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TITLE: Improving Immune Response in Ovarian Cancer by Modulating the Wnt Pathway

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13. SUPPLEMENTARY NOTES
NA

14. ABSTRACT:

In ovarian cancer, upregulation of the Wnt/β-catenin pathway leads to chemoresistance, poor prognosis, and has been correlated to T-cell exclusion in the tumor microenvironment. Our objective was to investigate whether inhibiting the Wnt pathway in the tumor could reverse this, creating a more T-cell inflamed TME, and thus, decreasing tumor growth and improving survival in a syngeneic ovarian cancer model.
Additionally, we investigated whether the absence of β-catenin in antigen-presenting cells would decrease tumor growth. In order to clarify if improved tumor recognition with decreased Wnt signaling was dependent on CD8+ T-cells, we treated our mouse models with anti-CD8+β antibody in combination with Wnt inhibition. We investigated the effects of inhibiting Porcupine with a small molecule inhibitor, CGX1321.
Mice injected with ID8 or ID8p53-/- cells were treated with CGX1321.Treatment decreased ID8 tumor burden and improved survival. Using Nanostring, showed that CGX1321 treatment leads to an increase in T-cell, macrophage, and dendritic cell functions. Macrophages and DCs increased in the TME with CGX1321 treatment. In mice that lacked β-catenin in DCs, there was less tumor growth, showing that not only decreasing Wnt signaling in the tumor itself can cause decreased tumor growth, but also decreasing it in DCs has a similar effect. CGX1321 treatment did not have the same effect on tumor burden when given with anti-CD8+β antibody, thus supporting that PORCN inhibition is partially dependent on CD8+ T-cells.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

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

Ovarian cancer is the fifth leading cause of death in women in the USA and the most lethal gynecologic malignancy. Given the poor overall survival, high recurrence rates, and rapid development of resistance to chemotherapy in HGSOC, we urgently require new methods to treat this disease. In addition to classic prognostic factors like stage and debulking status, mutations in *BRCA1* and *BRCA2*, components of the homologous recombination (HR) DNA repair pathway, are linked to long-term prognosis in HGSOC. *BRCA1/2* mutations are found in ~20% of HGSOC tumors and are associated with improved prognosis. Interestingly, most BRCA-deficient tumors have activated tumor-infiltrating lymphocytes (TILs), which are also linked to improved outcomes. In contrast, immunosuppressive T regulatory cells (Tregs) and tumor-associated macrophages (TAMs), correlate with a worse prognosis. Despite the link between TILs and positive clinical outcomes, the use of immune checkpoint inhibitors (ICIs) in HGSOC has been disappointing in part due to the "cold" immune landscape surrounding these tumors. A "cold" immune landscape is characterized by the lack of TILs, which sensitize tumors to ICI. Thus, in order to develop better treatments for HGSOC, we need to understand the mechanisms that regulate anti-tumor immune responses, including the role of BRCA1/2 and the HR DNA repair pathway. WNT/β-catenin signaling is also linked to the progression of HGSOC by directly triggering tumor growth (1, 23), and promoting resistance to platinum agents. Interestingly, melanoma-intrinsic activation of the WNT pathway leads to the exclusion of TILs and immune escape by repressing local chemokine expression. In addition, WNT/β-catenin signaling in DCs triggers the expression of immunosuppressive molecules like IL- 10, TGFβ and RALDH, which in turn promote the differentiation of Tregs. Given that infiltrating Tregs and TAMs correlate with a worse prognosis in HGSOC, and that these cells are associated with WNT/β-catenin signaling in other tumors, it is likely that WNT signaling in ovarian cancer also leads to immune suppression. In fact, expression data from 8890 tumor samples (including HGSOC) in The Cancer Genome Atlas (TCGA), show that activating mutations in the WNT/β-catenin pathway, such as *CTNNB1*, encoding β-catenin, and inactivating mutations in negative regulators, such as Axin1, Axin2, APC1, and APC2, are inversely related to inflammatory T cell gene expression signatures. Thus, our central hypothesis is that inhibition of WNT/β-catenin signaling will repress tumor growth and promote anti-tumor immune responses in ovarian cancer patients with an intact or altered HR DNA repair pathway, thereby improving clinical outcomes.

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

Ovarian cancer, murine ovarian cancer, Wnt, β-catenin, Wnt inhibition, tumor microenvironment, ID8 cells, ID8p53$^{-/-}$ cells, PORCN, WNT-974, CGX-132, DKK1, DKN-01

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.

PROPOSED SPECIFIC AIMS:

AIM 1: To determine the relationship between WNT/β-catenin signaling, the DNA repair pathway, T cell responses and clinical outcomes in ovarian cancer.

Proposed Approach: Using whole tumor RNA-seq data from 971 subjects with high-grade serous ovarian carcinoma (HGSC) enrolled in GOG 218, we will group subjects by the presence or absence of a T cell gene expression signature and determine whether the WNT/β-catenin signaling pathway is active and whether the homologous recombination (HR) DNA repair pathway, including BRCA1 and BRCA2, is intact in these groups. We will apply and develop, as needed, composite genes to rank tumors by HRD, T cell infiltration and WNT pathway activity using gene expression data. This will be integrated with mutation analysis and these profiles will be correlated with treatment group (bevacizumab).

AIM 2: To determine how tumor-intrinsic and DC-intrinsic inactivation of the WNT pathway impacts T cell responses and tumor growth using immunocompetent mouse models of ovarian cancer.

Proposed Approach: We will initially determine whether pharmacological inhibition of the WNT pathway impacts T cell responses using a mouse model of spontaneous ovarian cancer (MISIIR-Tag mice). To determine whether tumor-intrinsic WNT signaling impacts T cell responses, we will use a luciferase-labeled ovarian cancer cell line derived from MISIIR-Tag mice (MOVCAR-luc), in which β-catenin has been knocked out using CRISPR/Cas9. To determine whether DC intrinsic WNT signaling impacts T cell responses, we will implant CD11c-cre x β-catenin fl/fl mice with WT MOVCAR-luc cells. In each case, we will evaluate the number, function and TCR repertoire of effector CD4, effector CD8 and regulatory T cells.

AIM 3: To determine whether mutations that affect the HR DNA repair pathway impact T cell responses following treatment with WNT inhibitors using immunocompetent mouse models of ovarian cancer.

Proposed Approach: We will implant C57BL/6 mice in the peritoneal cavity with ID8 ovarian cancer cells or ID8 cells that have been modified using CRISPR/Cas9 to lack TRP53 or both TRP53 and BRCA2. Tumor-bearing mice will subsequently be treated with WNT inhibitors and we will evaluate the number, function and TCR repertoire of CD4, CD8 and regulatory T cells.

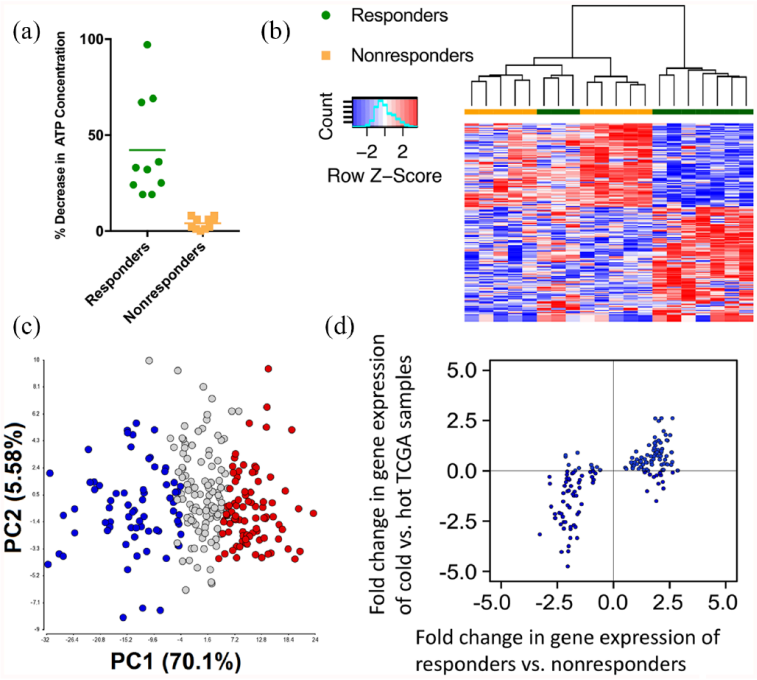
What was accomplished under these goals?

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

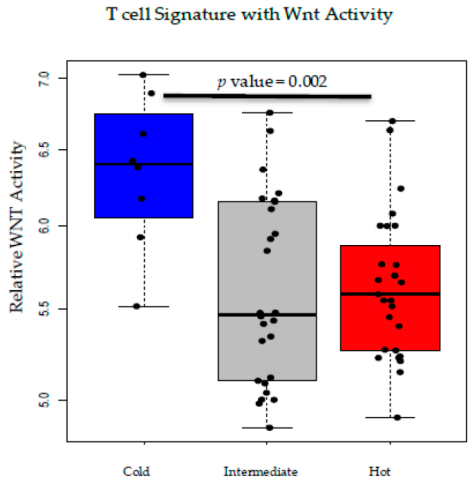
achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

AIM 1: To determine the relationship between WNT/β-catenin signaling, the DNA repair pathway, T cell responses and clinical outcomes in ovarian cancer.

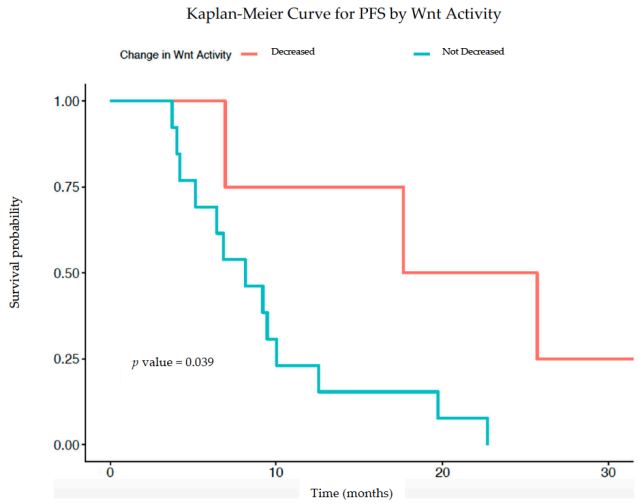
1. **Major activities:** We were able to find significant correlations between T cell signatures and Wnt signaling activity in ovarian cancer, as well as between ovarian patient survival and Wnt signaling activity using multiple platforms.
2. **Specific objectives**
   - **(A)** Determine if there is a correlation between T cell gene signatures and Wnt signaling activity in ovarian cancer.
   - **(B)** Investigate the correlation between Wnt signaling activity and ovarian cancer patient survival.
3. **Significant results/key outcomes with conclusions**
   - **(A)** Shown are ovarian cancer ascites samples with ⩾19% decrease in ATP concentration (n = 10) and those that had <10% decrease in ATP concentration (n = 10), which were deemed 'responders' and 'non-responders', respectively. (b) RNA-Seq revealed 187 differentially expressed genes (DEGs) between responders (green) and non-responders (yellow). (c) Principle component analysis (PCA) of 261 TCGA primary ovarian tumor samples segregated patient groups based on the expression of a defined T-cell inflamed gene signature (blue = non-T-cell inflamed 'cold' group; red = T-cell inflamed 'hot' group; gray = intermediate). (d) Log2-transformed expression fold changes of 161 significant DEGs from the ascites samples treated with WNT-974 that were also found in the TCGA dataset. The majority of the genes that had a positive fold change in the WNT-974 responders (relative to non-responders) also had a positive fold change in the non-T-cell inflamed 'cold' (relative to T-cell inflamed 'hot') TCGA samples (blue samples from panel (c)).



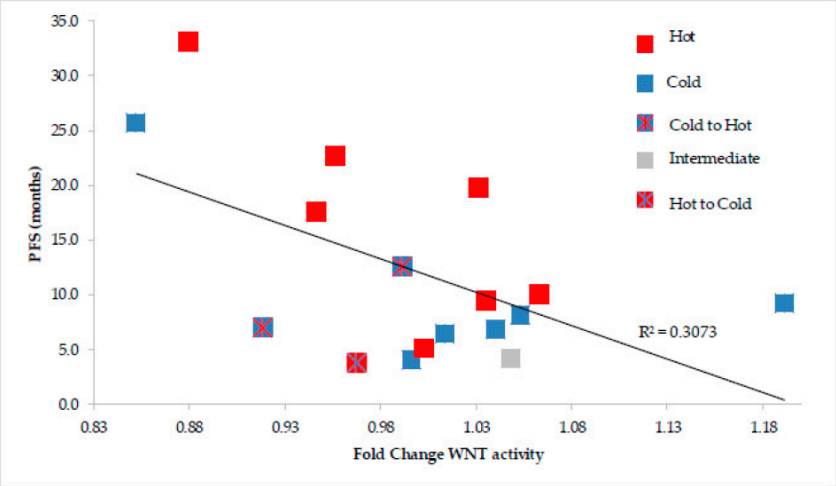
(B) We found a negative correlation between Wnt pathway activity and T cell signatures in ovarian cancer patient samples. Relative Wnt activity and T cell scores calculated from RNA-seq data for 57 treatment naïve human high grade serous ovarian cancer (HGSOC) tissue.



(C) Kaplan-Meier curve for progression-free survival (PFS) (n=17) based on decreases in Wnt activity after neoadjuvant chemotherapy (NACT). High Wnt signaling activity corresponds to decreased ovarian cancer patient PFS.



(D) PFS shows a negative correlation with fold-change in Wnt activity measured by signature genes in matched post- versus pre-NACT in 17 HGSOC patients. Patients are labeled based on T cell signature change, with solid color indicating no change, blue square with red lines indicating cold-to-hot signature change, and red square with bluelines indicating a hot-to-cold signature change.

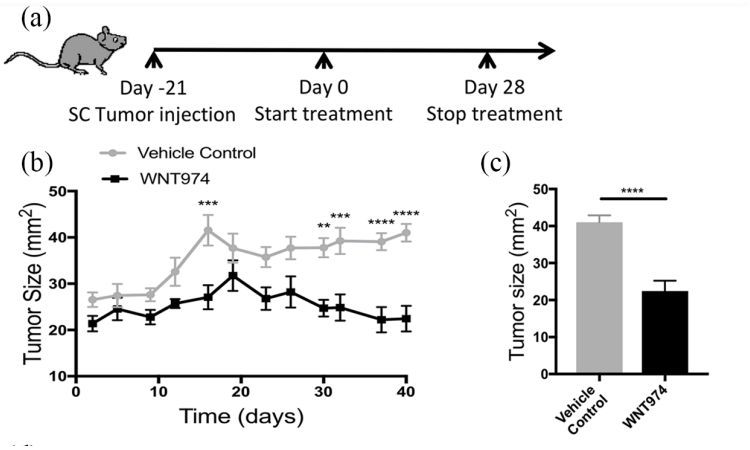


4. **Other achievements:** We were able to use these data for manuscript publications and presentations at national conferences.
5. **Goals not met:** We were not able to analyze data from GOG268 or GOG218 trials.

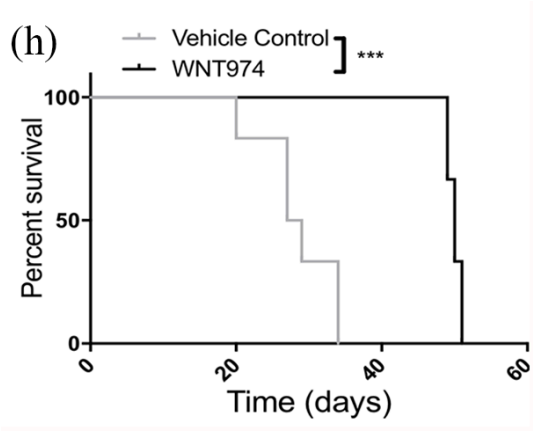
AIM 2: To determine how tumor-intrinsic and DC-intrinsic inactivation of the WNT pathway impacts T cell responses and tumor growth using immunocompetent mouse models of ovarian cancer.

1. **Major activities:** We determined that Wnt inhibition significantly reduced tumor burden in multiple murine ovarian cancer tumor models.
2. **Specific objectives:**
   (A) Determine if Wnt inhibition affects tumor burden in murine ovarian cancer models.
   (B) Investigate whether Wnt inhibition affects immune response in murine ovarian cancer models.
3. **Significant results/key outcomes with conclusions**

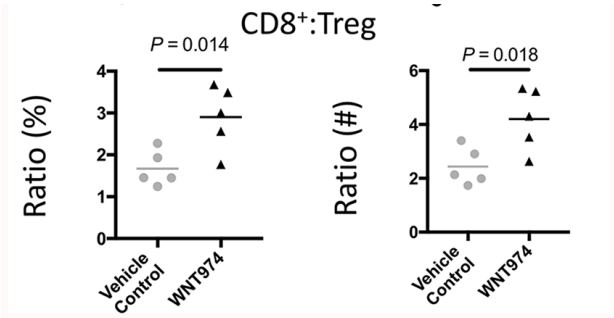
   (A) Wnt inhibition via WNT-974 significantly reduced murine ovarian tumor burden.



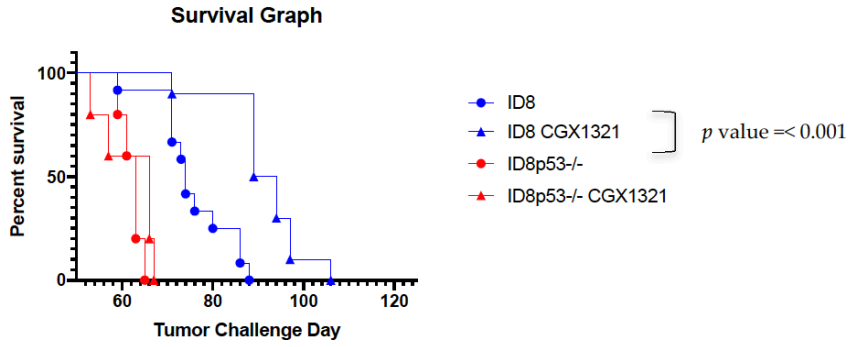
   (B) Wnt inhibition via WNT-974 significantly increased survival in murine ovarian cancer model.



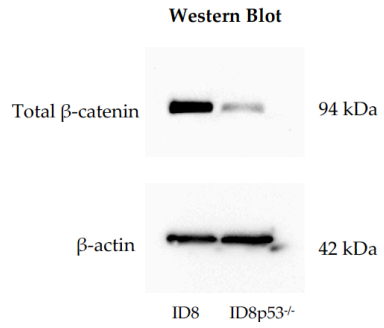
(C) Wnt inhibition via WNT-974 significantly increased CD8+ T cell and regulatory T cell (Treg) ratio in the omental tumor of murine ovarian cancer model.



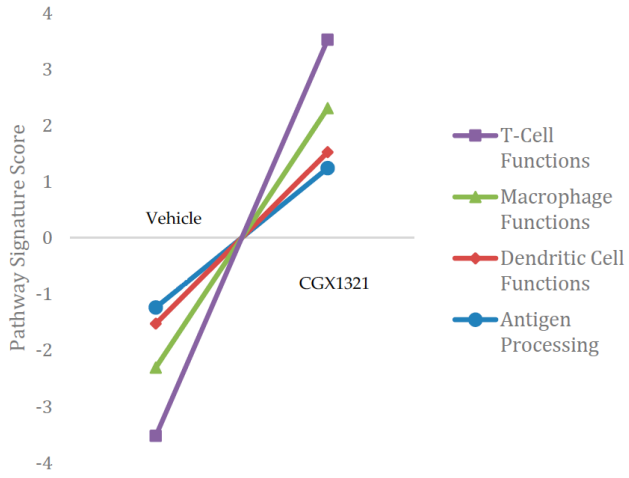
(D) *In vivo* inhibition of Wnt signaling using CGX-1321 increased survival in ID8 tumor challenge, but not tumor challenge with ID8p53$^{-/-}$.



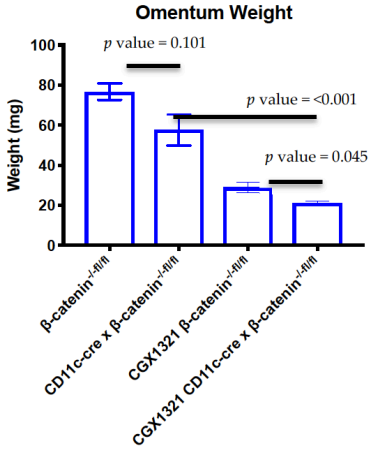
(E) Western blot analysis revealed reduced beta-catenin levels in the ID8p53$^{-/-}$ cell line comparted to ID8 cell line.



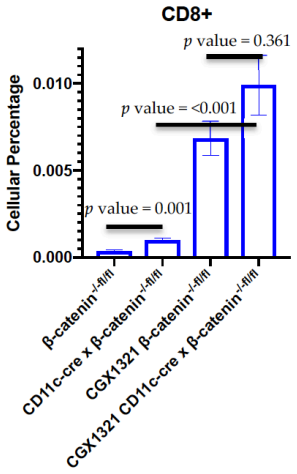
(F) *In vivo* effect of Wnt signaling inhibition via CGX-1321 in omentum tumor and the microenvironment of ID8 model showed an increase in gene signatures for T cell functions, macrophage functions, dendritic cell functions, and antigen processing with CGX-1321 treatment via NanoString analysis.



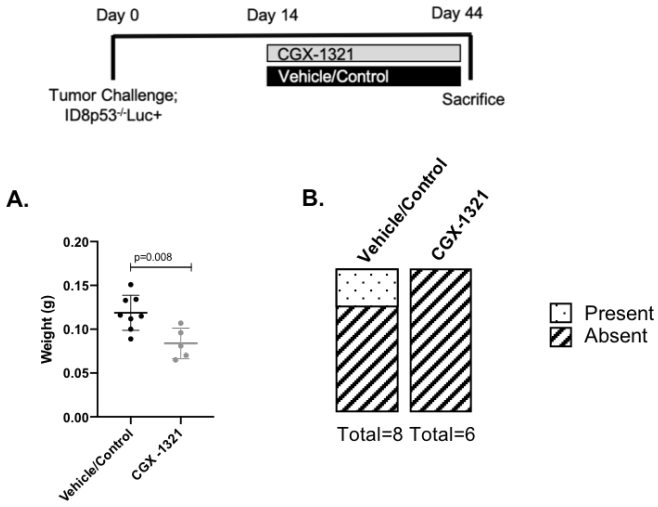
(G) Inhibition of beta-catenin signaling in dendritic cells decreases tumor burden. Omentum weight decreased with loss of beta-catenin in CD11c-cre x Beta-catenin$^{-/-}$ $^{fl/fl}$ mice, and treatment with CGX-1321 further increased this difference.



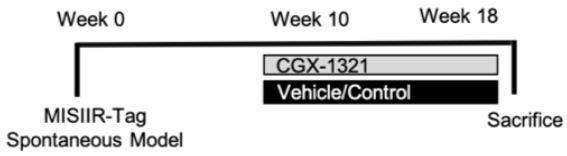
(H) CD8+ T cells increased in the tumor microenvironment in CD11c-cre x Beta-catenin$^{-/-fl/fl}$ mice with ID8 tumor challenge, a finding that was further exaggerated with CGX-1321 treatment.

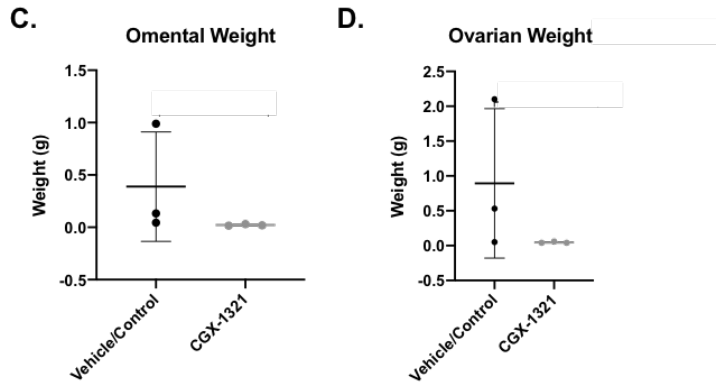


(I) Inhibition of Wnt signaling via CGX-1321 significantly decreased ID8p53$^{-/-}$ tumor burden via omentum weights and ascites volumes.

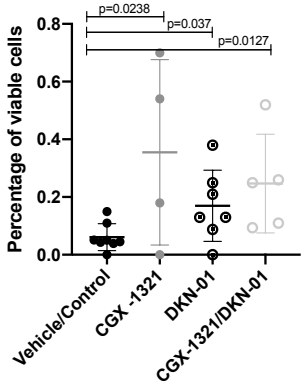


(J) Inhibition of Wnt signaling via CGX-1321 significantly decreased MISIIR-Tag tumor burden via omentum weights and ascites volumes.





(K) Inhibition of Wnt signaling signficantly up-regulates T cell levels in the tumor microenvironment of omentum in ID8p53$^{-/-}$ model.



4. **Other achievements:** We were able to use these data for manuscript publications and presentations at national conferences.
5. **Goals not met:** Last year, we lost our MISIIR-Tag(low) colony at UAB, and because of this we were unable to accomplish part of Aim 2, in which we want to show the DC intrinsic WNT pathway effects on T cell response. We are in process of writing the MTA to acquire the mouse strain from Dr. Connolly's lab at Fox Chase Cancer Center.

AIM 3: To determine whether mutations that affect the HR DNA repair pathway impact T cell responses following treatment with WNT inhibitors using immunocompetent mouse models of ovarian cancer.

1. **Major activities:** N/A
2. **Specific objectives**
   (A) Determine if treatment sensitivity with CGX-1321, DKN-01, or both in ovarian cancer is affected by mutations in the HR DNA pathway
   (B) Investigate whether T cell response to CGX-1321, DKN-01, or both in ovarian cancer is affected by mutations in the HR DNA pathway

3. **Significant results/key outcomes with conclusions:** N/A
4. **Other achievements:** N/A
5. **Goals not met:** N/A

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.

Gynecologic oncology clinical fellows Jackie Wall, M.D., Whitney Goldsberry, M.D, and David Doo, M.D. were trained on this grant. They had the opportunity to explore the role of the Wnt signaling pathway in progression of ovarian cancer.

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.

Nothing to Report.

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

AIM 1: To determine the relationship between WNT/β-catenin signaling, the DNA repair pathway, T cell responses and clinical outcomes in ovarian cancer.

Future directions: We will analyze data from the GOG218 trial through collaboration with Dr. Birrer, and determine if they line up with data we were able to retrieve from TCGA.

AIM 2: To determine how tumor-intrinsic and DC-intrinsic inactivation of the WNT pathway impacts T cell responses and tumor growth using immunocompetent mouse models of ovarian cancer.

Future directions: We do not plan to do any further investigation for this aim at this time.

AIM 3: To determine whether mutations that affect the HR DNA repair pathway impact T cell responses following treatment with WNT inhibitors using immunocompetent mouse models of ovarian cancer.

Future directions: Determine if treatment sensitivity and/or T cell responses to CGX-1321, DKN-01, or both in ovarian cancer is affected by mutations in the HR DNA pathway.

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.

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.

Aim 1: As we were unable to secure data from GOG218 or 268 trials, we had to alter our retrieval of data and used the The Cancer Genome Atlas (TCGA) project which was a secure, public platform where we were able to retrieve data without hindrance. **Aim 2:** N/A **Aim 3:** N/A

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.

Last year, we lost our MISIIR-Tag(low) colony at UAB, and because of this we were unable to accomplish part of Aim 2, in which we want to show the DC intrinsic WNT pathway effects on T cell response. We are in process of writing the MTA to acquire the mouse strain from Dr. Connolly's lab at Fox Chase Cancer Center.

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.

Nothing to Report.

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

Aim 1: We had technical difficulties in retrieving data from GOG268 or GOG218 clinical trials, therefore we used publicly available human data from TCGA project.

Aim 2: N/A

Aim 3: N/A

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:** *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).*

  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).

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.*

Publications

1. Wall, J., Meza-Perez, S., Scalise, C., *et al*. Manipulating the Wnt/Beta-catenin signaling pathway to promote anti-tumor immune infiltration into the TME to sensitize ovarian cancer to ICB therapy. *Gynecol Oncol*. (*August 2020 – planned submission)*.
2. Betella I, Turbitt WJ, Szul T, *et. al*. Wnt signaling modulator DKK1 as an immunotherapeutic target in ovarian cancer. *Gynecol Oncol. (July 2020 – Awaiting publication)*.
3. Wall, J., *et. al.* (2020). The anti-DKK1 antibody DKN-01 as an immunomodulatory combination partner for the treatment of cancer. *Expert Opin Investig Drugs.* DOI: 10.1080/13543784.2020.1769065.
4. Doo D., Meza-Perez S, Londono A. (2020). Inhibition of the Wnt/β-catenin pathway enhances anti-tumor immunity in ovarian cancer. *Ther Adv Med Oncol*. DOI: 10.1177/1758835920913798.
5. Goldsberry W., Meza-Perez S., Londoño A., *et al.* (2020). Inhibiting WNT Ligand Production for Improved Immune Recognition in the Ovarian Tumor Microenvironment. *Cancers (Basel)*. 12(3):766. DOI:10.3390/cancers12030766.
6. Goldsberry, W., et al. (2019). A review of the role of Wnt in cancer immunomodulation. *Cancers.* 11, 771. DOI: 10.3390/cancers11060771.

Presentations

1. *AACR Ovarian Conference – Atlanta, GA. Goldsberry W, Wall JA, Meza-Peres S, *et. al*. (2019). PORCN Inhibition Prolongs Survival, decreases tumor Burden, and Alters the Immune Microenvironment in Ovarian Cancer. *Poster Presentation.*
2. IGCS Annual Meeting – Rio de Janeiro, Brazil. Arend RC (2019). Immunotherapeutic potential of non-immunotherapy drugs: enhancing immunogenicity of cold tumors. *Oral Presentation.*
3. *SGO Annual Meeting – Virtual. Goldsberry W, Wall JA, Meza-Perez S, *et. al.* (2020). Inhibition of PORCN in a p53-/- Knockout Syngeneic Ovarian Cancer Model. *Abstract.*
4. SGO Annual Meeting – Virtual. Arend RC, Castro C, Matulonis U, *et. al.* (2020). Dkn-01 treated patients with recurrent epithelial endometrial (EEC) or ovarian (EOC) cancers which harbor Wnt activating mutations have longer progression free survival and improved clinical benefit. *Oral Presentation.*
5. ASCO Annual Meeting – Virtual. Wall JA, Katre A, Meza-Perez S, *et. al.* (2020). Utilizing porcupine (PORCN) and DKK1 inhibition to improve anti-tumor immunity in a murine model of ovarian cancer. *Poster Presentation.*

- **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:	***Dr. Rebecca Arend***
Project Role:	*Investigator*
Researcher Identifier (e.g. ORCID ID):	*3*
Contribution to Project:	*Dr. Arend has conceptualized and designed all the mouse model experiments. She has given expert advice for treatment regimen and harvesting and processing tissues from experiments.*
Funding Support:	*NA*
Name:	***Dr. Michael Birrer***
Project Role:	*Mentor*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Birrer has provided guidance in analyzing data. He is also helping in acquisition of data from GOG trials.*
Funding Support:	*NA*
Name:	***Dr. Kunle Odunsi***
Project Role:	*Mentor*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Odunsi has provided guidance in analyzing data.*
Funding Support:	*NA*
Name:	***Dr. Troy Randall***
Project Role:	*Mentor*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Randall provided guidance in experimental design.*
Funding Support:	*NA*
Name:	***Dr. Sara Cooper***
Project Role:	*Faculty Investigator at Hudson Alpha Institute for Biotechnology*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*9*
Contribution to Project:	*Dr. Cooper has analyzed RNA sequencing data for this study.*
Funding Support:	*NA*

Name:	***Ashwini Katre***
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*9*
Contribution to Project:	*Ashwini Katre has performed animal experiments described in the study.*
Funding Support:	*NA*

Name:	***Dr. Jaclyn Wall***
Project Role:	*Clinical Gynecologic Oncology Fellow*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*9*
Contribution to Project:	*Dr. Wall has performed non-animal experiments described in the study.*
Funding Support:	*NA*

Name:	***Dr. David Doo***
Project Role:	*Clinical Gynecologic Oncology Fellow*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*9*
Contribution to Project:	*Dr. Doo has performed non-animal experiments described in the study.*
Funding Support:	*NA*

Name:	***Dr. Whitney Goldsberry***
Project Role:	*Clinical Gynecologic Oncology Fellow*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*9*
Contribution to Project:	*Dr. Goldsberry has performed non-animal experiments described in the study.*
Funding Support:	*NA*

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.

Nothing to Report.

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.*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

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

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

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

Nothing to Report.