AWARD NUMBER: W81XWH-19-1-0014

TITLE: Cytomegalovirus reactivation in ovarian cancer

PRINCIPAL INVESTIGATOR: Heather Nelson

CONTRACTING ORGANIZATION: University of Minnesota

REPORT DATE: July 2020

TYPE OF REPORT: ANNUAL

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| JULY 2020 | Annual | July 1,2019 – June 30,2020 |

**4. TITLE AND SUBTITLE**
Cytomegalovirus reactivation in ovarian cancer

**5a. CONTRACT NUMBER**

**5b. GRANT NUMBER**
W81XWH-19-1-0014

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
Heather Nelson, Melissa Geller, Rachel Vogel

E-Mail: hhnelson@umn.edu

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

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

University of Minnesota
Masonic Cancer Center
425 East River Road
Minneapolis, MN, 55455

**8. PERFORMING ORGANIZATION REPORT NUMBER**

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

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

**10. SPONSOR/MONITOR'S ACRONYM(S)**

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

**12. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**
There is a pressing need to identify new biomarkers that can be used to tailor treatment and improve outcomes in ovarian cancer. This project will test the hypothesis that a common herpes virus, cytomegalovirus (CMV), re-emerges from latency during ovarian cancer and negatively impacts ovarian cancer treatment. Among 50 women diagnosed with ovarian cancer and receiving chemotherapy we will measure: CMV in blood at the time of diagnosis, CMV in tumor, CMV in blood during chemotherapy treatment, inflammation, and severity of symptoms during treatment. Our objective is to determine whether this very common virus re-emerges during chemotherapy and negatively impacts the patient during ovarian cancer treatment.

**15. SUBJECT TERMS**
Ovarian cancer, cytomegalovirus, viral reactivation

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| Unclassified | Unclassified | Unclassified | Unclassified | 10 | 19b. TELEPHONE NUMBER *(include area code)* |

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## 1. INTRODUCTION:

Cytomegalovirus (CMV) infection has emerged as a major driver of inflammation and immune function, and the goal of this Pilot Award is to document the occurrence and kinetics of CMV reactivation at the time of ovarian cancer treatment, and how these reactivation events may negatively impact treatment. We have developed an innovative digital PCR method to assess CMV infection in serum and tumor. We will enroll 50 women with newly diagnosed ovarian cancer undergoing debulking surgery and adjuvant chemotherapy at the University of Minnesota. In Aim 1 we will determine the proportion of patients with CMV reactivation at the time of diagnosis (as determined by DNAemia and high CRP), and determine the correlation between serum biomarkers of infection and tumor CMV DNA levels. We will prospectively follow these 50 patients during the course of adjuvant chemotherapy, and in Aim 2 we will determine the kinetics of CMV reactivation during chemotherapy, and in Aim 3 we will determine whether CMV reactivation is associated with significant clinical symptoms during treatment.

## 2. KEYWORDS:

Ovarian cancer, cytomegalovirus, viral reactivation

## 3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

  The major goals of the project are to recruit 50 patients with ovarian cancer undergoing debulking surgery followed by chemotherapy. Biospecimens (tumor and blood) will be collected at the time of surgery, and a blood sample will be collected at each chemotherapy visit. We will evaluate biomarkers of CMV and inflammation at each timepoint to assess CMV reactivation as a function of treatment. The initially approved SOW is outlined in the table below.

| **OC180211** | **Target completion** | **Actual completion** |
|---|---|---|
| **Major Task 1: Receive local IRB and USAMRMC ORP administrative review and approval for use of human subjects in protocol.** | | |
| Refine eligibility criteria, exclusion criteria, screening protocol | 08/2019 | 05/2019 |
| *Milestone Achieved: University of Minnesota IRB Approval/Amendment* | *09/2019* | *delayed* |
| *Milestone Achieved: HRPO Approval* | *11/2019* | *delayed* |
| **Major Task 2: Conduct prospective study among individuals with ovarian cancer to obtain biospecimens and significant clinical symptoms** | | |
| Create RedCap instrument and calendar for study protocol | 09/2019 | 05/2019 |
| *Milestone: First patient consented and enrolled* | *11/2019* | Not started |
| Recruitment (n=50 patients at the time of debulking surgery with planned adjuvant chemotherapy) | 09/2020 | Not started |
| Biospecimen collection and storage (at each chemotherapy visit, and completion of treatment) | 03/2021 | Not started |
| Clinical data abstraction (for significant clinical symptoms) | 03/2021 | Not started |
| *Milestone: Enrollment of 50 consenting participants* | *09/2020* | Not started |
| *Milestone(s): Completion of patient visits and data abstraction* | *03/2021* | Not started |
| **Major Task 3: Biospecimen Testing** | | |
| CMV IgG and CRP testing | 03/2021 | Not started |
| CMV DNA testing | 03/2021 | Not started |
| *Milestone: All samples analyzed for CMV and CRP* | *03/2021* | Not started |
| **Major Task 4: Data analysis** | | |
| Aim 1: correlation between serum and tumor CMV DNA levels. (n=50 patients). | 09/2021 | Not started |
| Aim 2: kinetics of CMV control during ovarian cancer treatment (debulking surgery through end of adjuvant chemotherapy) | 05/2021 | Not started |

| | | |
|---|---|---|
| Aim 3: determine whether loss of CMV control is associated with significant clinical symptoms and adherence to treatment. | 05/2021 | Not started |
| *Milestone: Data analysis complete* | *05/2021* | Not started |
| **Major Task 5: Dissemination of Results** | | |
| Manuscript preparation | | |
| Aim 1: correlation between serum and tumor CMV DNA levels. (n=50 patients). | 10/2021 | Not started |
| Aim 2: kinetics of CMV control during ovarian cancer treatment (debulking surgery through end of adjuvant chemotherapy) | 06/2021 | Not started |
| Aim 3: determine whether loss of CMV control is associated with significant clinical symptoms and adherence to treatment. | 06/2021 | Not started |
| *Milestone: Submit manuscript(s) for publication* | *06/2021* | Not started |

- **What was accomplished under these goals?**

  Major Task 1 IRB/HRPO approval: Prior to the start of the grant a UMN IRB approved biobanking protocol was in place for patients with a solid tumor diagnosis seeking care at the University of Minnesota, which included tumor and blood collection at the time of diagnosis, and blood collection at standard of care clinic visits. The intention was to use this protocol for the current study.

  The team established the eligibility criteria, exclusion criteria and screening protocols for identifying ovarian cancer participants. The existing IRB was deemed too broad to be submitted to the DOD HRPO, and there has been a delay in having a new protocol/IRB approved.

  Major Task 2 prospective study of ovarian cancer patients: We worked closely with the Masonic Cancer Center (MCC) Clinical Trials Office (CTO) to operationalize the study. This included creation of the study calendar in Oncore and developing SOP's for all elements of patient recruitment, including coordination with other clinical studies, acquisition and tracking of samples, and processing of samples. The remaining work has not been initiated pending resolution of Task 1.

  Major Tasks 3-5: Not started.

- **How were the results disseminated to communities of interest?**
  No results have been reported to date. We have expanded on material from our grant proposal and drafted a review article on CMV reactivation in solid tumor patients. In addition, preliminary data from the grant proposal which describes CMV reactivation in ovarian cancer patients has been drafted into a manuscript. It is anticipated both manuscripts will be submitted in the fall.

- **What do you plan to do during the next reporting period to accomplish the goals?**
  The COVID-19 pandemic has placed constraints on the ability to conduct clinical research, including the cessation of enrollment into human subjects research involving in-person research interactions at the University of Minnesota starting March 2020. We have identified two directions to continue research to address the study objectives during this unprecedented time.

  (1) We will work with our Program Officer to determine whether previously collected samples may be used to meet our study objectives. The UMN cancer biobank has samples available from 33 ovarian cancer patients who meet our study eligibility criteria who have consented to sharing their biospecimens and data with UMN researchers. A total of 33 tumors and 104 blood samples from this biobank are available for CMV testing and could be used to advance Specific Aim 1 (the prevalence of CMV in blood and tumor at the time of diagnosis) and Specific Aim 2 (the kinetics of CMV reactivation during the course of chemotherapy).

  (2) As the health system has transitioned to heavy use of telemedicine the use of remote consent has become available. We will move forward with a protocol that utilizes remote consent. In addition, we have put in place SOP's so that women who are receiving their chemotherapy at satellite locations in the

metro area can participate in the research study. When the University re-opens new clinical research protocols we can implement both remote consent and collection of blood samples at satellite clinics.

## 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

- **Changes in approach and reasons for change**
  As described above, we will work with our Program Officer to determine whether a change in the statement of work is feasible that will allow us to study previously biobanked specimens from ovarian cancer patients who meet our study criteria and who have consented to have their specimens shared. This would allow us to immediately begin laboratory data collection on CMV biomarkers. The COVID-19 pandemic has dramatically impacted clinical research. However, Dr. Nelson's laboratory was reopened in June and staff are available to conduct the biomarker studies. Currently there is a hold at our institution on the initiation of new tier 4 studies (defined as non-COVID observational studies). Once this hold is lifted, we can submit a protocol that includes remote consent of participants.

- **Actual or anticipated problems or delays and actions or plans to resolve them**
  See above.

- **Changes that had a significant impact on expenditures**
  There have been limited expenditures to date given our delay in implementing Task 1.

- **Significant changes in use or care of human subjects**
  No human subjects research has been conducted to date.

- **Significant changes in use or care of vertebrate animals.**
  N/A

- **Significant changes in use of biohazards and/or select agents**
  N/A

## 6. PRODUCTS

- **Publications, conference papers, and presentations**
  *Nothing to report*

- **Website(s) or other Internet site(s)**
  *Nothing to report*

- **Technology or techniques**
  *Nothing to report*

- **Inventions, patent applications, and/or licenses**
  *Nothing to report*

- **Other Products**

*Nothing to report*

## 7. PARTICIPANTS & OTHER COLLABORATING INSTITUTIONS

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

| | |
|---|---|
| **Name:** | Heather Nelson, MPH, Ph.D. |
| **Project Role:** | PI |
| **Nearest person month worked:** | 1 |
| **Contribution to Project:** | Study leader, responsible for study protocol and implementation. Will oversee the laboratory data collection and lead analysis and manuscript preparation |

| | |
|---|---|
| **Name:** | Rachel Isaksson Vogel, Ph.D. |
| **Project Role:** | Co-I |
| **Nearest person month worked:** | 0 |
| **Contribution to Project:** | Study statistician; will guide analysis of data in year 2. |

| | |
|---|---|
| **Name:** | Melissa Geller, M.D., M.S. |
| **Project Role:** | Co-I |
| **Nearest person month worked:** | 0 |
| **Contribution to Project:** | Clinical partner; assists in decision making regarding patient recruitment and retention, interpretation of data, and presentation of results. |

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

**Heather Nelson**

New Active Support:

R03CA249461 (Prizment) 3/1/2020 – 2/28/2022 0.12 calendar months
NIH/NCI $50,000

**Immune-regulating MHC class I-like proteins and colorectal cancer risk**

*Major Goals:* We will test the hypothesis that MHC class I-like proteins contribute to the risk of colorectal cancer development. We will conduct a secondary data analysis in the Atherosclerosis Risk in the Community cohort using existing information on six plasma MHC class I-like proteins measured three times over 20 years of follow-up, genotyping data in MHC class I-like genes and data about CRC and its risk factors.

*Role:* Co-I

*Overlap:* None

*Agency Contact:* Program Official: Danielle M Carrick

Grants Closed:

U2CES026533 (Peterson/Hecht) 9/1/2015 – 8/31/2019 0.6 calendar months
NIH/NIEHS $871,098 direct costs/year

**Minnesota CHEAR Exposure Assessment Hub**

*Major Goals:* To provide children's health researchers with access to state-of-the-art infrastructure for both targeted and untargeted analysis of biological samples as well as characterization of biological responses associated with those exposures.

*Specific Aims:*

1) This resource will provide a reliable platform for conducting timely and comprehensive metabolite analyses of biological samples.

2) This resource will conduct comparative analysis of metabolomic data based on the classification or stratification information on samples.
3) This resource will guide research efforts on new exposure markers in the development core and to deposit data in the data repository, analysis and science center.
*Role:* Co-Investigator
*Overlap:* None
*Agency Contact:* Program Official: David M Balshaw

5R01CA122320-10 (Turesky) 8/1/2014 – 7/31/2019 0.3 calendar months
NIH/NCI $294,011 direct costs/year
**Chemical markers of heterocyclic aromatic amines for human biomonitoring**
*Major Goals:* The major goals of this project are to establish biomarkers (DNA and Protein Adducts and urinary metabolites) of heterocyclic amines for human biomonitoring studies.
*Specific Aims:*
1) HAA exposure will be assessed by measurement of HAAs accrued in hair;
2) Formalin-fixed paraffin embedded prostate tissue, an underutilized biospecimen in biomonitoring DNA damage, will be employed to screen for HAA-DNA adducts in subjects undergoing prostatectomy.
3) We will conduct high density genotyping of genes encoding enzymes involved carcinogen metabolism that may impact DNA damage in the prostate.
*Role:* Co-Investigator
*Overlap:* None
*Agency Contact:* Program Official: Harold E Siefried

**Rachel Vogel**
New Active Support:
1R03HS026982-01 (D. Teoh) 07/01/19-06/30/21 0.36 calendar months
Agency for Healthcare Research and Quality $54,765
**Optimizing cervical cancer screening for HPV-vaccinated women: Evaluation of post-vaccination cervical cancer screening test**
*Major Goals:* The objectives of this pilot research are to 1) determine if the prevalence of HPV infection and cervical dysplasia have decreased with HPV vaccination and resultantly changed the PPV of cervical cancer screening tests, and 2) determine if cervical cancer screening test accuracy varies by age at HPV vaccine initiation, number of doses, or interval between HPV vaccine doses.
*Specific Aims:*
(1) Determine if the decrease in prevalence of HPV infection and cervical dysplasia among vaccinated women has resulted in a decrease in the positive predictive value of cervical cancer screening tests.
(2) Determine if cervical cancer screening test accuracy varies by age at vaccine initiation, number of doses received, and/or interval between doses.
*Role:* Biostatistician
*Overlap:* None
*Agency Contact:* Steven W. Young, Grants Management Specialist; steven.young@ahrq.hhs.gov

133512-RSG-19-014-01-CPPB Research Scholar Grant (R.I. Vogel)
American Cancer Society 07/01/19 – 06/30/23 2.4 calendar months
$165,000
**Wearable Device Intervention to Improve Sun Behaviors in Melanoma Survivors**
*Major Goals:* The goal of this project is to test whether a wearable UVR-sensor enabled technology device and corresponding mobile application improve sun protection behaviors and reduce sun exposure among melanoma survivors.
*Specific Aims:*
(1) Evaluate the effectiveness of a UVR-sensor wearable device intervention to improve sun protection behaviors and reduce sunburns in a randomized controlled trial in melanoma survivors.
*Role:* Principal Investigator
*Overlap:* The Melanoma Research Alliance pilot grant budget was updated starting 6/1/2019 and the scientific aims were modified to ensure synergy between the two funded projects.
*Agency Contact:* Ellie Daniels, MD, MPH, Scientific Director, Cancer Prevention and Control Research

ellie.daniels@cancer.org

1P01CA234228-01A1 (R. Harris, D. Yee) 07/01/19-06/30/24 1.20 calendar months
National Institutes of Health, NCI $1,331,894
**APOBEC mutagenesis in breast cancer**
*Major Goals:* The goal of this proposed work is to take a multidisciplinary approach to better understand the mechanism of APOBEC mutagenesis in breast cancer, with the goal of diagnosing and improving treatments for patients whose tumors are fueled by this process.
*Specific Aims:*

- Project 1 will develop a cell-autonomous APOBEC activity reporter and delineate mechanisms responsible for APOBEC regulation at the protein level and for genomic uracil (mis)repair.
- Project 2 will leverage chemical biology techniques to characterize APOBEC–ssDNA molecular recognition and to develop novel chemical probes that directly inhibit APOBEC activity in breast cancer cells.
- Project 3 will use structural biology approaches to investigate the mechanisms by which APOBEC enzymes deaminate DNA cytosines within specific trinucleotide contexts and how these activities may be inhibited.

*Role:* Biostatistician
*Overlap:* None
*Agency Contact:* Jacquelyn Saval, Administrative Contact; savalj@mail.nih.gov

Grants Closed:
NIH/NCI P30CA77598 (D. Yee) 02/01/14-01/31/24 1.20 calendar months
National Institutes of Health, National Cancer Institute $2,342,880
**Cancer Center Support Grant**
*Major Goals:* To provide an infrastructure for cancer research, education and patient care for the citizens of the Minnesota and the surrounding region. Our mission is to create a collaborative environment that advances knowledge about the causes, prevention, detection and treatment of cancer.
*Role:* Biostatistician
*Overlap:* This funding is to cover unfunded statistical analyses; this funding is reduced or removed to accommodate funded projects.
*Agency Contact:* Sonya Roberson, NIH/NCI Office of Cancer Centers, Program Official robersos@mail.nih.gov

RSG-14-151-01-CCE (M. Geller) 01/01/15–12/31/19 0.36 calendar months
American Cancer Society $165,000
**Natural Killer Cell Immunotherapy for Ovarian Cancer**
*Major Goals:* The objective of this project is to create a next-generation immunotherapy product by expressing an anti-mesothelin chimeric antigen receptor (CAR) in iPSCs to generate targeted NK cells with increased ability to kill human ovarian cancer cells.
*Specific Aims:*

(1) Express an anti-mesothelin chimeric antigen receptor (CAR) in human induced pluripotent stem cells (iPSCs) to create targeted NK cells with increased ability to kill human ovarian cancer cells.
(2) Evaluate in vivo anti-ovarian cancer activity of NK cells derived from human iPSCs expressing anti-mesothelin chimeric receptors.
(3) Evaluate the in vivo effectiveness of combining an indoleamine-2,3-dioxygenase (IDO) inhibitor with NK cells. IDO is a key enzyme expressed by ovarian cancer as well as other solid tumors.

*Role:* Biostatistician.
*Overlap:* None
*Agency contact:* William C. Phelps, PhD*;* William.Phelps@cancer.org

W81XWH-17-1-0445 (M. Bazzaro) 09/01/17-08/31/21 0.60 calendar months
Department of Defense Ovarian Cancer Research Program $387,855
**Breaking Off Cancer Cell's Addiction to Prevent and Treat Recurrent Ovarian Cancer**
*Major Goals:* The goal of this study is to understand whether USP14/UCHL5 are responsible for ovarian cancer recurrence and chemoresistance to aid in the clinical management of ovarian cancer
*Specific Aims:*

(1) Determining whether USP14 expression levels and activity profile are associated with ovarian cancer chemoresistance.
(2) Determine the biological relevance of USP14/UCHL5 and their inhibition in the context of chemoresistant ovarian cancer.
(3) Determine whether the FDA approved USP14 inhibitor VLX1570 can be used as a maintenance therapy to prevent ovarian cancer recurrence.
(4) Determine whether the FDA approved small-molecule USP14 inhibitor VLX1570 can be used alone or in combination with standard chemotherapy to treat chemoresistant ovarian cancer.

*Role:* Biostatistician.
*Overlap*: None
*Agency Contact:* Susan M. Dellinger, Grants Officer; susan.dellinger@us.army.mil

**Melissa Geller**
New Active Support:
WS00336369-W81XWH-19-OCRP-IIRA (Geller, M) 09/01/2020-08/31/2023 1.2 calendar months
2019 DOD OCRF Investigator Initiated $450,000 total direct costs (all years)
**Manipulating the ovarian cancer tumor microenvironment to enhance natural killer (NK) cell killing**
*Goal:* Determine the effect that IL-15 can rescue NK cell function and expansion in the ovarian cancer tumor microenvironment as well as to generate immunotherapeutic molecules.
*Role:* Principle Investigator
*Overlap*: None
*Agency Contact:* Karen Wylie, Ph.D, Science Officer/Health Science Program Manager
karen.m.wylie.civ@mail.mil

Grants Closed:
RSG-14-151-01-CCE (Geller, M) 1/01/15 – 12/31/19 2.4 calendar months
American Cancer Society $660,000 total direct costs (all years)
**Natural Killer Cell Immunotherapy for Ovarian Cancer**
*Major Goals:* We are developing an anti-mesothelin chimeric antigen receptor (CAR) in iPSCs to produce a targeted NK cell population effective against ovarian cancer, where 70% of tumors express mesothelin. Our goal is for CAR-expressing NK cells to be used as a readily available, "off-the-shelf" product for anti-tumor immunotherapy.
Specific Aims:
1) Express an anti-mesothelin chimeric antigen receptor (CAR) in human induced pluripotent stem cells (iPSCs) to create targeted NK cells with increased ability to kill human ovarian cancer cells.
2) Evaluate in vivo anti-ovarian cancer activity of NK cells derived from human iPSCs expressing anti-mesothelin chimeric receptors.

*Role:* Principal Investigator
*Overlap:* None
*Agency contact:* William C. Phelps, PhD

- **What other organizations were involved as partners?**
  *Not applicable*

**8. SPECIAL REPORTING REQUIREMENTS**
*Not applicable*

**9. APPENDICES:** None