AWARD NUMBER: W81XWH-21-1-0604

TITLE: Novel Synergistic ATR Inhibitor Combinations for Ovarian Cancer Therapy

PRINCIPAL INVESTIGATOR: Panagiotis A. Konstantinopoulos, MD, PhD

CONTRACTING ORGANIZATION: Dana-Farber Cancer Institute, Boston, MA

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

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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)

Dana-Farber Cancer Institute
450 Brookline Avenue,
Boston, MA 02215-5450

8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Development Command
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14. ABSTRACT

Large scale genomic studies have demonstrated that high grade serous ovarian cancers (HGSOCs) exhibit increased replication stress due to near universal loss of the G1/S checkpoint, premature S phase entry, oncogenic driver activation and deficiency in homologous recombination repair. In this application we address the potential of targeting the replication stress (RS) and the replication stress response (which is facilitated by the ATR kinase) in ovarian cancer and have proposed a set of experiments to facilitate preclinical development of novel synergistic ATRi combinations in this disease. In the Aims 1 and 2 of this award we have proposed to perform in vitro and in vivo studies to evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC lines, organoid models and PDX models. In Aim 3, we have proposed to evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in genetically engineered mouse models (GEMMs) and in Aim 4 we propose to define and validate a RS biomarker of response to ATRi in tumors from patients with platinum resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib. In the first year of the award, we have been doing preclinical work on combinations of ATRi with PI3Ki and CDK5i inhibitors as well as anti-PD-1 antibodies and we have been able to define a biomarker of replication stress that correlates response to gemcitabine versus combined gemcitabine and ATR inhibitor therapy in HGSOC ovarian cancer.

15. SUBJECT TERMS Epithelial Ovarian Cancer, Replication stress, ATR inhibitors, Gemcitabine, PI3K inhibitors, CDK5 inhibitors, anti-PD-1 antibodies					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRDC
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Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

1. INTRODUCTION:

Large scale genomic studies have demonstrated that high grade serous ovarian cancers (HGSOCs) exhibit increased replication stress due to near universal loss of the G1/S checkpoint, premature S phase entry, oncogenic driver activation and deficiency in homologous recombination repair. In this application we address the potential of targeting the replication stress (RS) and the replication stress response (which is facilitated by the ATR kinase) in ovarian cancer and have proposed a set of experiments to facilitate preclinical development of novel synergistic ATRi combinations in this disease. In the Aims 1 and 2 of this award we have proposed to perform in vitro and in vivo studies to evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC lines, organoid models and PDX models. In Aim 3, we have proposed to evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in genetically engineered mouse models (GEMMs) and in Aim 4 we propose to define and validate a RS biomarker of response to ATRi in tumors from patients with platinum resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib.

2. KEYWORDS:

Epithelial Ovarian Cancer, Replication stress, ATR inhibitors, Gemcitabine, PI3K inhibitors, CDK5 inhibitors, anti-PD-1 antibodies

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Throughout the timeline of the award the following goals have been proposed:
Specific Aim 1: To perform in vitro studies of targeted inhibition of our high-confidence 'hits' from PRISM and CRISPR, alone and in combination with ATRi, in HGSOC lines and organoid models to extend mechanism-of-action studies and inform on potential combination strategies.
Specific Aim 2: To evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC PDX models.
Specific Aim 3: To evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in HGSOC GEMMs.
Specific Aim 4: To define a biomarker of response to ATRi in tumors from patients with platinum-resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib.

What was accomplished under these goals?

Regarding Aims 1 and 2, amongst our high confidence "hits" we were particularly interested in actionable targets for which inhibitors already exist, therefore can be improved to clinical-grade, to use with ATR inhibitors in novel combinatorial strategies. These included: (i) CDK5 (ii) the epigenetic regulator EZH2; and iii) genes that were members or indirectly affected the PI3K signaling pathway. CDK5 was further

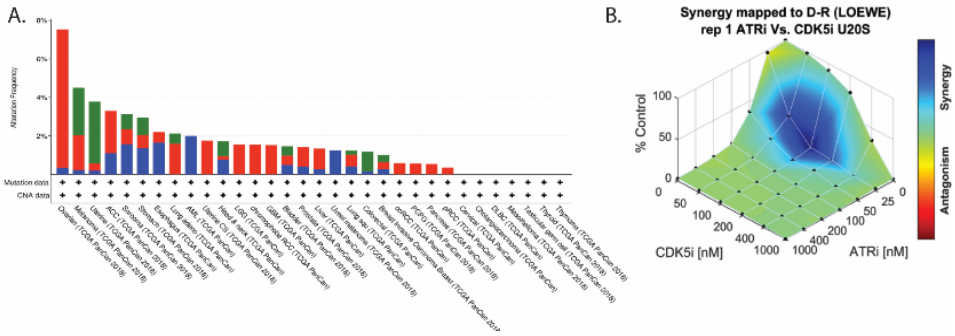

Figure 1: A) Analysis of TCGA showing that CDK5 is amplified specifically in HGSOCs. B) Combifit analysis of CDK5i and ATRi reveals significant synergy in viability assays.

prioritized as it is amplified specifically in HGSOC, more than other tumor types (Fig. 1).

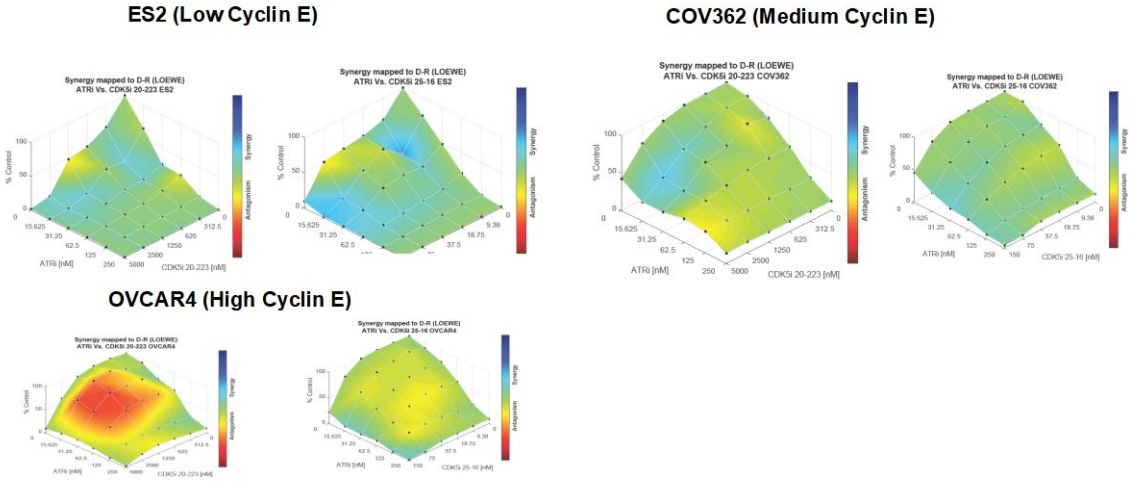

Figure 2: Combifit analysis of CDK5 inhibitor 20-223 or CDK5 inhibitor 25-16 and ATRi was conducted in indicated HGSOC lines with different levels of CCNE1 as indicated. Our analysis reveals significant synergy in viability assays only in CCNE1 low cells.

CCNE1 (Cyclin E) amplification has been identified as a primary oncogenic driver in a subset of HGSOC and associated with genomic instability and refractory to platinum therapy. Furthermore, CCNE1 amplification is an established marker of replication stress (RS). Recent pre-clinical data demonstrated better ATRi responsiveness in CCNE1 amplified tumors because of the high RS background. In ovarian cancer, CCNE1 amplification is detected in about 20% of tumors, in a manner largely mutually exclusive with CDK5 amplification (data not shown). We used two independent CDK5 inhibitors (20-223 and 25-16) Interestingly, we observed synergy between ATR inhibitor BAY1895334 both the CDK5 inhibitors 20-223 and 25-16 specifically in low CCNE1-expressing HGSOC cells (Figure 2). CDK5 inhibitor 20-223 had a more significant synergistic effect with ATRi. This suggests that CDK5 inhibition and CCNE1 overexpression may be redundant in sensitizing cells to ATRi. Based on these results, we postulate that CDK5 is an actionable target that may expand the scope and efficacy of ATRi in a normal/low cyclin E expressing cancers. Also, low CCNE1 potential maybe a biomarker for CDK5 inhibitors. We further aim to elucidate the interplay between CDK5/CCNE1 in S-phase and its relevance to ATRi sensitivity. As we move onto animal studies and HGSOC organoid treatment with CDK5 inhibitors (Aim 2) we will also focus on the other actionable targets, EZH2 and PI3-K pathway.

Regarding Aim 3 we have been performing efficacy studies evaluating the combination of ATR inhibitors with anti-PD-1 in GEMMs and we expect to report on these studies in the next year of this award.

Regarding Aim 4, we have evaluated the following candidate biomarkers of benefit of addition of berzosertib to gemcitabine.

i) ATM expression by immunohistochemistry (IHC): We did not observe any difference in the benefit of addition of berzosertib to gemcitabine between patients with tumors without ATM expression **(ATM negative)** vs tumors with low ATM expression **(ATM low)** or normal ATM expression **(ATM positive).**
ii) Homologous recombination repair (HRR) deficiency: We assessed three different biomarkers of HRR deficiency, i.e. *BRCA1/2* mutation status, presence of HRR mutations by targeted sequencing (using our CLIA certified institutional assay OncoPanel assay) and presence of mutational signature 3. We did not observe any difference in the benefit of addition of berzosertib to gemcitabine between patients with HRR deficient vs non-HRR deficient tumors as defined by any of these 3 biomarkers (i.e. *BRCA1/2* mutation status, HRR mutation status and mutational signature 3 status).
iii) Replication Stress (RS) Alterations: Based on results from targeted next sequencing OncoPanel assay we assigned patients **into two different groups** based on the **presence or not of genomic alterations of RS** in their tumors:

a. Patients with tumors with replication stress (RS) alterations **(RS-high tumors)**: These tumors exhibited **at least one of the following alterations**, including alterations associated with **oncogene-induced replication stress** (*KRAS* amplification/mutations, *NF1* two-copy loss/mutations, *ERBB2* amplification, *MYC* amplification, *MYCL* amplification) and alterations **associated with loss of RB pathway regulation and premature entry into the S phase** (*CCNE1* amplification, *RB1* two-copy loss and *CDKN2A* two-copy loss).
b. Patients with tumors without any RS alterations **(RS-low tumors):** These tumors **exhibited none of the above RS alterations (see point a above).**

Overall, about 53% of tumors were RS-low and 47% were RS-high. Interestingly, the PFS benefit of addition of berzosertib to gemcitabine **was evident only in the RS-low tumors** (berzosertib **PFS HR = 0.34, 90% CI, 0.13-0.86)**, but **was not observed in the RS-high tumors** (berzosertib PFS HR = 1.11, 90%

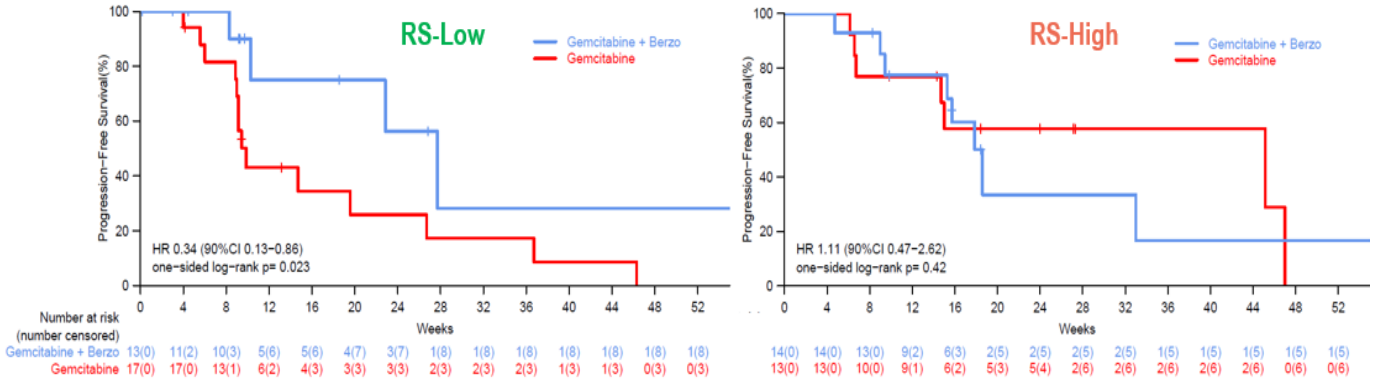

Figure 1. Gemcitabine/Berzosertib vs Gemcitabine alone in patients with RS-Low (left) and RS-High (right)

CI, 0.47-2.62), Figure 1.
Importantly, **berzosertib benefit in RS-low tumors was observed regardless of the PFI stratum** (Berzosertib **HR was 0.47** in the PFI < 3 months stratum and **0.25** in the PFI 3-6 months stratum).

This finding (i.e. that the benefit of addition of berzosertib to gemcitabine was evident only in the RS-low tumors) may be explained by the fact that patients with RS-low tumors who received gemcitabine alone did significantly worse compared to patients with RS-high tumors (i.e. **RS-high may be a biomarker of response to gemcitabine alone**). Specifically, as seen in Figure 2 below, patients with RS-high tumors did significantly better with gemcitabine alone compared to patients with RS-low tumors (HR=0.38, 90% CI, 0.17-0.86, one-sided p=0.022).

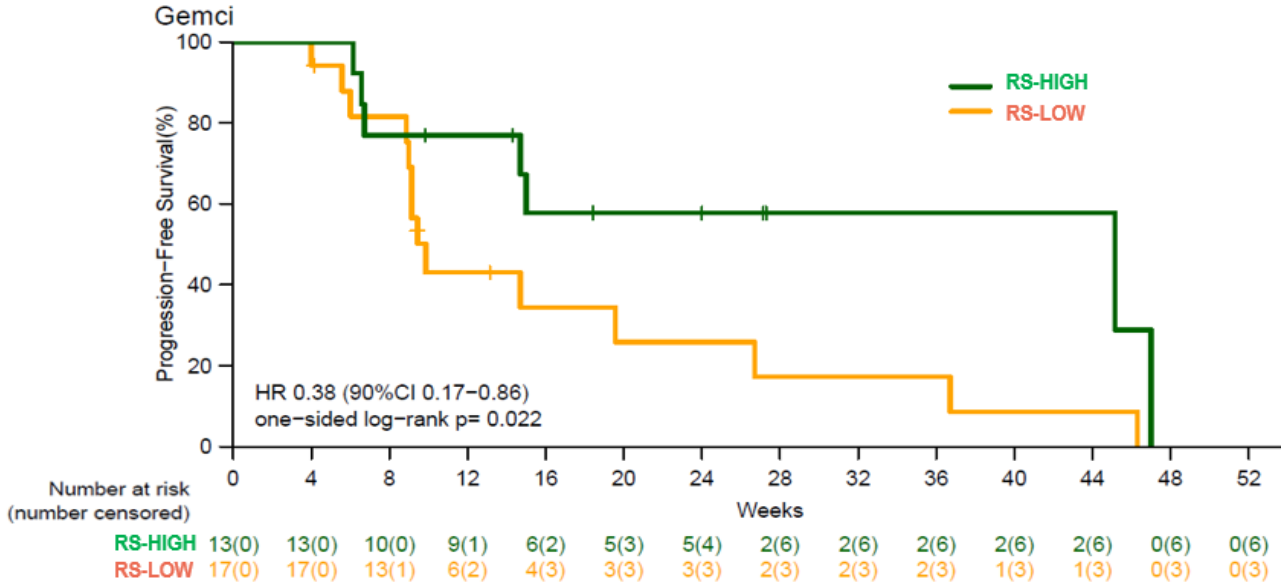

Figure 2. PFS of patients who received gemcitabine alone by RS-High vs RS-Low status

Taken together, our findings suggest that **patients with RS-high tumors may do significantly better with gemcitabine alone and that for these patients, addition of berzosertib does not appear to provide benefit** (although a berzosertib benefit may have been missed due to the small size). Conversely, **patients with RS-low tumors do significantly worse with gemcitabine alone and for these patients, addition of berzosertib provides significant PFS benefit.** Figure 3 below, presents a working hypothesis model highlighting: **i) the better outcome with gemcitabine alone among patients with RS-high tumors (compared to RS-low tumors)** and ii) **the benefit of addition of berzosertib to gemcitabine among patients with RS-low tumors.** According to this model, **gemcitabine, a drug which increases replication stress**, **has better monotherapy activity against RS-high tumors (left panel) than RS-low tumors (right panel). Unlike RS-high tumors, RS-low tumors need the addition of the ATRi berzosertib for lethality to occur, which explains why the benefit of addition of berzosertib to gemcitabine is only observed among RS-low tumors.**

This work was published in Nature Communications (Konstantinopoulos PA, da Costa AABA, Gulhan D, Lee EK, Cheng SC, Hendrickson AEW, Kochupurakkal B, Kolin DL, Kohn EC, Liu JF, Stover EH, Curtis J, Tayob N, Polak M, Chowdhury D, Matulonis UA, Färkkilä A, D'Andrea AD, Shapiro GI. A Replication stress biomarker is associated with response to gemcitabine versus combined gemcitabine and ATR inhibitor therapy in ovarian cancer. Nat Commun. 2021 Sep 22;12(1):5574. doi: 10.1038/s41467-021-25904-w. PMID: 34552099; PMCID: PMC8458434.)

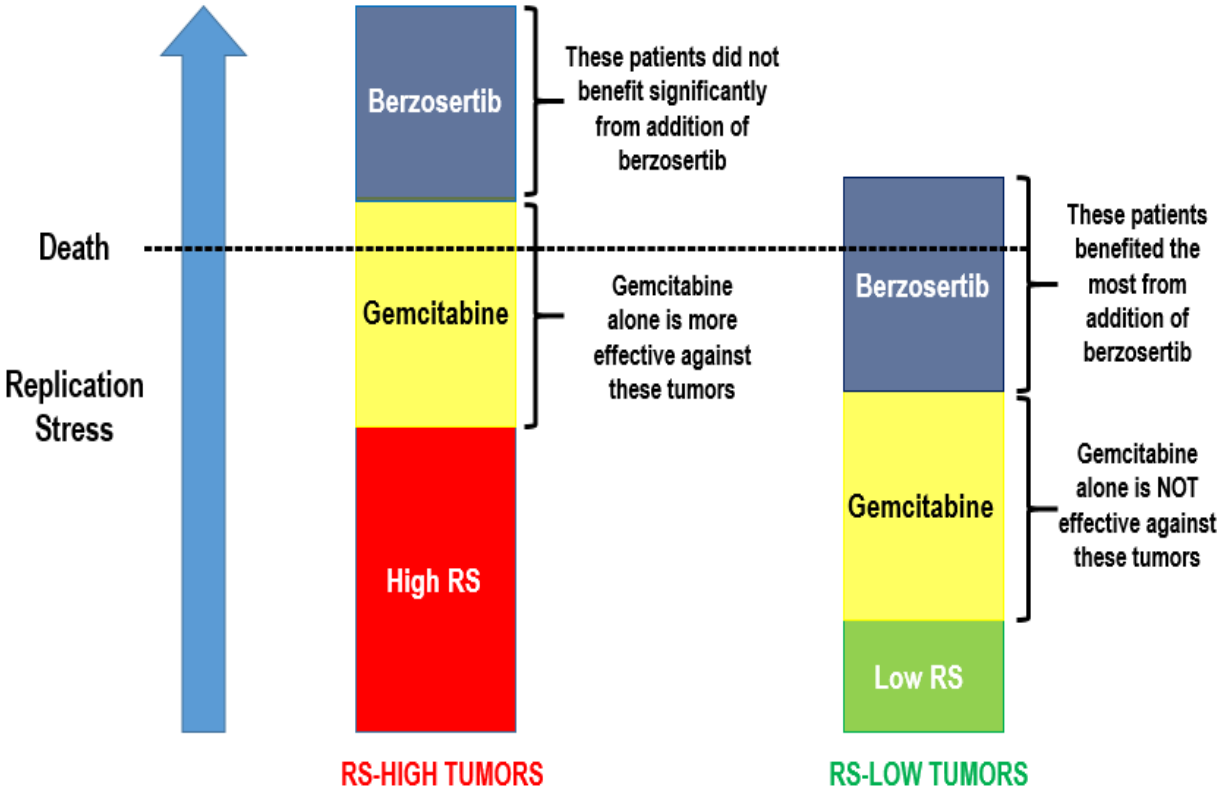

Figure 3. Working hypothesis model summarizing the effects of gemcitabine alone and of gemcitabine/berzosertib combination in patients with RS-High (left) and RS-low tumors (right). **LEFT PANEL:** Gemcitabine alone is more effective against RS-High tumors (compared to RS-low tumors) and addition of berzosertib does not add much to gemcitabine alone for these (RS-High) tumors. **RIGHT PANEL:** Conversely, gemcitabine alone is ineffective against RS-low tumors; addition of berzosertib to gemcitabine in these (RS-low tumors) is beneficial over gemcitabine alone.

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

"Nothing to Report."

How were the results disseminated to communities of interest?

"Nothing to Report."

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

In the next reporting period we aim to continue the in vitro and in vivo experiments as relevant to Aims 1, 2 and 3 and we will continue to optimize our biomarker on Aim 4.

4. IMPACT:

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

"Nothing to Report."

What was the impact on other disciplines?

"Nothing to Report."

What was the impact on technology transfer?

"Nothing to Report."

What was the impact on society beyond science and technology?

"Nothing to Report."

5. CHANGES/PROBLEMS:

As discussed above, regarding Major Task 1 (AIM 1), our clinical trial has not been activated yet but we do expect this will happen in July-August 2020. The reason for that was that we had encountered problems initiating the study mainly because of an issue with the peptide manufacturing process for the neoantigen vaccine. These issues have been completely resolved and we are now ready to initiate the trial. There is significant patient interest in our study and we expect to enroll promptly when the study is activated.

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

"Nothing to Report."

Changes that had a significant impact on expenditures

"Nothing to Report."

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

Significant changes in use or care of human subjects

"Nothing to Report."

Significant changes in use or care of vertebrate animals

"Nothing to Report."

Significant changes in use of biohazards and/or select agents

"Nothing to Report."

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

1. Konstantinopoulos PA, da Costa AABA, Gulhan D, Lee EK, Cheng SC, Hendrickson AEW, Kochupurakkal B, Kolin DL, Kohn EC, Liu JF, Stover EH, Curtis J, Tayob N, Polak M, Chowdhury D, Matulonis UA, Färkkilä A, D'Andrea AD, Shapiro GI. A Replication stress biomarker is associated with response to gemcitabine versus combined gemcitabine and ATR inhibitor therapy in ovarian cancer. Nat Commun. 2021 Sep 22;12(1):5574. doi: 10.1038/s41467-021-25904-w. PMID: 34552099; PMCID: PMC8458434.

Books or other non-periodical, one-time publications.

"Nothing to Report."

Other publications, conference papers and presentations.

"Nothing to Report."

- **Website(s) or other Internet site(s)**

"Nothing to Report."

- **Technologies or techniques**

"Nothing to Report."

- **Inventions, patent applications, and/or licenses**

"Nothing to Report."

- **Other Products**

"Nothing to Report."

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Panagiotis Konstantinopoulos
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-1032-1479
Nearest person month worked: 1
Contribution to Project: Dr Konstantinopoulos is working on all aims on this work
Funding Support: DOD W81XWH-21-1-0604, 2P50CA240243-01Al, UMl CA186709-06, Gray Foundation Basser Initiative, 5U10CA180868, and BCRF.

Name: Dipanjan Chowdhury
Project Role: Co-PD/PI
Researcher Identifier (e.g. ORCID ID): 0000-0001-5645-3752
Nearest person month worked: 1
Contribution to Project:Dr Chowdhury is working on Aims 1-4 of this work.
Funding Support: Dr. Chowdhury is supported by the following grants: DOD W81XWH-21-1-0604, 5R01CA208244-05, 5R01CA214912-02, 1R01CA264900 - 01A1, The Honorable Tina Brozman Foundation for Ovarian Cancer (2), Gray Foundation Basser Initiative, Breakthrough Cancer Center (BTC), V Foundation for Cancer Research

Name: Xiao-Feng Zheng
Project Role: Instructor
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Dr Zheng is working on Aims 1 and 2 of this work.
Funding Support: Xiao is supported by this DoD grant W81XWH-21-1-0604 and 5R01CA208244-05

Name: Tahireh Markert
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 12
Contribution to Project: Tahireh has assisted Dr. Chowhdury and Zheng on their work

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

Newly awarded/renewed for Dr. Konstantinopoulos

(THIS GRANT)
W81XWH211060401
The Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense ***Title: Novel Synergistic ATR Inhibitor Combinations for Ovarian Cancer Therapy***
Goals: Aim 1. To perform in vitro studies of targeted inhibition of our high-confidence 'hits' from PRISM and CRISPR, alone and in combination with ATRi, in HGSOC lines and organoid models to extend mechanism-of-action studies and inform on potential combination strategies. Aim 2 .To evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC patient derived xenograft (PDX) models. Aim 3 -To evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in HGSOC GEMMs. Aim 4- To define and validate a RS biomarker of response to ATRi in tumors from patients with platinum-resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib.
Role: Principal Investigator
Dates: 8/1/21-7/31/25
Effort: 5% (0.6 CM)
Level of Funding:
POC: Stephanie Davis
Grant Specialist

(RENEWAL)
Matulonis
Breast Cancer Research Foundation

Genomic relationship between ovarian and breast cancers: Predictors for chemotherapy and targeted therapy response
Goal: This study intends to explore the genetics of these two diseases with the purpose of uncovering the similarities,and studying them more carefully. The genetic alterations in common may be the most important clues to the determining the cause and treatment of the two diseases individually. 1) Generate a genomic dataset using OncoScan technology from high grade serous ovarian cancer in patients receiving PARP inhibitors and perform genomic profiling of chromosomal alterations and mutations of common tumor suppressor and oncogenic genes to identify genomic features associated with therapy response to a PARP inhibitor. 2) Profile somatic gene mutations using whole-genome exome sequencing in cancers from aim 1 and to correlate genome-wide mutation burden and clinical response to therapy with PARP inhibitor. We will also aim to identify the mutation signature associated with outcome of therapy.
Role: Co- Investigator
Date: 10/1/2008-9/30/2022
Effort: 4.20 Calendar Months
Level of Funding:
POC:
Margaret Flowers, PhD
28 West 44th Street, Suite 609
New York, NY 10036
Toll-free:
Fax: 646-497-0890 bcrf@bcrf.org

Recently completed for Dr. Konstantinopoulos

OCRP-OC170322
Department of Defense Ovarian Cancer Research Program
Title: Phase 1 Safety and Feasibility Study of a Personal Neoantigen-Targeting Vaccine in Combination with Immune Checkpoint Blockade in Ovarian Cancer
Goals: To conduct a study of a neoantigen targeting vaccine with PD-1 inhibition in ovarian cancer.
Role: Principal Investigator
Date: 10/1/18-9/30/21
Effort: 1.80 Calendar Months
Level of Funding:
POC:
Christopher Baker
Department of the army
US Army Medical Research Acquisition Activity
820 Chandler Street Fort Detrick MD 21702-5014
Ph:

Newly awarded/renewed for Dr. Chowdhury

(THIS GRANT)
W81XWH211060401
The Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense

Title: Novel Synergistic ATR Inhibitor Combinations for Ovarian Cancer Therapy
Goals: Aim 1. To perform in vitro studies of targeted inhibition of our high-confidence 'hits' from PRISM and CRISPR, alone and in combination with ATRi, in HGSOC lines and organoid models to extend mechanism-of-action studies and inform on potential combination strategies. Aim 2 .To evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC patient derived xenograft (PDX) models. Aim 3 -To evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in HGSOC GEMMs. Aim 4- To define and validate a RS biomarker of response to ATRi in tumors from patients with platinum-resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib.
Role: CO PI
Dates: 8/1/21-7/31/25
Effort: 0.3 Calendar Months
Level of Funding:
Overlap: None
POC:
Stephanie Davis
Grant Specialist

Stephanie.p.davis12.civ.@mail.mil

Breakthrough Cancer Center (BTC)
Title: Understanding, assessing and intercepting ovarian carcinogenesis (Minimal Original Disease (MOD) Ovarian Cancer Team)
Goals: Goals: To deliver biological insight into how ovarian cancer arises, tools for its diagnosis, and surgical approaches to prevent ovarian cancer.
Aim 1. Elucidate the biology and translational implications of early ovarian cancer lesions through establishing the world's first Ovarian Precancer Atlas and corresponding computational analyses for both high-risk and average risk women. (INCLUDING THE COMPUTATIONAL BIOLOGY TEAM)
Aim 2. Engineer novel devices to rapidly image and diagnose STIC lesions in salpingectomy specimens from high-risk women.
Aim 3. Expand opportunistic salpingectomy for primary prevention in average risk women.
PD/PI: Alan D'Andrea
Role: CO PI / Lab Head
Dates: 3/1/22-2/28/25
Effort: 1.2 Calendar Months
Level of Funding:
Overlap: None
POC
Jesse Boehm, PhD
Chief Science Officer
jsb@breakthroughcancer.org

Breakthrough Cancer Center (BTC)
Title: Targeting Ovarian Cancer Minimal Residual Disease (MRD) Using Immune and DNA Repair Directed Therapies
Goals: focuses on longitudinal analyses of ovarian cancer cells and their environment.
Aim 1 We will begin with patients undergoing standard neoadjuvant therapy, interval debulking surgery, SLL, and maintenance treatment and optimize the selection of multi-dimensional analyses based on the amount and types of tissues available at various time points. Following the launch of the randomized trial of neoadjuvant chemotherapy +/- i.p. IL-12 (Subaim 2.1), optimized protocols will be applied to the precious clinical trialrelated
biospecimens. Aim 1 will also focus on developing non-invasive liquid biopsy technologies for sensitive detection of MRD and monitoring of tumor burden and response using existing specimens.
Aim 2 will leverage clinical trials and observational studies to maximize the biological understanding of MRD. The aforementioned randomized trial will test the hypothesis that inducing inflammation in the tumor environment can reduce MRD rates, while establishing an important precedent for revolutionizing testing of investigational frontline therapies using MRD rate as the primary endpoint. The second key objective of Aim 2 is to develop more efficacious and personalized maintenance and salvage therapies by incorporating knowledge of MRD and DNA damage repair vulnerabilities.
Aim 3 is closely aligned and complements Aim1 and 2 by modeling MRD in immune-competent mouse models and engaging in preclinical testing of the most promising novel therapies and targeted nanoparticle delivery modalities. This Aim is crucial for development of enabling technologies and rational therapeutics that will iteratively by incorporated in future BTC trials for clinical testing.
PD/PI: Alan D'Andrea
Role: CO PI / Lab Head
Dates: 3/1/22-2/28/25
Effort: 0.6 Calendar Months
Level of Funding:
Overlap: None
POC:
Jesse Boehm, PhD
Breakthrough Cancer Center
jsb@breakthroughcancer.org

1R01CA264900 - 01A1
NIH
Title: Elucidating the molecular mechanism and physiological relevance of TIRR mediated inhibition of p53
Goals: : Our proposal utilizes a combination of genomic, proteomic and genetic tools to understand how TIRR inhibits p53 to promote tumor development.
PD/PI: Dipanjan Chowdhury
Dates: 7/1/2022-6/30/2027
Effort: 2.4 Calendar Months

Level of Funding:
Overlap: None
POC:
Ronald L Johnson
Program Director
NATIONAL CANCER INSTITUTE
rjohnso2@mail.nih.gov

T2022-010
V Foundation for Cancer Research
Title: Blood-based screening for identification and monitoring of women at elevated risk for breast and ovarian cancer
Goals: Aim 1. Validate models for circulating miRNA profiles for identification of BRCA1 and BRCA2 mutation carriers. Aim 2. Test models for identification of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers.
PD/PI: Dipanjan Chowdhury
Dates: 8/1/22-8/1/2025
Effort: 0.6 Calendar Months
Level of Funding:
Overlap: None
POC:
Carole C. Wegner, PhD
Senior Vice President, Research and Grants Administration
the V Foundation for Cancer Research
grants@v.org

The Honorable Tina Brozman Foundation for Ovarian Cancer
Title: Circulating microRNA signatures among BRCA1/2 mutation carriers
Goals: Aim 1. To define circulating miRNA profiles for BRCA1 and BRCA2 mutation carriers and incorporate this information into dynamic screening for ovarian cancer. Aim 2. To perform mechanistic studies exploring the effects of BRCA1 or BRCA2 mutations on miRNA expression and secretion from ovarian cancer precursor cells.
PIs: Chowdhury/Elias
Role: CO PI
Dates: 1/1/22-12/31/2023
Effort: 0.3 Calendar Months
Level of Funding:
Overlap: None
POC:
Beverly Wolfer
Executive Director
Phone:
bwolfer@tinaswish.org

Recently completed for Dr. Chowdhury

2R01CA142698-10
NIH
Title: Molecular mechanism and relevance of microRNAs in DSB repair pathway choice
The major goal of this study is to investigate the impact of microRNAs on repair of DNA double strand break (DSB)s, and specifically choice of DSB repair pathways during the cell cycle.
Aim 1: Systematic identification and validation of target transcripts regulated by candidate miRNAs influencing HR- and NHEJ mediated DSB repair.Aim 2: Defining the physiological relevance of candidate miRNAs influencing HR- and NHEJ mediated DSB repair.Aim 3: To evaluate candidate miRNAs influencing HR- and NHEJ mediated DSB repair as prognostic and predictive biomarkers in epithelial ovarian cancer (EOC) and lymphomas.
Role: Principal Investigator
Date: 4/1/2015-3/31/2021*NCE
Effort: 1.92 Calendar Months
Level of Funding:
POC:
Rebecca Brightful, Grant Management Officer
RIVER 5 BG RM4083
8490 Progress Drive
Frederick, MD 21701

5R01GM129066-02
NIH
Title: Computational analysis of mutation patterns in somatic genomes
The central hypothesis of this project is that loss of DNA repair proteins representing specific pathways impacts the mutational landscape of somatic genomes providing mechanistic insights into underlying DNA damage and repair processes. Aim 1: Study epigenomic context preferences of point mutation signatures to predict etiologyAim 2: Identify tissue-level differences in mutation patterns arising from DNA repair defects.
Aim 3: Infer cell lineage-dependent patterns of mutation accumulation from the mutational landscape of terminal cells
Role: Subaward PI
Date: 4/1/2019-6/30/2021
Effort: 0.24 Calendar Months
Level of Funding:$115,784
POC:
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What other organizations were involved as partners?

"Nothing to Report."

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

None.

9. APPENDICES:

None.