMT expression levels differ in recurrent vs. primary tumors and whether expression levels at enrollment or changes induced by DNMTIs correlate with

clinical benefit and survival.
3: To determine whether specific genes methylation levels at enrollment and changes induced by DNMTIs correlate with clinical benefit and survival.
Agency Contact: Carole Wegner, cwegner@jimmyv.org

***R21 CA198409 (Hurley) 07/01/15 - 06/30/18 0.96
Calendar Months
NIH/NCI
Targeting Ovarian Cancer Stem Cells Through Selective Inhibition of ALDH1A1
We propose to optimize and validate the lead inhibitor for the first time in a cancer model, focusing on inhibiting the functions of ALDH1A1+ ovarian CSCs. We will determine the lead inhibitor's target specificity and its cytotoxic activity in ALDH1A1+ ovarian cancer cells and will measure its anti-cancer activity in an animal model that replicates tumor recurrence after chemotherapy.
Aims: The aim is stated as the
goal statement. Role: co-PI
Agency Contact: Suresh Arya, aryas@mail.nih.gov

R01 EB016582 (Nolte) 05/01/13 - 04/30/18 1.00
Calendar Months
NIH/NIBIB
Tissue-dynamics Imaging for Therapeutic Efficacy in Ovarian Cancer
We propose that by exploiting the intracellular dynamical properties of ovarian tumors or metastatic implants ex-vivo, this new technology can be adapted to overcome a problem of high clinical relevance for women with ovarian cancer. A commercial partner, Animated Dynamics LLC, will receive technology transfer and construct the first clinic-based TDI system.
Aims: The aim is stated as the
goal statement. Role: co-PI
Agency Contact: Behrouzb Shabestari, shabestb@mail.nih.gov

***R01 CA182832 (Matei) 02/14/14 - 01/31/20 1.20
Calendar Months
NIH/NCI (NCE)
An Epigenetic Strategy for Restoring Carboplatin Sensitivity in Ovarian Cancer
This study will bring epigenetic interventions to the forefront of therapy for ovarian cancer impacting treatment strategies and outcomes for this deadly cancer. Successful completion of this study will move forward the field of epigenome-targeted therapy for solid tumors and will provide key information for biologically- directed future design of phase III trials.
Aims:
1. To measure DNMTI (SGI-110)-induced changes in the OC methylome by performing MethylCap-seq.
2: To determine if DNMT expression levels differ in recurrent vs. primary tumors and whether expression levels at enrollment or changes induced by DNMTIs correlate with clinical benefit and survival.
3: To determine whether specific genes methylation levels at enrollment and changes induced by DNMTIs correlate with clinical benefit and survival.

Agency Contact: Min-Kyung Song, songm@mail.nih.gov

***Agreement 01/23/17 (Nephew) 01/01/17 - 02/01/20 0.60
Calendar Ovarian Cancer Research Fdn (IUPUI Subcontract)
Epigenetic Vulnerabilities of Ovarian Cancer Stem Cells

The goal is to identify how key pathways are epigenetically maintained and regulated in ovarian cancer stem cells and epigenetic vulnerabilities that can be targeted to switch off paths responsible for ovarian cancer stem cell survival after platinum therapy.
Role: Co Investigator
Aims are as stated in goals

Pending**

P20CA233304 (Simon) 04/01/20 – 03/31/23 1.20 Calendar

NIH/NCI *JIT/Revisions Requested The Northwestern University Cancer Health Equity Research SPORE (NU-CHERS) will generate scientific
Aim (1) understanding racial disparities in endometrial cancer through tumor genomics and Aim (2) revealing critical molecular insights into the mechanisms governing disease progression and response to treatment in ovarian cancer accounting for racial disparities in clinical outcomes.
Role: Core Co-Lead (AC); Basic Co-Lead (P2)
Agency Contact: Tiffany Wallace, wallaceti@mail.nih.gov
Aims are as stated in goals

R01CA224275 (Matei, Cheng) 08/01/20 - 07/31/23 0.00
Calendar
NIH/NCI
Targeting Lipid Unsaturation in Ovarian Cancer Stem Cells
Diversity Supplement: The focus of this R01 application is to characterize and target a new metabolic vulnerability of ovarian cancer stem cells (CSCs) described by our collaborative team. By using hyperspectral stimulated Raman scattering imaging of single living cells and mass spectrometry analysis of extracted lipids we identified increased levels of unsaturated lipids in ovarian CSCs compared to non-CSCs.
Role: PD/PI
Agency Contact: Arya Suresh Email: aryas@mail.nih.gov

Aims of parent R01:
1: Determine the mechanisms by which lipid unsaturation mediated by SCD1 promotes stemness
2: Use label free chemical imaging to identify and characterize ovarian CSCs within the tumor microenvironment (TME).
3: Define anti-tumor and metabolic effects of SCD1 inhibition or knock down *in vivo*.

R21CA258155 (Matei) 04/01/21-03/31/23 1.20 Calendar months
NIH
Targeting De Novo Pyrimidine Synthesis To Reverse Platinum Resistance in Ovarian Cancer
We propose that under the pressure exerted by chemotherapy, cancer cells undergo metabolic reprogramming, which allows them to adapt and to survive noxious stimuli. We have developed stable OC models of platinum-tolerance in vitro and in vivo.
Role: PD/PI
Agency Contact: Sean Hine, hines@mail.nih.gov

Aims: 1: Determine whether platinum-tolerant OC cells and tumors are dependent on the de novo pyrimidine synthesis pathway. 2: Determine whether inhibition of DHODH will prevent or reverse platinum-tolerant cellular state in HGSOC cells and tumors.

Overlap: None

OTHER SUPPORT

ZHANG, BIN

***Bold and italic indicates update from last submission**

Current Support

Title: The role of GPSM3 in tumor-promoting emergency myelopoiesis
Time Commitments: 2.40 Calendar
Supporting Agency: NIH/NCI
R01CA208354 9606 Medical
Center Drive
Bethesda, MD 20892-9760
Grants Officer: Barbara Hodgkins, barb.hodgkins@nih.gov,
(240) 276-6294 Performance Period: 03/01/2017 - 02/29/2022
Level of Funding:
Goals: The goal of this project is to determine the role of GPSM3 in regulating the cancer-driven myelopoiesis.
Specific Aims:
Aim 1: Define the role of GPSM3 in regulating the cancer-driven myelopoiesis.
Aim 2: Determine whether cytokine-induced GPSM3 regulates critical transcriptional mediators of cancer-associated myelopoiesis.
Aim 3: Study the role of GPSM3 in MDSC-mediated immune suppression and tumor promotion. Role: PI

Title: Project #3 SNAs as Immunotherapeutic Agents for
Prostate Cancer Time Commitments: 1.20 Calendar
Supporting Agency: NIH/NCI
U54CA199091 (Mirkin) 9606 Medical
Center Drive
Bethesda, MD 20892-9760
Grants Officer: Barbara Hodgkins, barb.hodgkins@nih.gov,
(240) 276-6294 Performance Period: 09/01/2015 - 07/31/2020
Level of Funding:
Goals: The goal of Project 3 is to develop SNAs that are capable of inducing an immune response that will destroy prostate tumors.
Specific Aims:
Aim 1: Design, synthesize and characterize IS-SNAs for activation of lymphocytes.
Aim 2: Analyze the immunostimulatory activity of IS-SNAs with a panel of standardized in vitro assays. Aim 3: Assess and characterize IS-SNA activity in immunocompetent mouse models.
Aim 4: Development of combination therapies for an optimized cancer immunotherapy: Immunostimulation by IS-SNAs combined with modulation of the

immunosuppression of solid tumors. Role: Project 3 Co-Leader

Title: CCNE Pilot Project: Engineered Spherical Nucleic Acids for Advanced Cellular Therapy
Time Commitments: 0.12 Calendar
Supporting Agency: NIH/NCI
U54CA199091 (Mirkin) 9606 Medical
Center Drive
Bethesda, MD 20892-9760
Grants Officer: Barbara Hodgkins, barb.hodgkins@nih.gov,
(240) 276-6294 Performance Period: 09/01/2015 - 07/31/2020
Level of Funding:
Goals: To develop T cell chaperones with IS-SNAs for ACT is based on the properties and cellular
interactions that are unique to SNAs and distinguish SNAs from other nanoparticle systems
for cancer therapy: highly efficient uptake of SNAs into T-cells is in a controlled, ex vivo environment.

Title: Epigenomic Priming to Enhance Immunotherapy in Ovarian Cancer
Time Commitments: 0.12 Calendar
Supporting Agency: DOD/CDMRP W81XWH-17-1-0141
Performance Period: 05/01/2017
- 04/30/2021
Level of Funding:
Goals: The goal of this project is to test if treatment with a DNMT inhibitor increases the anti-tumor activity of PD-1 blockade by enhancing tumor cell recognition by CD8+ effector T cells in a phase II clinical trial.
Specific Aims:
Aim 1: Measure the antigen burden induced by treatment with guadecitabine in human tumors in relationship to clinical response.
Aim 2: Demonstrate that the combination of guadecitabine and pembrolizumab blockade increases anti- tumor efficacy of cytotoxic CD8+ T cells in vivo.
Role: Co-PI

Title: WEE1 inhibition and tumor immunity
Time Commitments: 1.20 Calendar
Supporting Agency: NIH/NCI R01CA222963
9606 Medical
Center Drive
Bethesda, MD
20892-9760
Grants Officer: Barbara Hodgkins, barb.hodgkins@nih.gov,
(240) 276-6294 Performance Period: 07/01/2018-06/30/2023
Level of Funding:
Goals: The goal of this project is to characterize the novel regulatory perspectives of

WEE1-mediated crosstalk between tumor cells and host immune cells that should significantly forward the field. Our work will identify an unappreciated role of WEE1 inhibition in reversing tumor-induced immune suppression of Tregs, in addition to its direct cytotoxic activity.
Specific Aims:
Aim 1: To determine the intrinsic role of WEE1 in inducible Tregs for tumor promotion.
Aim 2: To determine the immunomodulatory effects of WEE1 expression in tumor cells.
Aim 3: To determine the therapeutic efficacy of WEE1 inhibition in combination with the anti-PD-1/PD-L1 immunotherapy.
Role: PI

Title: Tumor microenvironment-induced natural killer cells (MINK) for cancer immunotherapy
Time Commitments: 0.60 Calendar
Supporting Agency: AbbVie Inc.
Grants Officer: Jesseca Rodgers
Performance Period: 12/13/18-12/12/20
Level of Funding:
Goal: The goal of this project is to evaluate a novel strategy for potentiating antitumor immune responses by engineering natural killer cells to sense and therapeutically respond to general features of the tumor microenvironment.
Specific Aim 1: To evaluate whether NK cells may be engineered to sense hypoxia in vitro and in vivo.
Specific Aim 2: To evaluate whether NK cells may be engineered to sense VEGF in vitro and in vivoSpecific
Aim 3: To evaluate whether MINK can
therapeutically modulate tumor growth and local immune state.
Role: Co-PD/PI

***Title: Immune control of triple negative breast cancer by WEE1 inhibition** Time Commitments: 1.2 Calendar
Supporting Agency: DOD/CDMRP
Performance Period: 03/15/2019 – 03/14/2022
Level of Funding:
Goals: The goal of this project is to propose a novel strategy to enhance efficacy of immunotherapy using DNA replication checkpoint WEE1 inhibition.
Specific Aim 1: To determine the immunomodulatory effects of WEE1 expression in tumor cells.
Specific Aim 2: To determine the immunomodulatory effects of WEE1 expression in T cells.
Specific Aim 3: To determine the therapeutic efficacy of WEE1 inhibition in combination.
Role: PD/PI

***Title: Targeting CysLTR1 in triple negative breast cancer**

Time Commitments: 1.8 Calendar
Supporting Agency: DOD/CDMRP
Performance Period: 07/01/2020 – 06/30/2023
Level of Funding:
Goals: The goal of this project is to explore CysLTR1 inhibitors alongside agents that stimulate CD8+ T cell activity, including the checkpoint blockade therapies that target PD-1 and PD-L1, which are both in clinical development in treating TNBC.
Specific Aim 1: Define the role of CysLTR1 in regulating accumulation and function of tumor-infiltrating MDSCs.
Specific Aim 2: Determine whether CysLTR1 is required for critical transcriptional regulation of MDSCs.
Specific Aim 3: Determine the therapeutic efficacy of CysLTR1 inhibition in combination with anti-PD-1/PDL1immunotherapy.
Role: PD/PI

Pending Support

Title: Exploitation of Acetylated Androgen Receptor for Immunotherapy for Prostate Cancer
Time Commitments: 0 Calendar
Supporting Agency: DOD/CDMRP
Performance Period: 09/01/2019 - 08/31/2022
Level of Funding:
Goals: This proposal will pursue the idea that post translationally modified (PTM) androgen receptor (AR) should be exploited as a neoantigen in the development of immunotherapy for prostate cancer (PC). This proposed research aims to discover epitopes designed from PTM isoforms of AR, particularly acetylated AR, that are capable of raising antigen-specific cellular immune response (expansion and cytotoxicity of CD8+ T-cells). It will also show that such PTM forms of AR are prevalent in PC patient tissues and determine whether this prevalence is in contrast with healthy tissue, and thus establish PTM forms of AR as potential molecular markers for immunological recognition and attack.
Specific Aim 1: Discover epitopes designed form PTM isoforms of AR, particularly acetylated AR.
Specific Aim 2: Demonstrate PTM forms of AR are prevaltent in PC patient tissues.
Specific Aim 3: Determine whether the prevelance of AR in PC patient tissues is in contrast with health tissue and establish PTM forms of AR as potential molecular markers for immunological recognition and attack.
Role: Collaborator

Title: The distinct role of cysteinyl leukotriene receptor for myeloid-derived suppressive cells
Time Commitments: 2.4 Calendar
Supporting Agency: NIH/NCI
Performance Period: 09/01/2019 - 08/31/2024
Level of Funding:

Goals: The goal of this project is to explore the novel role of CysLTR1 as a distinct GPCR signaling modulator in tumor-induced immune evasion. Our preliminary data show that CysLTR1 is expressed selectively in myeloid cells from tumor-bearing hosts with the most significant expression in infiltrating MDSCs, and elevated levels of CysLTs were observed in the tumor.
Specific Aim 1: Define the role of CysLTR1 in regulating accumulation and function of tumor-infiltrating MDSCs.
Specific Aim 2: Determine whether CysLTR1 is required for critical transcriptional regulation of MDSCs.
Specific Aim 3: Determine whether CysLTR1 on MDSCs is a central mediator of tumor-Induced immune suppression and tumor promotion.
Role: PD/PI

Title: Enhancing efficacy of immune checkpoint blockade in pancreatic cancer
Time Commitments: 1.8 Calendar
Supporting Agency: Pancreatic Cancer Action Network, Inc.
Performance Period: 07/01/2019 – 06/30/2024
Level of Funding:
Goals: The goal of this project is to identify combination regimens to improve immunotherapy responses against PDAC.
Specific Aim 1: Characterize the mechanism by which MNK inhibitors increase PD-L1 in cancer cells.
Specific Aim 2: Define the mechanism by which MNK inhibitors promote T cell infiltration in vivo.
Specific Aim 3: Determine the effects of combining immune checkpoint inhibitors with MNK inhibitors on PDAC progression in vivo.
Role: Co-I

Title: Oncolytc virotherapy enhances checkpoint inhibitor’s in pancreatic cancer
Time Commitments: 0.60 Calendar
Supporting Agency: Pancreatic Cancer Action Network, Inc.
Performance Period: 07/01/2019 – 06/30/2021
Level of Funding:
Goals: The goal of this project is to address these questions: Will the combination of REO and CPI be more effective to treat advanced PDAC and can we identify biomarkers predictive of clinical efficacy in a subset of pts for future studies?
Specific Aim 1: To determine the clinical efficacy of the combination of REO and pembrolizumab.
Specific Aim 2: To evaluate viral replicative potential, immune-cell infiltration and intrinsic tumor factors that regulate immune heterogeneity.
Specific Aim 3: Define changes of peripheral immune-cell repertoire and identify biomarkers of response to oncolytic viral therapy.
Role: Co-I

Title: Distinct roles of the CD73 in anti-VEGF therapy for established cancer
Time Commitments: 1.80

Calendar Supporting Agency:
NIH/NCI R01CA234352
9606 Medical
Center Drive
Bethesda, MD
20892-9760
Grants Officer: Barbara Hodgkins, barb.hodgkins@nih.gov,
(240) 276-6294 Performance Period: 09/01/2018-08/31/2023
Level of Funding:
Goals: The goal of this proposal seeks to characterize the novel and co-operative roles of both tumor and endothelial CD73 in anti-VEGF treatment, and identify therapeutic means of targeting CD73-mediated pathways in anti-angiogenic cancer therapy.
Specific Aims:
Aim 1: To explore the molecular mechanisms by with CD73 regulates VEGF-A production from tumor cells.
Aim 2: To determine whether tumor CD73 is required for recruitment of patrolling monocytes that are sufficient to confer tumor refractoriness to anti-VEGF therapy.
Aim 3: To define whether CD73 expression on both tumor cells and endothelial cells is required to confer refractoriness to anti-VEGF therapy.
Role: PI

Title: Mechanism-based novel combination therapies for pancreatic cancer
Time Commitments: 0.60 Calendar
Supporting Agency: NIH/NCI
Performance Period: 09/01/2019 – 08/31/2024
Level of Funding:
Goals: The goal of this project is to identify therapeutic combinations with improved efficacy against PDAC.
Specific Aim 1: Determine the effects of combining MNK inhibitors with immune checkpoint inhibitors on PDAC progression in vivo.
Specific Aim 2: Define and target MNK kinase activation to enhance the anti-tumorigenic effects of BET inhibitors in vivo.
Role: Co-I

Previous Support

***Title: PARP inhibition and tumor immunity**
Time Commitments: 0.36
Calendar Supporting Agency:
AbbVie, Inc
Grants Officer: Eric Johnson
Performance Period: 09/29/2017 -
09/29/2019 Level of Funding:

Specific Aims

Aim 1: Define the role of PARPi in regulating the cancer-driven Myelopoiesis Aim 2: Determine the molecular mechanism by which PARPi regulates MDSCs Aim 3: Determine the immunoregulatory effect of PARPi on tumor cells
Role: PI

***Title: Spherical Nucleic Acids as Therapeutic Vaccines for the Treatment of Prostate Cancer** Time Commitments: 1.20 Calendar
Supporting Agency: Prostate Cancer Foundation
Grants Officer: Audrey Gardner agardner@pcf.org
(310) 570-4792 1250 Fourth Street
Santa Monica, CA 90401
Performance Period: 09/01/2017 -
08/31/2019 Level of Funding:

Goals: To develop and test a novel nanoparticle-based therapeutic prostate cancer vaccine in preclinical models which may lead to a new immunotherapy for prostate cancer.
Role: Co-Investigator

***Title: Targeting chemokine signaling and MAPK/ERK pathway in advanced prostate cancer**
Time Commitments: 0.36 Calendar
Supporting Agency: Prostate Cancer Foundation
Performance Period: 12/31/2017-12/31/2019
Level of Funding:
Goals: The goal of this project is to prove that CXCR7/MAPK/ERK signaling drives CRPC progression and resistance to AR-targeted therapies and that clinically available MAPK/ERK inhibitors might delay or overcome CRPC drug resistance.
Aim 1. To analyze CXCR7-MAPK-ERK pathway in PCa models and in mCRPC patient specimens.
Aim 2. To determine the functional importance of the CXCR7-MAPK-ERK pathway in CRPC progression and Enz resistance using preclinical models and in the tumor microenvironment using transgenic mice.
Aim 3. To test the efficacy of MAPK-ERK inhibitors in overcoming CRPC Enz resistance using preclinical and PDX models and to develop novel CXCR7 antagonists.

Title: Treating Breast Cancer by Novel WEE1 inhibitors
Time Commitments: 0.36 Calandar
Supporting Agency: NMG Lynn Sage
Grants Officer:
Performance Period: 9/1/2016- 8/31/2018
Level of Funding:
Goals: The Goal of this study is to explore the translation relevance of the use of FDA-approved WEE1 inhibitors MK-1775 as modulators of the antitumor immune response

in breast cancer.
Specific Aims:

Title: Therapeutic T-cell Chaperones with SNAs for the Treatment of Melanoma Time Commitments: 0.60 Calendar
Supporting Agency: IDP-Sherman Fairchild Challenge Award Irene Pritzker
321 North Clark Street, Suite 2350
Chicago, IL 60654
Grants Officer: Renay Wilson-Brown, renay@northwestern.edu, (312) 695-1318 Performance Period: 06/01/2016- 05/31/2018
Level of Funding:

Goals: The goal of this project is to devise a new clinically applicable strategy for active targeting of immunoadjuvants/checkpoint disruption to established melanomas, using T lymphocytes as living chaperones to deliver IS-SNAs to tumor sites.

Role: PI

Title: A novel mechanism of melanoma immunotherapy resistance Time Commitments: 1.20 Calendar
Supporting Agency: Melanoma Research Alliance, Research Pilot Study 347520 1101 New York Ave, NW
Suite #620
Washington, DC 20005
Grants Officer: Laura Brockway-Lunardi, lbl@curemelanoma.org, (202) 336-8937 Performance Period: 05/01/2015 - 10/31/2017
Level of Funding:
Goals: The goal of this project is to explore the novel mechanisms of melanoma resistance to agonistic costimulatory molecule-targeting therapy.
Specific Aims:
Aim 1: To determine whether Treg cells are an important cellular target of the combination therapy using agonistic anit-OX40 mAbs and CD73 blockade.

Aim 2: To determine whether tumor cells expressing CD73 are resistant to agonistic anti-OX40 therapy, but not combination of anti-CD73 and agonistic anti-OX40 therapy.
Role: PI

Title: CD73 and tumor immunity
Time Commitments: 3.60 Calendar
Supporting Agency: NIH/NCI
CA149669 9606 Medical Center Drive
Bethesda, MD 20892-9760

Grants Officer: Barbara Hodgkins, barb.hodgkins@nih.gov,
(240) 276-6294 Performance Period: 03/01/2011 - 02/29/2017
Level of Funding:
Goals: The major goal of this project is to study the mechanisms of CD73 in the tumor microenvironment through its enzymatic activity prevent tumor destruction by incoming anti-tumor T cells.
Specific Aims:
Aim 1: To define the effects of tumor CD73 on T cell-mediated tumor immunity Aim 2: To define the effects of host CD73 on T cell-mediated tumor immunity
Aim 3:To determine whether blocking CD73 using its selective inhibitor APCP or anti-CD73 mAb enhances CTL therapy of cancer

Title: Treating breast cancer by novel WEE1 inhibitors
Time Commitments: 0.36 Calendar
Supporting Agency: Lynn Sage Cancer Research Foundation Award 251 East Huon Street, Galter Pavilion, Suite 3-200
Chicago, IL 60611
Grants Officer: Julie Lampert
Performance Period: 09/01/2016 - 08/31/2017 Level of Funding:

Goals: The goal of this project is to test if WEE1 inhibition improves breast cancer immunotherapy in addition to its direct cytotoxic effect.
Role: PI

Title: Development of Novel Prostate Cancer Immunotherapy
Time Commitments: 0.60 Calendar
Supporting Agency: NIH/NCI P550CA090386 Prostate Cancer SPORE
9606 Medical Center Drive
Bethesda, MD 20892-9760
Grants Officer: Connie Murphy
Performance Period: 02/01/2013 - 01/31/2014
Level of Funding:
Goals: The major goal of this project is to dissect the tumor-induced immune suppression in prostate cancer and provide clues to develop prostate tumor-specific immune therapy.
Specific Aims:
Aim 1: To determine whether DFMO alter the phenotype and suppressive function of tumor-educated human MDSC
Aim 2: To determine whether DFMO treatment reduces tumor-induced MDSC and augments the efficacy of adoptive T cell therapy.

Title: Improving Ovarian Cancer Therapy by alleviation of immune suppression

Time Commitments: 1.20 Calendar
Supporting Agency: NMF - Friends of Prentice
251 E. Huron Street
Galter Pavilion
Chicago, IL 60611
Grants Officer: Stephen Falk
Performance Period: 9/01/2013 - 08/31/2014
Level of Funding:
Goals: The goal of this project is to test a novel strategy to alleviate tumor-induced immunosuppression for ovarian cancer therapy.
Specific Aims:
Aim 1: To define the in vivo effects of DFMO in antitumor T Cell immunity
Aim 2: To determine whether DFMO administration enhances DC vaccines against ovarian cancer
Role: PI

Title: Targeting CD73 to improve ovarian cancer immunotherapy
Time Commitments: 2.40 Calendar
Supporting Agency: Liz Tilberis Scholar Funds
14 Pennsylvania Plaza
New York, NY 10122
Grants Officer: Audra Moran
Performance Period: 2/1/2011 - 01/31/2015
Level of Funding:
Goals: The major goal of this project is to study whether inhibiting CD73 using its selective inhibitor or anti-CD73 mAb improves DC vaccination against ovarian cancer.
Specific Aims:
Aim 1: To define the effects of tumor CD73 on T cell-mediated tumor immunity
Aim 2: To determine whether the blocking of CD73 using its selective inhibitor APCP or anit-CD73 mAb enhances DC vaccines against ovarian cancer
Role: PI

Title: Treating ovarian cancer by novel CD73 inhibitors
Time Commitments: 1.20 Calendar
Supporting Agency Marsh Rivkin Center for Ovarian Cancer Research Pilot Study Award
801 Broadway, Suite 701
Seattle, WA 98122
Grants Officer: Joe White
Level of Funding:
Goals: The goal of this project is to test the efficacy of CD73 enzymatic blockade with a FDA-approved drug as a novel means to enhance breast cancer immunotherapy.
Specific Aims:
Aim 1: To determine whether Tenofovir augments the immune response of tumor-reactive T cells through blocking of CD73 enzymatic activity.
Aim 2: To define the in vivo antitumor effects of combine inhibiting CD73 activity by Tenofovir with anti-CTLA-4 (Ipilimumab).

Role: PI

OVERLAP

None

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.