AWARD NUMBER: W81XWH-21-1-0282

TITLE: Identifying the Determinants of Clinical Responses to PARP Inhibitors in Ovarian Cancer Immunotherapy

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CONTRACTING ORGANIZATION: The University of Texas MD Anderson Cancer Center

REPORT DATE: MAY 2023

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
MAY 2023	Annual	15APR2022 - 14APR2023

4. TITLE AND SUBTITLE

Identifying the Determinants of Clinical Responses to PARP Inhibitors in Ovarian Cancer Immunotherapy

5a. CONTRACT NUMBER
W81XWH-21-1-0282

5b. GRANT NUMBER
OC200482

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

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

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

10. SPONSOR/MONITOR'S ACRONYM(S)

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

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
This is the annual report for Year 2 of DoD grant no. W81XWH-21-1-0282. Accomplishments, personnel involved, problems encountered, and other matters are described.

15. SUBJECT TERMS
Annual report, W81XWH-21-1-0282, OC200482

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

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

Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPis) are approved for the treatment of ovarian cancer in the maintenance setting, as well as for advanced ovarian tumors harboring *BRCA1 or BRCA2 (BRCA1/2)* mutations. Interestingly, studies from our group and others have shown that PARPis promote the accumulation of cytosolic DNA fragments due to unresolved replication-associated DNA lesion and activate the DNA sensing cyclic GMP-AMP Synthase (cGAS)-stimulator of interferon genes (STING) pathway-mediated type 1 interferon (IFN) response. Our clinical trial data have demonstrated promising patient benefit with durable radiological responses with this combinatorial regimen of PARPi+PD-1/L1i, but not all patients benefited from this combination. Our proposed research in this application is to identify molecular determinants of the immune-modulatory functions of PARPis and to develop clinically applicable biomarkers to predict PARPi therapeutic efficacy in potentiating immune checkpoint blockade (ICB). This goal will be achieved by addressing the specific aims: (1) Determine if the alteration of the immune checkpoint regulatory molecule B7-H3 in ovarian tumor cells is associated with PARPi-induced immune responsiveness and can be developed as a biomarker for determining the therapeutic efficacy of PARPis as immunomodulatory agents. (2) Determine if alterations of c-GAS-STING-type I IFN-dependent innate immune response pathway in ovarian tumor cells are associated with PARPi-induced immune responsiveness and can be developed as biomarkers for determining the therapeutic efficacy of PARPis as immunomodulating agents. (3) Characterize the transcriptional landscape in tumor immune microenvironment induced by PARPis by using single-cell genomics in ovarian cancer patient specimens.

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

PARPis, immunotherapy, cGAS, STING, B7-H3

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.

Aim 1: Major Task 1: Determine if PARPis induce B7-H3 expression in ovarian cancer cell lines. Major Task 2: Examine B7-H3 expression in ovarian cancer patient PDX tumor samples. Major Task 3: Examine B7-H3 protein expression in ovarian cancer patient tumor samples from PARPi+PD-1/L1i trials. **Aim 2:** Major Task 1: Analyze STING-dependent signaling in ovarian cancer cell lines in the presence and absence of PARPis. Major Task 2: Characterize STING-dependent signaling in ovarian tumors using bioinformatic approaches. Major Task 3: Assess STING-dependent signaling in ovarian tumors from PARPi+PD-1/L1i clinical trials. **Aim 3:** Major Task 1 Determine if ATRis induce cancer-cell intrinsic innate immune responses in PARPi-resistant PDX tumors in vivo

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.

In the second year of funding period, we conducted experiments to further confirm that PARPi induces B7-H3 expression in parental and PARPi-resistant ovarian cancer cells as described in Aim 1. We also conducted experiments to analyze the molecular impact of PARPi on the activation of cGAS-STING pathway and immune responses in ovarian cancer cells. Furthermore, we conducted bioinformatic analysis using the TCGA data to investigate the correlation between cGAS-STING pathway signaling and immune responsiveness of ovarian cancer tumors from patient-derived data.

PARPi treatment induces cancer cell-intrinsic B7-H3 expression in parental and PARPi-resistant cells (Fig. 1).

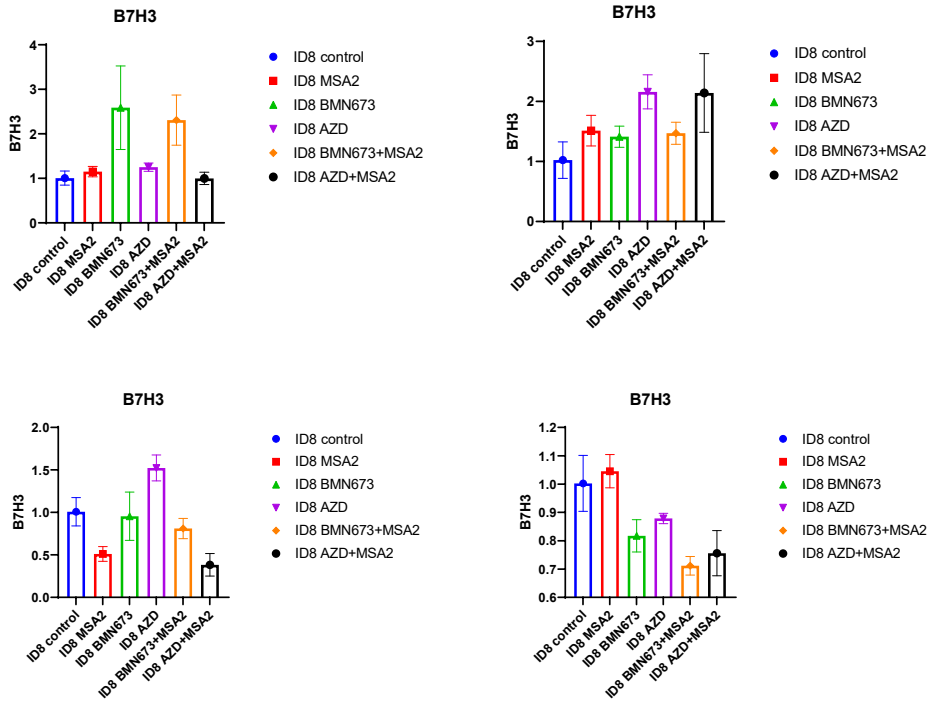

Fig. 1. PARPi treatment induces expression of B7-H3 in parental and PARPi-resistant cell lines. RT-PCR analysis of B7-H3 mRNA levels in ID-8 cells treated with indicated compounds. The bar graphs represent mean±STDEV from three independent experiments.
(A and B) Expression of B7-H3 in ID-8 cells treated with indicated compounds for 24 hrs (A) and 48 hrs (B). **(A and B)** Expression of B7-H3 in PARPi-resistant ID-8 cells treated with indicated compounds for 24 hrs (C) and 48 hrs (D).

In the first-year report, we found that PARPi can induce B7-H3 expression in ovarian cancer cells (HOC1 and ID8). In this funding period, we further compare the effects of PARPi on B7-H3 expression in parental and PARPi-resistant cells. As shown in Figure 1A and Figure 1B, in parental ID8 ovarian cancer cells, we treated cells with two different PARPis (BMN and AZD) from different pharmaceutical companies (Pfizer and AstraZeneca) for 24 hrs (A) and 48 hrs (B). PARPi can induced B7H3 expression at different time dynamics. BMN acted at the earlier time point compared to AZD PARPi. Interestingly, we used STING agonist MSA2 as a control to test whether STING signaling activation may change PARPi's effect on B7-H3. As we expected, regulation of B7H3 was not mediated by STING.
Furthermore, we conducted a similar experiment in ID-8 cells that developed PARPi-resistance (**Figure 1C and 1D**) at different time points 24 hrs (**Figure 1C**) and 48 hrs (**Figure 1D**). AZD PARPi exhibited a strong effect on upregulating B7H3 compared to BMN PARPis. The longer treatment did not correlate with a better effect. Collectively, these data showed the potential of PARPis in inducing B7-H3 in ovarian cancer cells, particularly in PARPi-resistant cancer cells.

PARPi treatment induces cancer cell-intrinsic c-GAS-STING pathway activation in parental and PARPi-resistant cells (**Fig. 2**).

We further used RT-PCR to analyze the transcriptional changes induced by PARPis in parental and also in PARPi-resistant cancer cells. We hypothesized that PARPis can induce a immune-related transcriptional program, which may not be dependent on cytotoxic effect of PARPi. If our hypothesis is correct, PARPi may still can function as immune modulating agents in PARPi-resistant cells.

We cultured ID-8 cells long-term in increasing dosages of PARPi BMN starting from 1uM to 10 uM. These cells developed resistance to PARPi after selection. These cells were also used in Fig 1 studies. As shown in Fig. 2, Indeed, we observed that PARPi treatment at different time points (24hrs or 48hrs) leads to activation of CCL5and CXCL10. It seemed that STING agonist we used MSA2 did not exhibit a synergy in combination with PARPis at different time points or in combination with different PARPis.

Interestingly, in PARPi-resistant cells, we did observe a significant induction of CCL5and CXCL10 after PARPi treatment. This effect is also not dependent on STING agonist. AZD PARPi seemed to have lower induction rate compared to BMN PARPi, which could be largely due to the concentration that we used in the treatment. We selected IC30 for each drug in this experiment. A dosage-dependent experiment might be needed to exclude the effect caused by different dosages.

In summary, this experiment indicated that PARPi induces STING-singling downstream effector CCL5 and CXCL10 expression in both parental cells and PARPi-resistant cells. It supports our hypothesis that PARPi-resistant cells may be subjected to immune modulating by PARPi treatment.

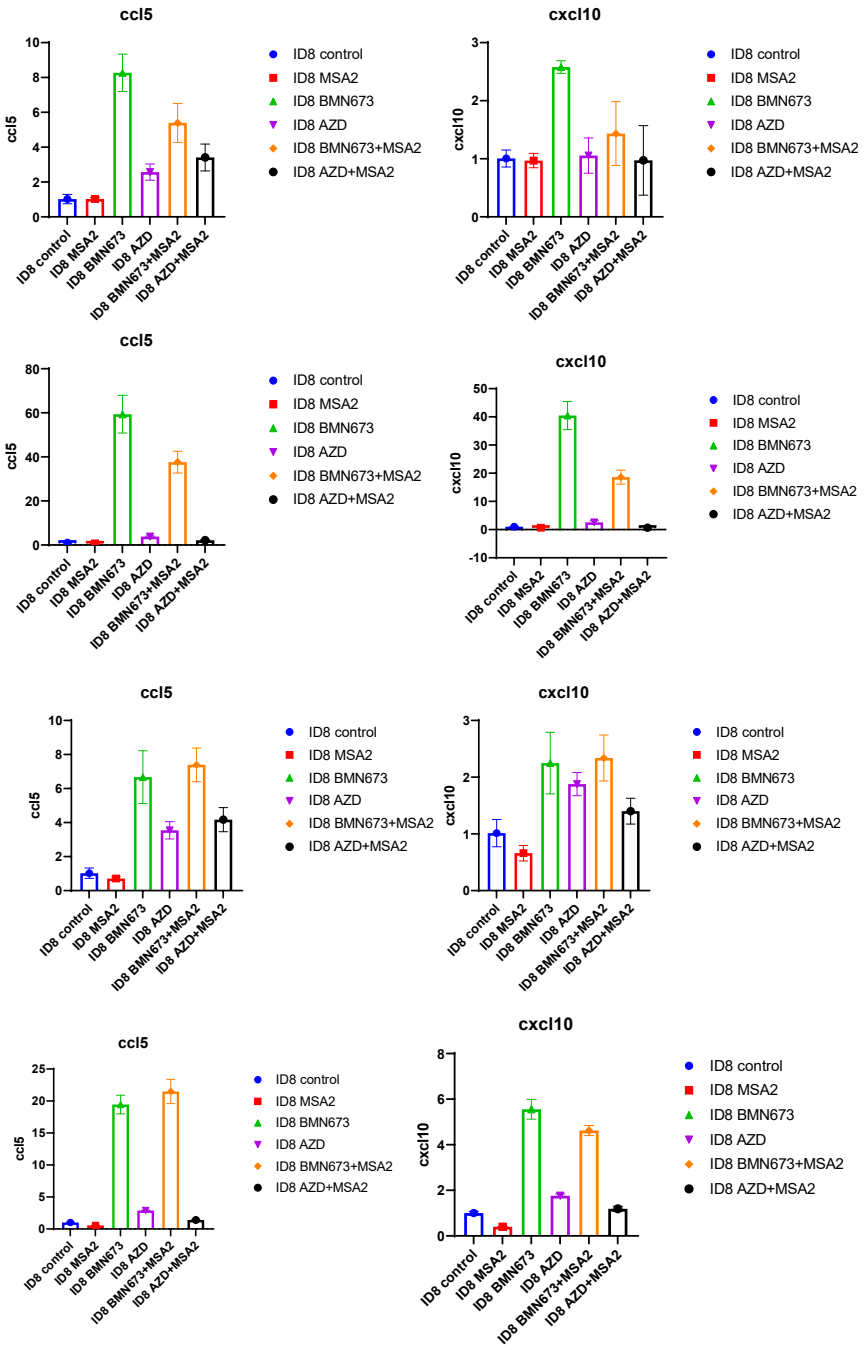

Fig. 2. PARPi treatment induces expression of STING-mediated downstream effectors CCL5 and Cxcl10 at mRNA levels. RT-PCR analysis of mRNA of indicated genes in ID-8 cells treated with indicated compounds for 24 hrs (upper graph in each panel) and 48 hrs (lower graph in each panel). Primers were designed and used to detect indicated gene expression. The bar graphs represent mean±STDEV from three independent experiments.

PARPi treatment induces c-GAS-STING pathway activation in human ovarian cancer cells (Fig. 3).

In our previous report, we observed that the increased cGAS and STING expression in cells with PARPis treatment using mouse cell as model systems. We further confirmed this observation using human ovarian cancer cell lines HOC1, HOC7 and UPN251. In these human cancer cells, we observed the induction of STING expression in all three different cell lines. As shown in the Figure 3, other key mediators of cGAS-STING pathway cGAS, IRF3, TBK1 expression levels were not altered by PARPis, which suggest a specific effect of PARPi on regulating STING expression. These data support a role of using STING expression as a biomarker to correlate immune modulating function of PARPis. Notably, PARPi also induced PD-L1 expression, another key immune checkpoint proteins in these cells.

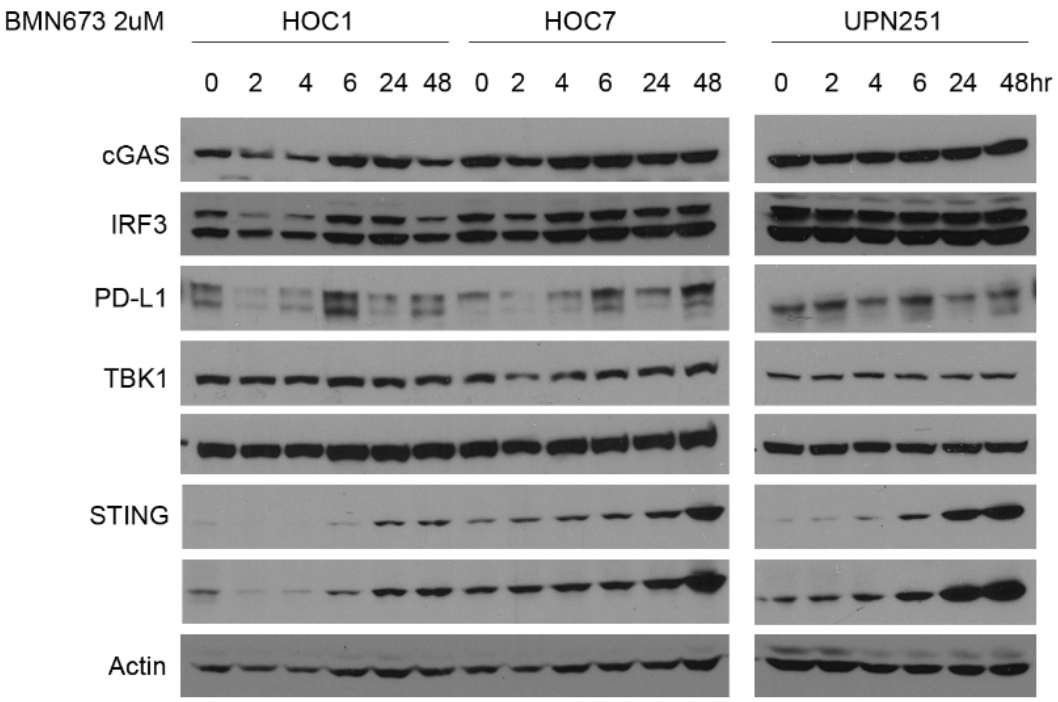

Fig. 3. PARPi treatment induces expression of STING at protein levels in human ovarian cancer cell lines. Western blots of protein expression of cGAS and STING treated with BMN673 (2 μM for 24 and 48 hrs) in HOC1, HOC7 and UPN251 ovarian cancer cells. Antibodies were used to detect indicated proteins in the presence or absence of BMN673.

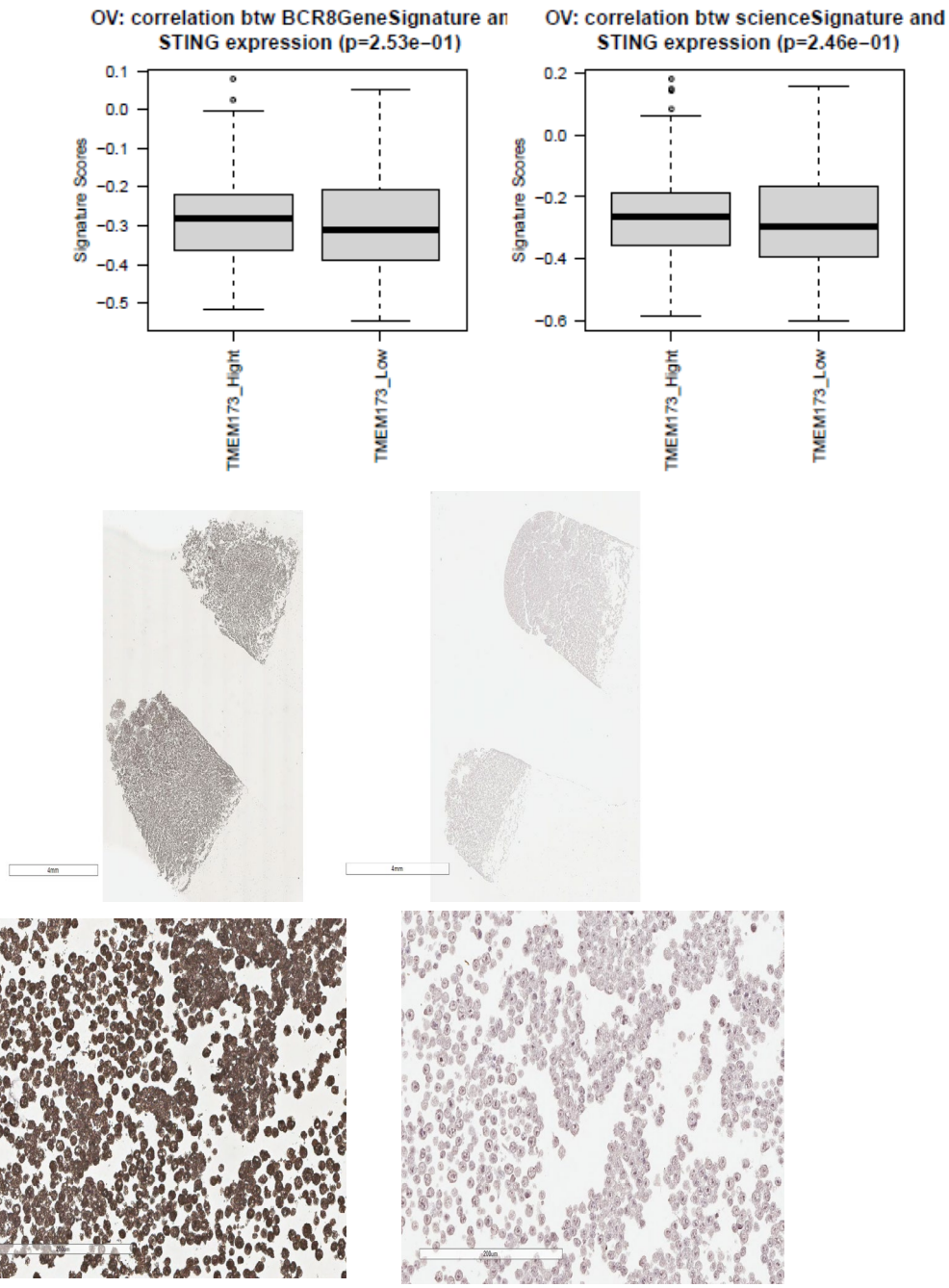

Figure 4 Testing STING as a potential biomarker for PARPi treatment. (A) Bioinformatic analysis in the TCGA ovarian tumors for STING expression and its correlation with TILs. (**B**) IHC staining to test the sensitivity and specificity STING antibody for detecting STING expression in ovarian cancer cells.

STING expression as a potential biomarker for PARPi-induced immune modulating effects (Fig. 4)

Having confirmed the role of STING in molecular changes induced by PARPis, we used bioinformatic analysis to test the clinical relevance of STING (TMEM173) expression in ovarian cancer patients. We first conduced the TCGA analysis using ovarian cancer tumors to examine whether expression levels of STING may correlate with molecular scores of tumor infiltrated lymphocytes (TIL). We used two published TIL signatures. As shown in **Figure 4A**, lower STING expression correlated with increased TIL score in ovarian tumors. These data suggested that high STING expression is likely associated with a better immune responsiveness of ovarian tumors. These data also support us to further test the STING expression in clinical samples derived from patients treated with PARPi.

To achieve this goal, we first conducted experiment to validate the antibody of STING for immunochemistry staining (IHC). As show in Figure 4B, we used WT cells and STING-knockdown cells as a control. As we expected, antibody showed a strong staining in WT cells. However, staining intensity was remarkably reduced in cells with STING knockdown. These data provide experiment evidence to test this antibody further in patient tissues.

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.

During the first year of funding of this project, Melissa Pham, Oncologist, from Investigational Cancer Therapeutics (ICT), who is working on this project received her fellowship award from The Foundation for Women's Cancer Research and Award Program. Her fellowship ended in the second year of our funding period.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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.

The results from this project have been presented in our department seminars inside our institution and also genomic instability working groups in the Texas Medical Center.

If this is the final report, state "Nothing to Report."

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

There will not be any changes to our original goals and major/sub tasks. We will conduct experiments as we proposed in the application to further test our hypothesis. The major goal for the next funding period is to conduct analysis utilizing preclinical animal models and clinical samples to test and validate our hypothesis.

4. **IMPACT:** D*escribe 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 this year.

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 this year.

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 this year.

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 this year.

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:*

Nothing to report this year.

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.

The recruitment of researchers on this project is challenging. We had a difficult time to identify candidates and recruit the candidates timely.

We will have job advertisements on multiple online sources including institutional job post webpage and commercial scientific journals (Nature Jobs; Science Jobs). We are working with the administrative team to promote a more efficient recruitment process.

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 are no significant changes on the original budget.

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

No significant changes will be made in use of human subjects and vertebrate animals.

Significant changes in use or care of vertebrate animals

No significant changes will be made in use of human subjects and vertebrate animals.

Significant changes in use of biohazards and/or select agents

No significant changes.

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 this year.

  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 this year.

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 this year.

- **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 this year.

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

Nothing to report this year.

- **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 this year.

- **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 this year.

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".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	*Timothy Yap*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.2*
Contribution to Project:	*Dr. Yap provides overall scientific and administrative leadership, and oversees collection of clinical specimens and data.*
Funding Support:	

Name:	*Guang Peng*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.8*
Contribution to Project:	*Dr. Peng designs experiments, interprets results and supervises postdoctoral fellows. She works with Dr. Yap to evaluate experimental results, and prepare data for public presentation or reporting.*
Funding Support:	

Name:	*Ruidong Chen*
Project Role:	*Postdoctoral Fellow*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3.5*
Contribution to Project:	*Dr. Chen conducts a variety of biochemistry and molecular biology assays, including immunofluorescent staining, animal models, genomic/proteomic analysis and tumorigenesis analysis.*
Funding Support:	

Name:	*Xueqian Cheng*
Project Role:	*Postdoctoral Fellow*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6.7*
Contribution to Project:	*Dr. Cheng conducts a variety of biochemistry and molecular biology assays, including immunofluorescent staining, animal models, genomic/proteomic analysis and tumorigenesis analysis.*
Funding Support:	

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.

Dr. Peng is now supported (1.2 CM) by a new DOD grant (BC220706 P1) to move PARP inhibitors beyond BRCAness as immune modulating agents for TNBC prevention.
Dr. Yap is now supported (0.12 CM) by a new R01 grant to study YAP1-mediated cancer stemness and immune suppression in advanced gastric adenocarcinoma, by a new CPRIT grant (0.12 CM) to block DNA damage response induction of dont eat me signals converts local radiotherapy into systemic immunotherapy, and by 3 new industry-sponsored clinical trials (0.48 CM).

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.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

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://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) 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.*