AWARD NUMBER: W81XWH-21-1-0840

TITLE: Exploiting Metabolic Vulnerabilities to Target Multidrug-Resistant Ovarian Cancer

PRINCIPAL INVESTIGATOR: Katherine M. Aird, PhD

CONTRACTING ORGANIZATION: University of Pittsburgh, Pittsburgh, PA

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6. AUTHOR(S)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

High-grade serous ovarian carcinoma (HGSOC) is the most prevalent histosubtype of epithelial ovarian cancer. Poly(ADP-Ribose) polymerase (PARP) inhibitors have become the standard-of-care for HGSOC patients. How-ever, resistance to PARP inhibitors occurs in homologous-recombination (HR)-proficient disease. Novel combi-natorial approaches are now being explored to overcome de novo or acquired resistance. For instance, inhibitors of the DNA damage response protein Ataxia Telangiectasia Mutated (ATM) are now in clinical trials in combination with PARP inhibitors. Unfortunately, our data and others demonstrates a multi-drug resistant subset of HGSOC cells that persist after combined treatment with ATM and PARP inhibitors. Thus, the long-term goal of this proposal is to develop a novel therapeutic strategy to overcome this multi-drug resistant phenotype.

15. SUBJECT TERMS

Ovarian cancer; Ataxia Telangiectasia Mutated; microenvironment; metabolism; branched chain amino ac-ids; macropinocytosis; immunotherapy

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1. INTRODUCTION

High-grade serous ovarian carcinoma (HGSOC) is the most prevalent histosubtype of epithelial ovarian cancer. Poly(ADP-Ribose) polymerase (PARP) inhibitors have become the standard-of-care for HGSOC patients. How-ever, resistance to PARP inhibitors occurs in homologous-recombination (HR)-proficient disease. Novel combinatorial approaches are now being explored to overcome de novo or acquired resistance. For instance, inhibitors of the DNA damage response protein Ataxia Telangiectasia Mutated (ATM) are now in clinical trials in combination with PARP inhibitors. Unfortunately, our data and others demonstrates a multi-drug resistant subset of HGSOC cells that persist after combined treatment with ATM and PARP inhibitors. Thus, the long-term goal of this proposal is to develop a novel therapeutic strategy to overcome this multi-drug resistant phenotype.

ATM has roles beyond the DNA damage response. Based on work from our funded OCRP Pilot Award, we previously demonstrated that inhibition of ATM in HGSOC cells increases nutrient uptake from the microenvironment via the non-specific endocytic process called macropinocytosis. Notably, inhibition of macropinocytosis in combination with ATM inhibitors decreased HGSOC proliferation and survival both in vitro and in vivo. This suggests that nutrient uptake via macropinocytosis is an unintended side effect of ATM inhibitors that promotes cell-intrinsic survival through regulating nutrient uptake and cellular metabolism. Assessment of microenvironmental metabolites from the ascites fluid and tumor interstitial fluid from our in vivo models demonstrated that ATM inhibited tumors increase uptake of branched chain amino acids (BCAAs). Supplementation of BCAAs rescued the proliferation and survival defects of combined ATM and macropinocytosis inhibition. Additionally, abundance of the BCAA leucine correlates with PARP inhibitor resistance. Together, these data suggest that increased BCAA uptake and metabolism by increased macropinocytosis may promote multi-drug resistance to combinatorial therapy with ATM and PARP inhibitors. The role of nutrient uptake and BCAA metabolism in therapeutic resistance in HGSOC has never been explored. This will be a direct expansion of the previous OCRP Pilot Award.

Microenvironmental metabolites are not only important for tumor cell survival, but also for immune cells. Previous studies have demonstrated that the BCAA leucine is critical for helper and effector T cell expansion, differentiation, and function. Therefore, decreased BCAA abundance in the tumor microenvironment due to ATM inhibition may also have tumor cell-extrinsic effects to dampen anti-tumor immunity. While HGSOCs do have tumor infiltrating lymphocytes (TILs), immune checkpoint blockade as a monotherapy has not been effective in HGSOC patients. Whether imbalanced microenvironmental metabolites suppress TILs in HGSOC is unknown. We aim to use our knowledge from the funded OCRP Pilot Award to go into a new direction, identifying whether changes in microenvironmental metabolites also affects the immune milieu.

Accordingly, the objectives of the proposed studies are:

1: Dissect the metabolic basis of resistance to ATM and PARP inhibitor combination therapy.

2: Develop novel therapeutic strategies to enhance ATM and PARP inhibitor combination therapy.

2. KEYWORDS

Ovarian cancer; Ataxia Telangiectasia Mutated; microenvironment; metabolism; branched chain amino acids; macropinocytosis; immunotherapy

3. ACCOMPLISHMENTS

What were the major goals of the project?
These are described below, broken down by Specific Aim, Major Task, and Subtask from the approved Statement of Work (SOW).

Specific Aim 1: Dissect the mechanistic basis of ATM inhibition and fenofibrate synthetic lethality.

- **Major Task 1:** To determine whether increased BCAA uptake and metabolism increases resistance of EOCs to combined inhibition of ATM and PARP.
  - *Milestone #1: To have determined the roles of BCAA uptake and metabolism on multi-drug resistance to combined ATM and PARP inhibition. Status: Subtask 1, 2, and 3 initiated with negative results. Subtasks 4-5 not initiated due to negative results. Change in approach and alternative strategies can be found in* ***Section 5***

    - Subtask 1: Validate BCAT1/2 and BCKDH knockdown and overexpression in cell lines.
      Results: We have successfully knocked down BCAT1/2 and BCKDH in cell lines. Over-expression studies have not yet been initiated due to negative results in Subtask 3 (change in approach and alternative strategies can be found in **Section 5**).

    - Subtask 2: Assess proliferation and apoptosis in BCAT1/2 and BCKDH knockdown cell lines treated with ATM inhibitor alone, PARP inhibitor alone, or the combination.
      Results: Knockdown of BCAT1/2 or BCKDH alone had significant effects on viability of cells. Thus, the subsequent inhibitor studies were not feasible (change in approach and alternative strategies can be found in **Section 5**).

    - Subtask 3: Determine whether supplementation of cells with exogenous BCAAs or over-expression of BCAT1/2 or BCKDH is sufficient for PARP inhibitor resistance.
      Results: Supplementation of physiological doses of BCAAs (100-400uM) did not rescue PARP inhibitor resistance (**Fig. 1**; change in approach and alternative strategies can be found in **Section 5**). High doses of BCAAs alone were relatively toxic to cells and were therefore not used for combination studies.

    - Subtask 4: Assess steady state abundance of BCAAs in cells from Subtasks 2-3.
      Results: As knockdown of BCAT1/2 or BCKDH had a significant effect on viability of cells, we were unable to assess steady state abundance of BCAAs. Overexpression studies have not yet been initiated due to negative results in Subtask 3 (change in approach and alternative strategies can be found in **Section 5**).

    - Subtask 5: Assess utilization of BCAAs in cells from Subtask 2-3 by isotope tracing studies.
      Results: As knockdown of BCAT1/2 or BCKDH had a significant effect on viability of cells, we were unable to assess steady state abundance of BCAAs. Overexpression studies have not yet been initiated due to negative results in Subtask 3 (change in approach and alternative strategies can be found in **Section 5**).

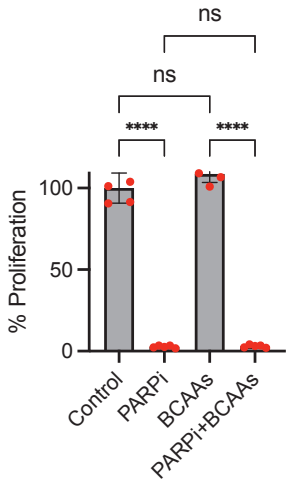

Figure 1. BCAAs do not rescue PARP inhibitor sensitivity. Ovcar3 HGSOC cells were treated with 200uM BCAAs, 15uM olaparib (PARPi), and the combination for 4 days. ****p<0.0001. ns = not significant

- **Major Task 2:** To assess T cell function in the context of combined ATM and PARP inhibitor treatment *in vitro* and *in vivo*.

    - *Milestone #2: IACUC approval received. Status: COMPLETED August 2021*

    - *Milestone #3: To have determined that inhibition of ATM and PARP in combination inhibits activation, differentiation, and metabolism of T cells due to BCAA changes in the microenvironment. Status: Not yet initiated.*

    - *Milestone #4: Manuscript submission describing role of BCAA metabolism in the multi-drug resistant phenotype to combined ATM and PARP inhibitors. Status: Not yet initiated.*

        - Subtask 1: Assess activation, differentiation, and metabolism of T cells after exposure to conditioned media from cells treated in Major Task 1, Subtasks 2-3
        - *Results:* Not yet initiated.

        - Subtask 2: Obtain IACUC approval
          Results: IACUC approval (21018654) was attained 01/12/2021 from University of Pittsburgh. ACURO approval was received 03/05/2021.

        - Subtask 3: Determine the effects of combined ATM and PARP inhibition on T cell activation, differentiation, and metabolism from omental tumors *in vivo*.
          Results: Not yet initiated.

        - Subtask 4: Determine the effects of combined ATM and PARP inhibition on T cell activation, differentiation, and metabolism from omental tumors *in vivo*.
          Results: Not yet initiated.

Specific Aim 2: Develop novel therapeutic strategies to enhance ATM and PARP inhibitor combination therapy.

- **Major Task 1:** To determine whether inhibition of macropinocytosis using FDA-approved inhibitors synergizes *in vitro* and *in vivo*.

    - *Milestone #5: To have determined tumor progression in mice treated with combination and correlated with molecular markers of both the tumor and immune cells. Status: Subtask 2 initiated with negative results. Subtasks 1, 3-5 not initiated. Change in approach and alternative strategies can be found in* ***Section 5***

        - Subtask 1: Subtask 1: Compare/contrast proliferation and apoptosis in cells treated with ATM inhibitors, PARP inhibitors, or macropinocytosis inhibitors alone or in combination.
          Results: We were unable to confirm inhibition of macropinocytosis using the 3 FDA-approved inhibitors (**Fig. 2**; change in approach and alternative strategies can be found in **Section 5**).

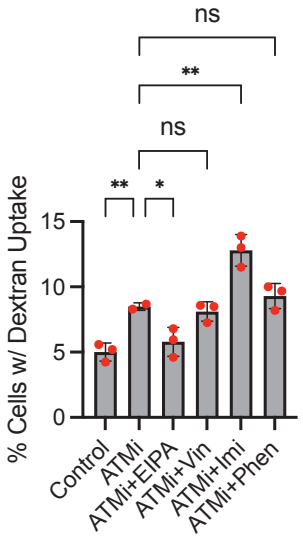

Figure 2. Three FDA-approved inhibitors do not decrease macropinocytosis. Ovcar8 cells were treated the ATM inhibitor (ATMi) KU60019 to increase macropinocytosis. The three FDA-approved inhibitors Vinblastine, Phenoxybenzamine, and Imipramine did not decrease macropinocytosis. EIPA was used as a positive control for macropinocytosis inhibition. *p<0.05, **p<0.01, ns = not significant

- Subtask 2: Confirm inhibition of macropinocytosis and decreased BCAA uptake and metabolism in cells from Subtask 2.
  Results: Initial studies with the FDA-approved inhibitors that have been published to inhibit macropinocytosis indicated that this was not the case in our model (change in approach and alternative strategies can be found in **Section 5**).

- Subtask 3: Determine the effects of ATM inhibitor, PARP inhibitor, macropinocytosis inhibitor and the combination on tumor burden *in vivo*.
  Results: Not yet initiated.

- Subtask 4: Determine molecular markers of proliferation, apoptosis, macropinocytosis, and metabolism of tumors.
  Results: Not yet initiated.

- Subtask 5: Determine immune cell infiltration and molecular markers of T cell activation and differentiation from tumor-bearing mice.
  Results: Not yet initiated.

- Subtask 6: Statistical analysis of *in vivo* studies.
  Results: Not yet initiated.

- **Major Task 2:** To investigate whether inhibition of macropinocytosis increases anti-tumor immunity. *Status: Not yet initiated.*

  - *Milestone #6: To have determined whether the combination affects T cell function either directly or through changes in microenvironmental metabolites.*

    - Subtask 1: Determine whether the combination of ATM inhibitors, PARP inhibitors, or macropinocytosis inhibitors affects T cell activation, differentiation, and metabolism *in vitro*.

Results: Not yet initiated.

- Subtask 2: Determine the effects of conditioned media from Major Task 1, Subtask 1 on T cell activation, differentiation, and metabolism *in vitro*.
  Results: Not yet initiated.

- Subtask 3: Determine the effects of the combination + anti-PD-1 inhibitors on tumor burden *in vivo*.
  Results: Not yet initiated.

- Subtask 4: Determine molecular markers of proliferation and apoptosis and immune cell infiltration of tumors.
  Results: Not yet initiated.

- Subtask 5: Statistical analysis of *in vivo* studies.
  Results: Not yet initiated.

- *Milestone #7 To have determined tumor progression in mice treated with the combination and anti-PD-1 inhibitors and correlated with molecular markers of proliferation and apoptosis. To be completed by September 2023.*

- *Milestone #8 Achieved: Manuscript submission describing inhibition of macropinocytosis as a mechanism to overcome resistance to combined ATM and PARP inhibitors through both decreasing cell-intrinsic metabolism and enhancing anti-tumor immunity. To be completed after the end of the study period (late 2023).*

- *Milestone #9: Submit grant application to NCI R01 for follow up work. To be completed after the end of the study period (Oct 2023 or Feb 2024).*

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

Nothing to Report

How were the results disseminated to communities of interest?

Results were disseminated to the scientific community as a manuscript (in revision) and an oral presentation to the Penn OCRC Forum (see Section 6).

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

During the Year 2 and final reporting period, we will continue to investigate the molecular mechanism underlying the role of BCAA uptake in ATM inhibited HGSOC cells. We will conduct many of the remaining experiments proposed in the SOW, including studies to assess T cell activation and function in the context of macropinocytosis-mediated uptake of BCAAs into tumor cells. We will also perform the in vivo experiments. We will report our findings at the AACR Ovarian Cancer Meeting in September 2023 and continue to provide updates to the Pitt ovarian cancer group. Finally, we plan to both submit a manuscript and R01 on this project l in late 2023 or early 2024.

4. IMPACT

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

This project is beginning to shed light on the mechanisms macropinocytosis plays in drug resistance in ATM-inhibited high grade serous ovarian cancer (HGSOC). HGSOC therapy remains an important

clinical problem as relapse and chemoresistance occurs in the majority of patients. Our lab has focused efforts on a novel combination of ATM inhibitors, PARP inhibitors, and macropinocytosis inhibitors as a potential triple combination for HGSOC patients. An important feature of our work is understanding the molecular mechanisms underlying cellular metabolism in ovarian cancer cells to determine whether exploitation of these pathways will ultimately result in new therapies. Ongoing work will finalize how uptake of nutrients from the tumor microenvironment allows tumors cells to grow and proliferate while starving immune cells of nutrients required for anti-tumor immunity.

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

Changes in approach and reasons for change

We have had to reconsider two of our initial hypotheses. Below are explanations of the data we generated, why we need to change our approach, and plans for the next reporting period for each point.

1. We hypothesized that inhibition of downstream BCAA catabolism would synergize with the combination of ATM and PARP inhibitors. Interestingly, knockdown of BCAT1/2 or BCKDH alone had significant effects on cell viability. Therefore, we were unable to perform synergy studies. However, this opens up a new area of research to better understand the necessity of these enzymes for HGSOC viability, which may be a therapeutic target of its own. BCAT inhibitors exist, and we plan to test these in a variety of HGSOC cell lines and normal fallopian tube cells to determine whether there is a therapeutic window for these agents in HGSOC.

During the course of our studies, we also found that downstream BCAA metabolites KIV/KIC and KMV were not affected by ATM inhibition (**Fig. 3**). These data provide evidence to suggest that the mechanism of PARP inhibitor resistance in ATM inhibited cells is likely not due to catabolism of BCAAs. During the next reporting period, in collaboration with our co-investigator Dr. Snyder, we will more globally assess metabolite abundance in ATM and PARP inhibitor treated cells to identify other pathways that may be important to investigate. Interestingly, we found that although mTORC1 activity was downregulated by the ATM inhibitor, protein synthesis was maintained (**Fig. 4**). Together, these data suggest that the increased BCAA uptake observed in ATM inhibited cells promotes resistance through continued protein synthesis. What protein or set of proteins is required for resistance is the next question. We plan to determine whether this maintained protein synthesis is mediated by BCAA uptake and required for resistance to the combination of ATM and PARP inhibitors in the next reporting period.

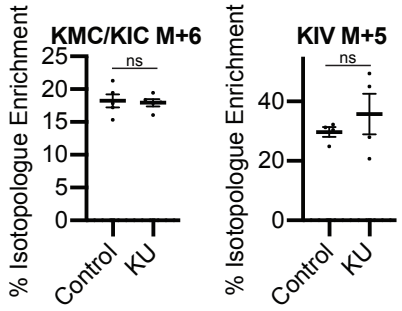

Figure 3. ATM inhibition does not increase BCAA catabolism. Ovcar8 cells were treated with the ATM inhibitor KU60019 (10μM) for 2h, and isotopologue enrichment of BCAAs was assessed by mass spectrometry. n=3/group, one of at least 3 experiments is shown. Data represent mean ± SD. ns = not significant; Student's t-test.

2. We hypothesized that supplementation with BCAAs would rescue sensitivity to PARP inhibitors; however, we did not observe a significant difference between PARP inhibitor treatment alone or in combination with physiological concentrations of BCAAs (**Fig. 1**). These experiments were performed in nutrient-replete media (RPMI-1640 + 5% FBS), which may mask metabolism-mediated effects. Therefore, we plan to repeat these experiments using more physiologically-relevant medias such as Human Plasma-Like Media (HPLM) with dialyzed FBS or ascites fluid taken from ovarian cancer patients. These alternative conditions may provide a different result, which could be explained by the differences in metabolite concentrations.

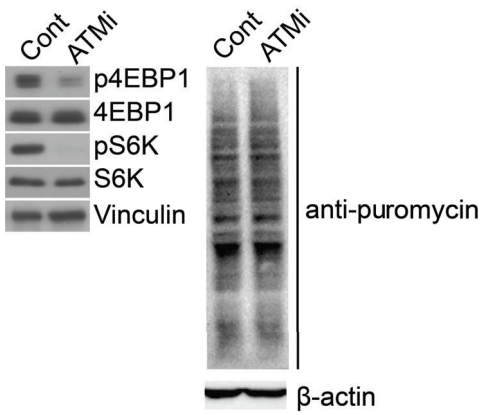

Figure 4. ATM decreases mTORC1 but protein synthesis is maintained. Ovcar8 cells were treated with the ATM inhibitor KU60019. mTORC1 activity was assessed by phosphorylation of 4EBP1 and S6K. Protein synthesis was assessed by treating cells with puromycin for 30min and blotting using an anti-puromycin antibody.

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

We have had an unanticipated problem in this reporting period. The lab moved to a new building in mid-June, significantly disrupting these studies as we were unable to perform experiments for 2 weeks prior to our move for packing and 3 months after the move due delays in approval of our BSL2+ cell culture room by Environmental Health & Safety. Similar delays were experienced by the Delgoffe lab (immunology collaborator). In all, we unfortunately lost ~4months of productivity. While we did our best to mitigate these circumstances by analyzing data previously generated, performing BSL1 and BSL2 work that was allowed by EH&S, and working with our collaborator Dr. Snyder at Temple University, momentum on these studies was significantly impacted. An additional delay that may occur in the next year is opening of the new animal facility. We plan to continue animal work in the old facility to mitigate these circumstances, but in that case, cage numbers may be limited.

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

Nothing to report

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

  Publication: Huang Z, Chen CW, Buj R, Tangudu NK, Fang R, Leon KE, Dahl ES, Varner EL, von Krusenstiern E, Cole AR, Snyder NW, and **Aird KM**. ATM inhibition drives metabolic adaptation via induction of macropinocytosis. bioRxiv. doi.org/ /10.1101/2020.04.06.027565 (Resubmitted)

  Presentation, Penn OCRC Virtual Seminar Series (2021), "Macropinocytosis induction in ovarian cancer"

- Website(s) or other Internet site(s)
  N/A
- Technologies or techniques
  N/A
- Inventions, patent applications, and/or licenses
  N/A
- Other Products
  N/A

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Katherine M. Aird
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	ORCID ID: 0000-0002-5828-2325
Nearest person month worked:	1.2mo
Contribution to Project:	Dr. Aird has designed and analyzed experiments proposed in both Specific Aims of this proposal.
Funding Support:	This award, R37CA240625, R01CA259111, RSG-19-113-01-CCG, U54AG075931, P50CA254865 (see below)

Name:	Zhentai Huang
Project Role:	Research Scientist
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	9mo
Contribution to Project:	Dr. Huang performed knockdown experiments, assessed macropinocytosis using dextran uptake, and performed western blots.
Funding Support:	N/A

Name:	Lucas Bittencourt
Project Role:	Postdoc
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	6mo
Contribution to Project:	Dr. Bittencourt performed synergy experiments.

Funding Support:	N/A

Name:	Ying Ding
Project Role:	Collaborator (Biostatistician)
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0.6mo
Contribution to Project:	Dr. Ding has assisted with biostatistics for experiments in Specific Aim 1.
Funding Support:	This award, R01GM141076, R21EY030488, R01MH116046, 5R01MH118497, P30CA047904, R01AG069912, R01MH125235, 62623530-157064 (see below)

Name:	Greg Delgoffe
Project Role:	Collaborator
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0.6mo
Contribution to Project:	Dr. Delgoffe has provided critical insights for planned immunology experiments of this proposal.
Funding Support:	This award, W81XWH1810211, R01 AI142354, R25 CA236620, 19-040-ELA, R01 CA236367, R01 AI148356, PA DOH, CRI 3447, Melanoma Research Alliance 700464, SRA00001379, SRA00001546, SRA00002131 (see below)

Name:	Nathaniel Snyder
Project Role:	Collaborator
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0.6mo
Contribution to Project:	Dr. Snyder has performed metabolomics experiments for Specific Aims 1 of this proposal.
Funding Support:	This award, R01 GM132261, R37CA240625, R01 DK116005, R01 CA228339, R01CA174761, R01 DK094004, R01CA259111, R56HL49887 (see below)

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

  Katherine M. Aird (PI)

  - R01CA259111 (PI: Aird/Snyder) is now active
    Title: Metabolic and epigenetic reprogramming in cyclin E high ovarian cancer
    Effort: 4 calendar months
    Sponsor Agency: National Institutes of Health
    Contracting/Grants Officer: Nailah Shaw
    Address of Funding Agency: 9609 Medical Center Drive, Rockville, MD 20850

Performance Period: 04/01/2021– 03/31/2026
Level of Funding: total costs
Specific Aims/Project Goals: The goal of this study is to determine whether nuclear acetyl-CoA synthesis affects DNA damage response in cyclin E-high ovarian cancer patients and whether targeting this pathway synergizes with PARP inhibitors.
Overlap: No scientific or budgetary overlap

- U54AG075931 (PI: Finkel) is now active
  Title: TriState SenNET (Lung and Heart) Tissue Map and Atlas Consortium
  Effort: 0.3 calendar months
  Sponsor Agency: National Institutes of Health
  Contracting/Grants Officer: Long Nguyen
  Address of Funding Agency: 9609 Medical Center Drive, Rockville, MD 20850 **Performance Period:** 09/01/2021 – 08/31/2026
  Level of Funding: DC (Year 1)
  Specific Aims/Project Goals: The major goals of this project are to characterize and map senescent cells in healthy, aged, and disease lung and heart.
  Overlap: No scientific or budgetary overlap

- P50CA254865 (PI: Zarour/Kirkwood) is now active
  Title: Melanoma and Skin Cancer SPORE
  Effort: 0.3 calendar months
  Sponsor Agency: National Institutes of Health
  Contracting/Grants Officer: Long Nguyen
  Address of Funding Agency: 9609 Medical Center Drive, Rockville, MD 20850 **Performance Period:** 08/15/2021 – 06/30/2026
  Level of Funding: TC (Year 1)
  Specific Aims/Project Goals: The goal of the UPMC Hillman Cancer Center Melanoma and Skin Cancer Program (MSCP) SPORE is to improve melanoma and skin cancer treatment through the understanding and development of novel approaches to immunotherapy in three translational research Projects, supported by three Cores, and vibrant Developmental Research and Career Enhancement Programs.
  Overlap: No scientific or budgetary overlap

<u>Ying Ding (Biostatistician)</u>

- R01GM141076 is now active
  Title: New statistical methods and software for modeling complex multivariate survival data with large-scale covariates
  Goal: The successful completion of the project will lead to a comprehensive methodological framework with easy-to-use software packages, which have the potential to fundamentally improve the current practice in analyzing such studies, and thus to enhance the understanding of disease risk factors, improve the prediction of disease progression profiles, and to increase the success of precision medicine development.
  Name of PD/PI: Ding, Ying
  Source of Support: NIH
  Primary Place of Performance: University of Pittsburgh, Pittsburgh
  Project/Proposal Start and End Date: 6/1/2022 - 5/31/2026
  Total Award Amount (including Indirect Costs):
  Overlap: No scientific or budgetary overlap

Greg Delgoffe (Collaborator)

- SRA00001546 is now active
  Title: TGF-b signaling in cancer
  Award Number: SRA00001546
  Agency: Kalivir Immunotherapeutics
  Role: Principal Investigator
  Level of Effort: 0.24 calendar months
  Level of Funding: total costs
  Performance Period: 07/22/21 – 07/21/22
  Contracting/Grants Officer: Steve Thorne; 412-435-6730
  Project Goals: In this SRA, we will be using oncolytic viruses to deliver a genetically encoded inhibitor of TGF-beta signaling, to temper this immunosuppressive signal in the tumor microen-vironment, and explore potential combinations with other forms of immunotherapy.
  Overlap: No scientific or budgetary overlap

- SRA00002131 is now active
  Title: Development of metabolic reprogramming strategies
  Award Number: SRA00002131
  Agency: Century Therapeutics
  Role: Principal Investigator
  Level of Effort: 0.60 calendar months
  Level of Funding: total costs
  Performance Period: 01/01/22-06/30/23
  Contracting/Grants Officer: Doug Carr; 267-885-8270
  Project Goals: The goal of this project is to assess whether improvements in mitochondrial capacity in process increase function, longevity and persistence of effector products and the creation of genetic strategies for metabolic reprogramming of effector products.
  Overlap: No scientific or budgetary overlap

Nathaniel Snyder (Collaborator)

- R01CA259111 (PI: Aird/Snyder) is now active
  Title: Metabolic and epigenetic reprogramming in cyclin E high ovarian cancer
  Effort: 4 calendar months
  Sponsor Agency: National Institutes of Health
  Contracting/Grants Officer: Nailah Shaw
  Address of Funding Agency: 9609 Medical Center Drive, Rockville, MD 20850 **Performance Period:** 04/01/2021– 03/31/2026
  Level of Funding: total costs
  Specific Aims/Project Goals: The goal of this study is to determine whether nuclear acetyl-CoA synthesis affects DNA damage response in cyclin E-high ovarian cancer patients and whether targeting this pathway synergizes with PARP inhibitors.
  Overlap: No scientific or budgetary overlap

- R56HL49887 (PI: Sato) is now active
  Title: Non-Canonical Role of GRK2 in Mediating Cardiac Function
  Effort: 0.6 calendar months
  Sponsor Agency: National Institutes of Health
  Contracting/Grants Officer: Ravi Balijepalli
  Address of Funding Agency: 9609 Medical Center Drive, Rockville, MD 20850

Performance Period: 09/021/2021– 08/31/2022
Level of Funding: total costs
Specific Aims/Project Goals: This research grant seeks to determine the role of pancreatic GRK2 in eliciting metabolic signals to the heart. The Snyder Lab will conduct metabolite profiling in selected experiments key to this proposal.
Overlap: No scientific or budgetary overlap

- **What other organizations were involved as partners?**

  Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

Not applicable

9. APPENDICES

None