AWARD NUMBER: W81XWH-17-1-0141

TITLE: Epigenomic Priming as an Immunotherapy Enhancer in Ovarian Cancer

PRINCIPAL INVESTIGATOR: Daniela Matei, MD

RECIPIENT: Northwestern University
Evanston, IL 60208

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TYPE OF REPORT: Annual

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

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Epigenomic Priming as an Immunotherapy Enhancer in Ovarian Cancer

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

5d. PROJECT NUMBER

5e. TASK NUMBER

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NORTHWESTERN UNIVERSITY
633 CLARK ST
EVANSTON IL 60208

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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
unclassified	unclassified	unclassified	U	29	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	21 of 35 patients enrolled
Subtask 2: Tumor biopsies, PBMC and plasma collection and storage	20 of 35 patients collected
Subtask 3: Extract DNA and RNA from tumor biopsies	75% completed
Subtask 4: Extract DNA from PBMC	ongoing
Subtask 5: LINE 1 and tumor antigen pyrosequencing	not started
Subtask 6: Tumor neoantigen measurement	3 paired samples submitted for analysis
Subtask 8: Q-RT-PCR in tumor biopsies—tumor antigens	50% completed
Subtask 9: Erv transcript assessment via PCR	performed on existing specimens

Major Task 2: Measure immune response in specimens collected from clinical trial: samples obtained, staining was not started

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1) Major activities and results

a) Clinical activities: The clinical trial was activated and 21 patients were enrolled to date, completing the first stage of accrual. Currently enrollment is suspended, pending the completion of the interim analysis. When it will be re-open (after DSMB review), up to 35 evaluable patients will be enrolled.
--Preliminary results:
-Efficacy: 1 complete responder, 1 partial responder, 1 minor response lasting 18 months, 2 patients with stable disease for 6 months.
-Toxicity: The regimen was generally well tolerated, with myelosupression as the main toxicity. Use of growth factors was recommended and mitigated this toxicity. 10 SAEs have been reported, of which 4 were considered related (1 colitis, 1 enterocolitis, 1 grade 3 neutropenia, 1 infection and allergic reaction). Of those, 3 events represent immune mediated toxicity. The toxicity is in line with what was expected.

b) Nucleic acid extraction from all tumor biopsies collected from the protocol completed for the available specimens. 31 RNA and DNA specimens were obtained and are in the process of analysis.

c) FFPE slides obtained from the enrolled patients. Staining is in progress, with emphasis on developing and validating multiplex IHC.

d) Evaluation of gene expression changes was obtained by RNA Sequencing (4 paired specimens) and by QRT PCR for specific genes (10 paired specimens). Here we show changes in gene expression (C2D8 vs. C1D1). These data are not final, as we anticipate analyzing more specimens, as they are being collected form the trial.

Significant results: RNA sequencing analysis of paired samples demonstrates upregulation of immune response pathways, specifically induction of IFNγ and Granzyme-A. However we also note up-regulation of IDO1, LAG3 and PD1, which might cause a feedback break on the anti-tumor response elicited.

Figure 1: Upregulation of immune related genes (mRNA level), as measured by RNA sequencing in RNA extracted from tumor biopsies obtained on C1D1 (baseline) and C2D2 (post-treatment).

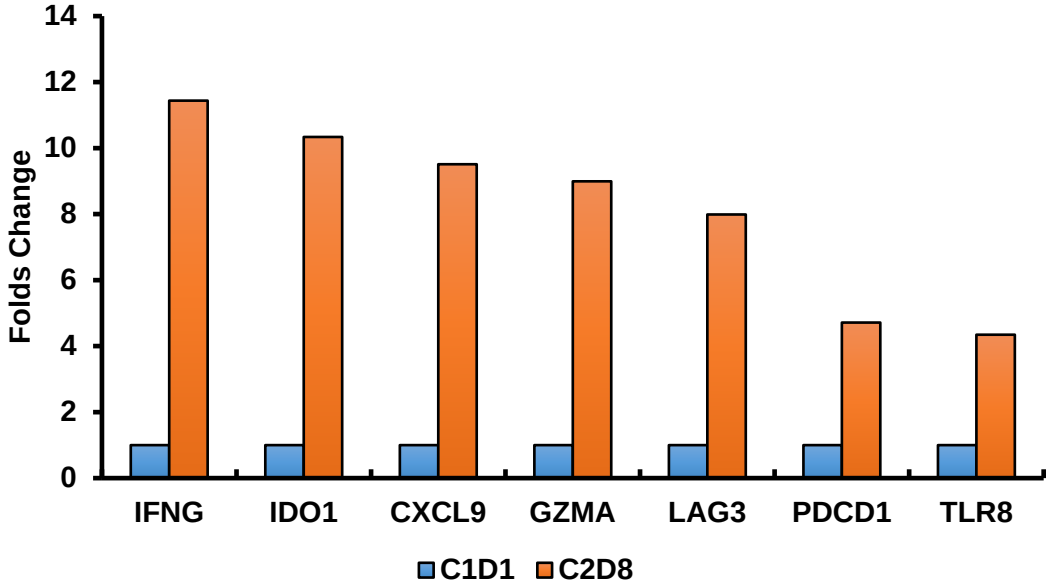
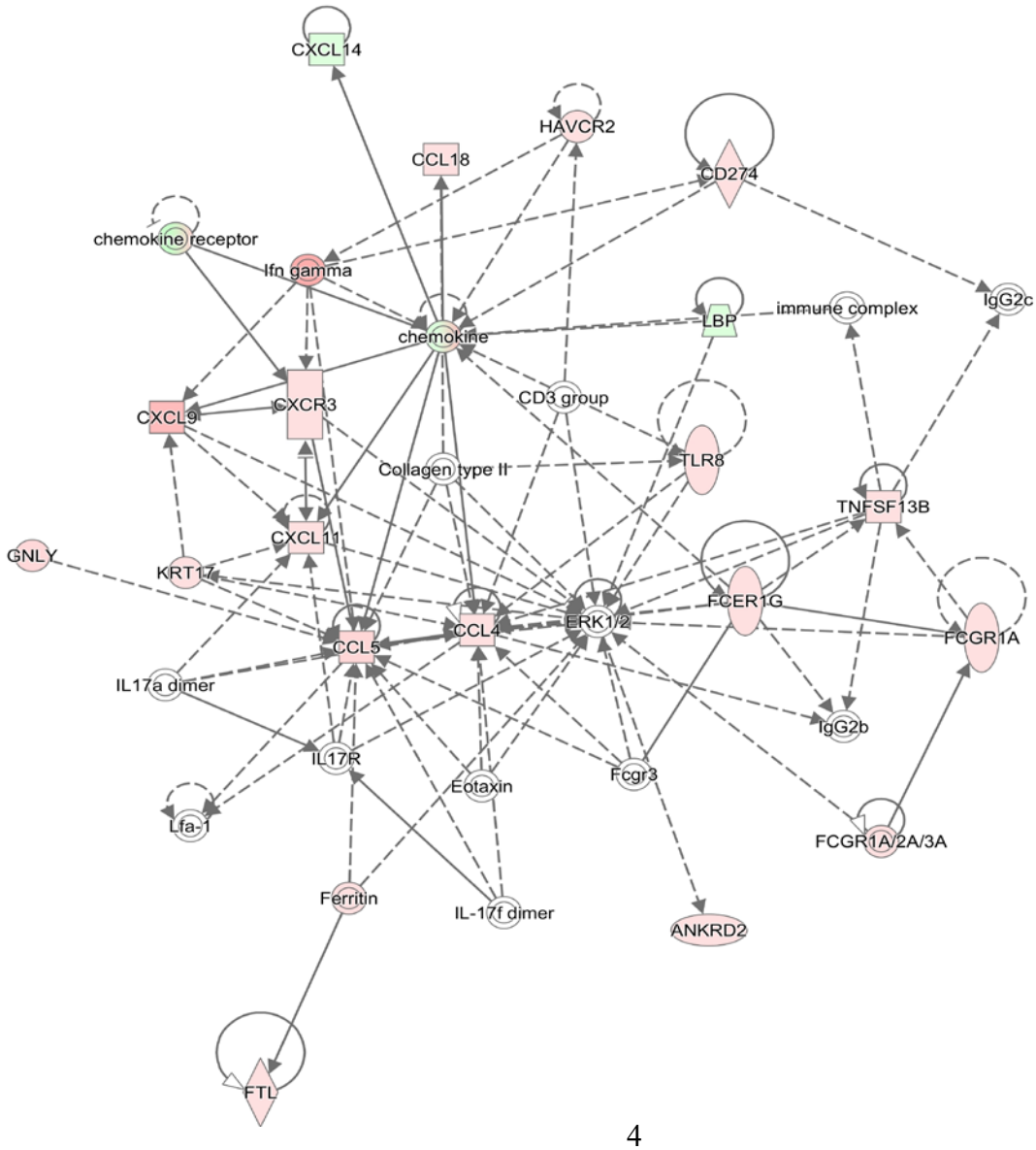


Table 1: Top 30 upregulated genes as measured by RNA sequencing in RNA extracted from tumor biopsies obtained on C1D1 (baseline) and C2D2 (post-treatment).

Gene Symbol	Fold Change	pvalue
TLR8	4.3	7.43E-05
CALHM6	4.5	7.99E-06
BIRC7	4.7	0.000150151
PDCD1	4.7	3.51E-05
EOMES	4.8	0.000174714
MT1L	5.0	0.000259089
GNLY	5.3	7.78E-05
HTRA4	5.4	7.20E-10
JAKMIP1	5.6	0.000406371
SIGLEC8	5.6	5.86E-05
CCL5	5.7	2.78E-05
TMIGD3	5.8	8.48E-09
GZMK	5.8	0.000112385
GBP5	5.9	6.64E-08
CD8A	6.3	6.31E-06
CXCR6	6.4	1.01E-05
GZMH	6.5	1.78E-07
NKG7	8.0	6.72E-07

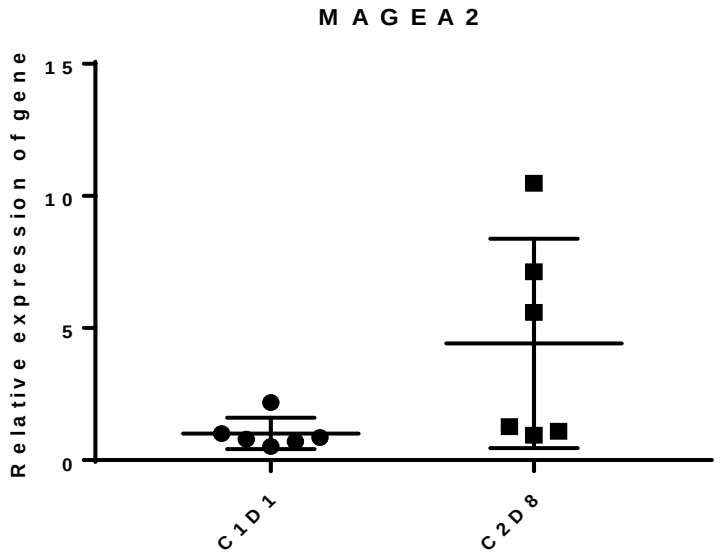
LAG3	8.0	3.03E-08
GZMA	9.0	3.09E-07
CXCL9	9.5	1.75E-09
MT1M	10.1	2.89E-06
IDO1	10.3	1.19E-07
IFNG	11.4	9.83E-05
ACOD1	11.5	0.000120561
AC106865.1	17.9	3.05E-05
ELF5	22.3	7.56E-05
HBG1	23.0	8.62E-06
MT1H	28.7	2.66E-05
MT1G	29.0	2.90E-12

Figure 2: IPA analysis identifies immune cell trafficking as one of the most significant pathways altered by treatment. These results are highly consistent with our hypothesis.



Expression of specific antigens (MAGE) was measured by QRT-PCR in RNA from paired tumor biopsies (n=7). Mage A11 was detectable only in 3 post-treatment biopsies (not shown); MAGEA2 was increased in post- vs. pre-treatment biopsies. These analyses will be continued for other antigens .

Figure 3: MAGEA2 mRNA expression in RNA extracted from tumor biopsies obtained on C1D1 (baseline) and C2D2 (post-treatment).



Expression of retroviral transcripts was measured by QRT-PCR in RNA from paired tumor biopsies (n=7). There was high variability between specimens, precluding definitive conclusions. We will try to expand measurements to additional specimens as they are being collected and correlate change in expression of these transcripts with clinical response.

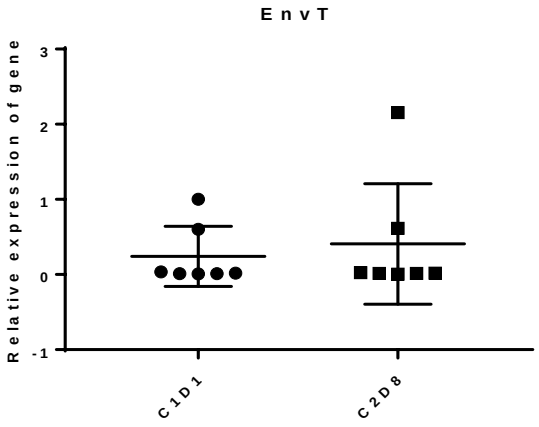


Figure 4: Expression of Env T in RNA extracted from tumor biopsies obtained on C1D1 (baseline) and C2D2 (post-treatment).

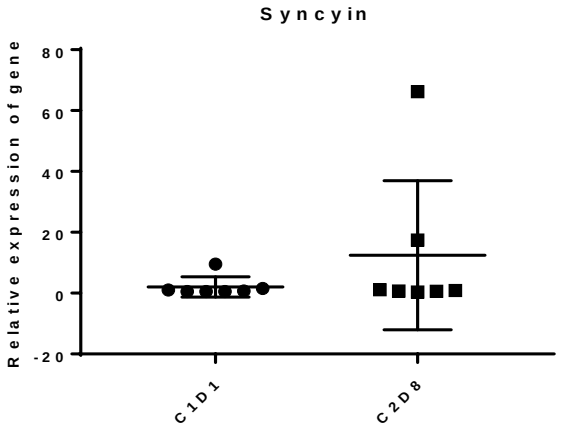


Figure 5: Expression of Syncyn in RNA extracted from tumor biopsies obtained on C1D1 (baseline) and C2D2 (post-treatment).

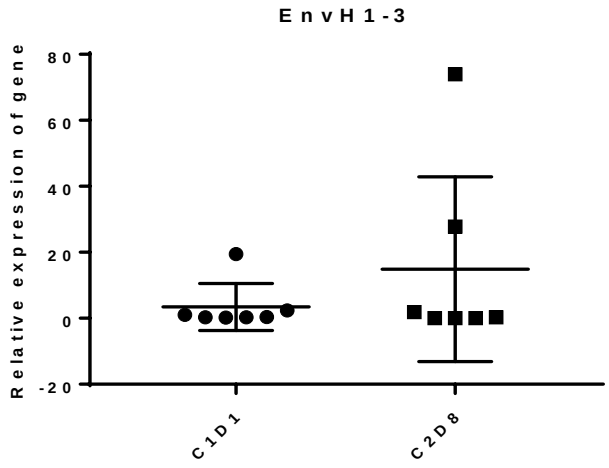


Figure 6: Expression of Env 1-3 in RNA extracted from tumor biopsies obtained on C1D1 (baseline) and C2D2 (post-treatment).

In conclusion, analyses are in progress and are proceeding according with proposed plan. Because of scant material obtained through tumor biopsies, we are prioritizing which genes to validate first and will use additional paired biopsies for RNA sequencing as the first priority.

DNA methylation analyses and IHC analyses will proceed in Year 2.

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 2018
Nikita Lavanya Mani PhD student, fall 2017
Renqiang Ma MD Visiting Scholar, spring 2018
Gaoxiang Wang MD Visiting Scholar, spring 2018

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

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

We anticipate completing enrollment to the trial; collecting all samples and processing for nucleic acid extraction, RT-PCR, sequencing, pyrosequencing, and IHC analyses. We will also optimize multichannel IHC to enable us to use multiple antibodies on the same slide to analyze immune cell populations.

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 genese) 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 will have to develop multi-channel IHC to allow examining multiple markers on the same specimen and maximize use of tissue. This is in line with the advancement of technology during the past 18 months and represents the current state of the art. The costs for these analyses will be higher than what is originally proposed and we will have to identify additional sources of funding for the specimens.

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.

Some delay with clinical trial accrual, but this is unpredictable and can fluctuate.

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.

Slight delay in start of the project due to IRB approval delay. Study will enter suspension phase for interim analysis after completion of stage 1, this will cause a temporary delay in specimen collection. There is a slight lag in expenditures.

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.*

Nothing to report

- **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: X
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: nucleic acid extraction, RT-PCR and sequencing, data analysis

Name: Horacio Cardenas
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution: specimen collection and logging, sequencing analysis, data analysis, pyrosequencing

Name: Siqi Chen
Project Role: Co-Investigator
Nearest person month worked: 11
Contribution: postdoctoral fellow, IHC, flow cytometry, data 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 submitted
**All Pending new since submitted
***Completed since submitted

Active

R01 CA182832 (Matei) 02/14/14 - 01/31/19 1.20 Calendar Months
NIH/NCI $257,789
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

I01 BX000792 (Matei) 10/01/10 - 12/31/18 4.20 Calendar Months
NIH/VA Merit Review Award $200,000
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.
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

R21 CA198409 (Hurley) 07/01/15 - 06/30/17 0.96 Calendar Months
NIH/NCI $128,346
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

***P30CA060553 (Platanias)** 09/16/13 - 07/31/18 0.60 Calendar
NIH/NCI $11,584

Northwestern University, Robert H. Lurie Comprehensive Cancer Center

The goals of this Cancer Center Support Grant are to conduct and support cancer research and to integrate cancer-related research throughout the university; to coordinate and integrate cancer-related activities of

the University including community outreach initiatives; to develop and conduct cancer education programs; to promote and participate in state-of-the-are care of cancer patients at the affiliated hospitals of the McGaw Medical Center of Northwestern University and; to develop and implement the initiatives in cancer prevention and control research. These goals are accomplished through the activities of the 10 establish programs and 13 shared resources.

Aims: The aim is stated as the goal statement.
Role: Co-Program Leader Translational Research in Solid Tumors

Agency Contact: Suresh Arya, aryas@mail.nih.gov

***Research Award (Nephew)** 01/01/17 – 02/01/20 0.60 Calendar
Ovarian Cancer Research Fdn (IUPUI Subcontract) $68,182
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.
Aims: The aim is stated as the goal statement.
Role: Co-Investigator
Agency Contact: Emily Hickey, ehickey@ocrfa.org

Pending

****R01CA224275 (Matei/Cheng)** 07/01/18 - 06/30/23 1.80 Calendar
NCI $507,686
Targeting Lipid Unsaturation in Ovarian Cancer Stem Cell
The goal of this multi-PI R01 application is to characterize and target a new metabolic vulnerability of ovarian cancer stem cells (CSCs) discovered by our collaborative team.

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.
Role: MPI

****R01CA235874 (Matei**) 09/01/18 - 08/31/23 2.40 Calendar
NCI $395,187
Novel Tissue Transglutaminase Inhibitors in Ovarian Cancer
Here we propose to continue optimizing and characterizing the newly discovered TG2/FN inhibitors with the ultimate goal of developing new agents that block cancer cell adhesion to the matrix and prevent OC metastasis
Aims: The aim is stated as the goal statement.
Role: PI

**I01BX000792 (Matei) 10/01/10 - 12/31/21 (renewal) 4.20 Calendar
Veterans Administration $200,000

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.
Aims: The aim is stated as the goal statement.

Role: PI

Completed

***R01 EB016582 (Nolte) 05/01/13 - 04/30/17 1.00 Calendar Months
NIH/NIBIB $257,755
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

***#T2013-003B (Matei) 01/01/16-01/01/17 N/A
The V Foundation for Cancer Research $188,636
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

(Matei, D.) 09/01/10 – 08/31/14 2.4 Calendar
US Department of Veterans Affairs ,VA Merit Review $125,000
The Functional Role of Tissue Transglutaminase in Ovarian Cancer
Objectives: This project will evaluate the role of TG2 in the process of peritoneal metastasis and EMT.
Contact: Julie Herbertz, julie.herbertz@va.gov
Aims:

1) Investigate whether TG2 modulates intra-peritoneal ovarian metastasis *in-vivo*
2) Investigate regulation of TG2 expression and function in response to TGFbeta in the peritoneal environment

P30 CA82709-09 (Loehrer, P.) 10/99-8/13 0.6 Calendar
NIH/NCI $786,011
Cancer Center Support Grant
The major goal of this project is to establish an NCI designated Cancer Center by facilitating cancer research, education, patient care, and cancer control and prevention to accomplish its mission of reducing the incidence, morbidity, and mortality of cancer.
Contact: Brett Hodgkins, Grants Management Specialist, (301) 496-8657, brett.hodgkins@nih.gov
Aims: The aim is stated as the goal statement.

R21 CA133877-02 (Matei, D.) 8/1/08 – 7/31/11 1.2 Calendar
NIH/NCI No cost extension year
A Low-Dose Decitabine Strategy for Restoring Ovarian Cancer Sensitivity
This is a clinical trial study.
Contact: Marie Moyer, moyerm@mail.nih.gov, 301-846-1007

Aims:

1) Determine whether a biologically active dose of decitabine administered i.v. qd for 5 days before carboplatin is tolerated in patients with recurrent, platinum-resistant or –refractory EOC
2) Determine clinical efficacy of decitabine and carboplatin in patients with platinum-resistant or –refractory EOC
3) Determine the pharmacodynamic activity of decitabine *in vivo*

RSG-09-167-01-CSM (Matei, D.) 1/1/10 – 12/31/13 4.8 Calendar
American Cancer Society $150,000
Targeting the Transglutaminase Fibronectin Interaction in Ovarian Cancer
The major goal of this project is to perform high throughput screening for inhibitors of TG2-fibronectin
Contact: Charles Saxe, Charles.Saxe@cancer.org, 404-929-6919
Aims:

1) To test if cancer cells engineered to contain increased amount of transglutaminase cause increased spread of tumors
2) To investigate if injection of transglutaminase in the abdomen of research mice increases the spread of ovarian tumors
3) To develop a test to measure the binding of transglutaminase to a protein commonly found in the tumor environment (fibronectin)

(Nephew, K.) 1/1/11 – 12/31/13 1.2 calendar
Ovarian Cancer Research Fund $272,727 (1/3 to Dr. Matei)
Epigenetic Modulation of Platinum Anti-Tumor Activity in Ovarian Cancer
Objective: This project will evaluate the role of DNA demethylating agents in responsiveness to platinum in preclinical models.
Contact: Jeff Boyd, Ph.D., 14 Penn Plaza, Suite 1400, New York, NY 10122
Aims:

1) To determine in-vivo efficacy of SGI-110 combined with cisplatin in cisplatin-sensitive ovarian carcinoma xenografts
2) To determine the in vivo activity of DNA methylation inhibitors against relapsed ovarian cancer and mechanisms of EMT
3) To determine mechanisms in addition to DNA methylation inhibition that play a role in the anticancer activity of DNA hypomethylating agents

Pending

R01CA219961 (Matei) 07/01/17 - 06/30/21 1.20 Calendar Months
NIH/NCI $ 1,100,009
Epigenomic Editing to Enhance Immunotherapy in Ovarian Cancer
Objective: The proposed translational project brings forward the concept of epigenomic editing in combination with immunotherapy as a new treatment strategy for ovarian cancer. Both preclinical and clinical analyses will test the hypothesis that agents inducing DNA hypomethylation reverse silencing of tumor antigens; restore their expression, and potentiate the effects of immune checkpoint inhibitors.
Agency Contact: Min-Kyung Song, songm@mail.nih.gov
Aim 1: To test the hypothesis that the tumor antigen burden induced by treatment with guadecitabine correlates with clinical response.
Aim 2: To test the hypothesis that anti-tumor activity of CD8+ effector T cells induced by treatment with guadecitabine and pembrolizumab correlates with expression of tumor antigens and clinical response.
Overlap: There is some scientific overlap with the current DOD application. This will be addressed if the R01 is awarded.

U01CA217520 07/01/17 - 06/30/22 1.20 Calendar Months
NIH/NCI $ 2,499,788

Epigenomic Signatures in Patient-Informed Models of Ovarian Cancer

The objective of this project is that altered epigenomic signatures associated with platinum resistance in ovarian cancer can be defined by using patient-derived biological platforms (tumor organoids and patient derived xenografts).

Aims:

1: Determine changes from the human tumor in the transcriptome and methylome
of high-grade serous OC (HGSOC)-derived PDX and organoids associated with platinum-resistance.

2: Determine changes from the human tumor in the chromatin regulatory regions
defined by histone marks in HGSOC-derived PDX and organoid cultures associated with platinumresistance.

3: Validate gene signatures associated with platinum-resistance in human HGSOC
tumors, PDX and organoids and in cancer stem cells (CSCs) isolated from these platforms.

Agency Contact: Michael Espey, sp@nih.gov

Overlap: None

OTHER SUPPORT
ZHANG, BIN

CHANGES
*Indicates New Award since submitted
**All Pending new since submitted
***Completed since submitted

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: $1,805,410
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 - 08/31/2020
Level of Funding: $663,685
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: $40,000

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: 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: $63,000

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: Epigenomic Priming to Enhance Immunotherapy in Ovarian Cancer Time Commitments: 0.60 Calendar
Supporting Agency: DOD/CDMRP W81XWH-17-1-0141
Performance Period: 05/01/2017 - 04/30/2020
Level of Funding: $945,000
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: 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: $236,148
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: 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: $350,000
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: 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: $50,000
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:

Pending Support

**Title: WEE1 inhibition and tumor immunity
Time Commitments: 2.40 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: $2,725,465
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: 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: $2,166,512
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

Previous Support

***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: $100,000
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: $1,066,270
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: $50,000
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: $22,537
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: $50,000
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: $228,306
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: $75,000
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

None Applicable

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.