AWARD NUMBER: W81XWH-22-1-1101

TITLE: Stromal Drivers of Ovarian Cancer Initiation

PRINCIPAL INVESTIGATOR: Lan G Coffman, MD, PhD

CONTRACTING ORGANIZATION: University of Pittsburgh, Pittsburgh, PA

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6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Purpose: Our overall goal is to define how cancer-supportive stromal cells contribute to high grade serous cancer initiation in order to develop improved early diagnostic and therapeutic strategies for high grade serous ovarian cancer.
Scope: We proposed three specific aims. Aim 1 is to perform cellular mapping to determine the abundance and spatial relationship of hrMSCs to p53 signature, serous tubal intraepithelial carcinoma (STIC) and invasive cancer in BRCA wild type and BRCA mutant fallopian tubes. Aim 2 is to assess the acquisition of malignancy-associated molecular changes in hrMSC-marked epithelium. Aim 3 is to assess the impact of hrMSCs on epithelial precursor lesion transformation.Major findings: To date, we have collected fallopian tube samples from BRCA wild type and BRCA mutant fallopian tubes and quantified the presence of hrMSCs in 20 samples. We have found hrMSC abundance is correlated with increasing age and is more prevalent in BRCA mutant fallopian tubes. We have obtained matching FFPE tissue and for Vectra multispectral analysis and digital spatial profiling. The Vectra imaging is complete and DSP is being analyzed by the bioinformatics team. Significance: Collectively, our work supports the hypothesis that stromal changes within the fallopian tube support high grade serous ovarian cancer initiation. This work is critical to understanding the pathogenesis of high grade serous ovarian cancer and the development of screening and early detection strategies for this deadly disease.

15. SUBJECT TERMS

None listed.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRDC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	25	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

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1 INTRODUCTION:

There are currently no effective early diagnostic tests for ovarian cancer. As a result, approximately 75% of patients with high grade serous ovarian cancer (HGSC) are not diagnosed until advanced stages when treatment is unlikely to be curative. Identifying women with early or precursor stage HGSC is thereby essential to saving the lives of women with HGSC, however the development of effective diagnostic and screening strategies have been hindered by an incomplete understanding of HGSC initiation. The current paradigm of HGSC carcinogenesis suggests that most ovarian cancers arise from fallopian tube epithelial precursor lesions called serous tubal intraepithelial carcinomas (STICs) that only later go on to progress into invasive carcinomas that are able to quickly metastasize to the ovary and surrounding tissues. However, which factors mediate the development and progression of these precursor lesions into invasive disease remains a critically-unresolved question. In our recent studies, we have uncovered strong evidence that HGSC and its associated precursor lesions develop, not only through changes in epithelial cells, but also through distinct, cancer-specific alterations in the surrounding stromal cells. Thus, our overall goal is to define how these cancer-supportive stromal cells contribute to HGSC initiation in order to develop improved early diagnostic and therapeutic strategies for HGSC. We found that stromal cells which support cancer growth, termed 'high risk mesenchymal stem cells' (hrMSCs) preceded the formation of HGSC and may play a critical role in HGSC initiation. We hypothesize that hrMSCs develop in fallopian tube stroma of women at high risk of developing HGSC where they facilitate epithelial transformation that ultimately lead to the progression of precursor lesions into invasive HGSC. We proposed 3 aims to test this hypothesis: 1) Perform cellular mapping to determine the abundance and spatial relationship of hrMSCs to p53 signature, STIC and invasive cancer in BRCA wild type and BRCA mutant fallopian tubes. 2) Assess the acquisition of malignancy-associated molecular changes in hrMSC-marked epithelium. 3) Assess the impact of hrMSCs on epithelial precursor lesion transformation.

2 KEYWORDS:

Ovarian cancer

STIC

Mesenchymal stem cell

Early detection

Stromal

Cancer initiation

3 ACCOMPLISHMENTS:

Aim 1. Perform cellular mapping to determine the abundance and spatial relationships of hrMSCs to p53 signatures, STIC and invasive cancer in BRCA wild type and BRCA mutant fallopian tubes

Major Task 1: Determine the abundance and location of hrMSCs in fallopian tubes.

Subtask 1: IRB approval for collection of human samples already received. Timeline: 0 months

IRB approval obtained

Subtask 2: Obtain DoD HRPO approval. Timeline: 1-3 months

DoD HRPO approval obtained

Subtask 3: Obtain DoD ACURO approval prior to any animal related tasks. Timeline: 1-3 months

All ACURO documents have been approved

Subtask 3: Collect fresh FT specimens from women at standard risk and high risk of ovarian cancer for flow cytometry quantification of MSCs (bulk, normal and hrMSCs). Timeline: 1-18 months

We continue our collection of fallopian tubes from women at high risk of ovarian cancer (BRCA mutation carriers) and those at standard risk (BRCA wild type). We have collected 18 fallopian tubes from high risk women and 15 fallopian tubes from standard risk women. We are continuing to increase our collection. We have used flow cytometry, RT-qPCR and western blot to quantify and phenotype the MSC populations from these patients. The portion of this data is presented in figure 1A, B demonstrating a larger proportion of fallopian tubes from women with BRCA mutations contain hrMSCs (33% vs 0%).

Subtask 4: Collect and section matching FFPE tissue from the fresh specimens collected in subtask 3 to evaluate for the presence of tubal lesions including invasive carcinoma, STIC and p53 signatures. Timeline: 3-18 months.

We have obtained the matching FFPE tissue from all the specimens collected in subtask 3. One case contained a p53 signature and one contained a STIC (Fig1C).

Subtask 5: Isolate MSCs from fresh FT specimen collected in subtask 3 for single cell RNA sequencing. Timeline: 1-18 months.

Cells have been isolated and prepared for single cell sequencing.

Subtask 6: Perform single cell RNA sequencing. Timeline: 4-12 months.

The process of single cell RNA sequencing is underway however this has not yet been completed.

Subtask 7: Analyze single cell RNA sequencing to determine the presence of subpopulations of hrMSCs. Timeline: 11-12 months.

Single cell RNA sequencing analysis is pending completion of subtask 6 (performing single cell sequencing).

Subtask 8: Vectra multispectral imaging of FFPE samples from subtask 4 with spatial relationships between hrMSC and precursor lesions quantified. Timeline: 12-20 months.

We have completed the Vectra multispectral imaging and performed analysis of spatial relationships between hrMSCs and the STIC lesion (Fig1D). We demonstrate a significant enrichment in hrMSCs

surrounding and adjacent to STIC lesions consistent with a 'field effect' of altered stroma in the STIC microenvironment.

A)

Age	BRCA mutation	classifier	hrMSC	nMSC
50	BRCA 2	0.01434	0	1
50	BRCA 2	0.95237	1	0
45	BRCA 2	0.12168	0	1
45	BRCA 2	0.99017	1	0
40	BRCA 1	0.03154	0	1
40	BRCA 1	0.05052	0	1
60	BRCA 2	0.99633	1	0
30	BRCA 2	0.04912	0	1
30	BRCA 2	0.39092	1	1
55	BRCA 2	0.81	1	1
55	BRCA 2	0.76785	1	1
50	BRCA 1	0.94384	1	0
50	none	0.146	0	1
75	none	0.102	0	1

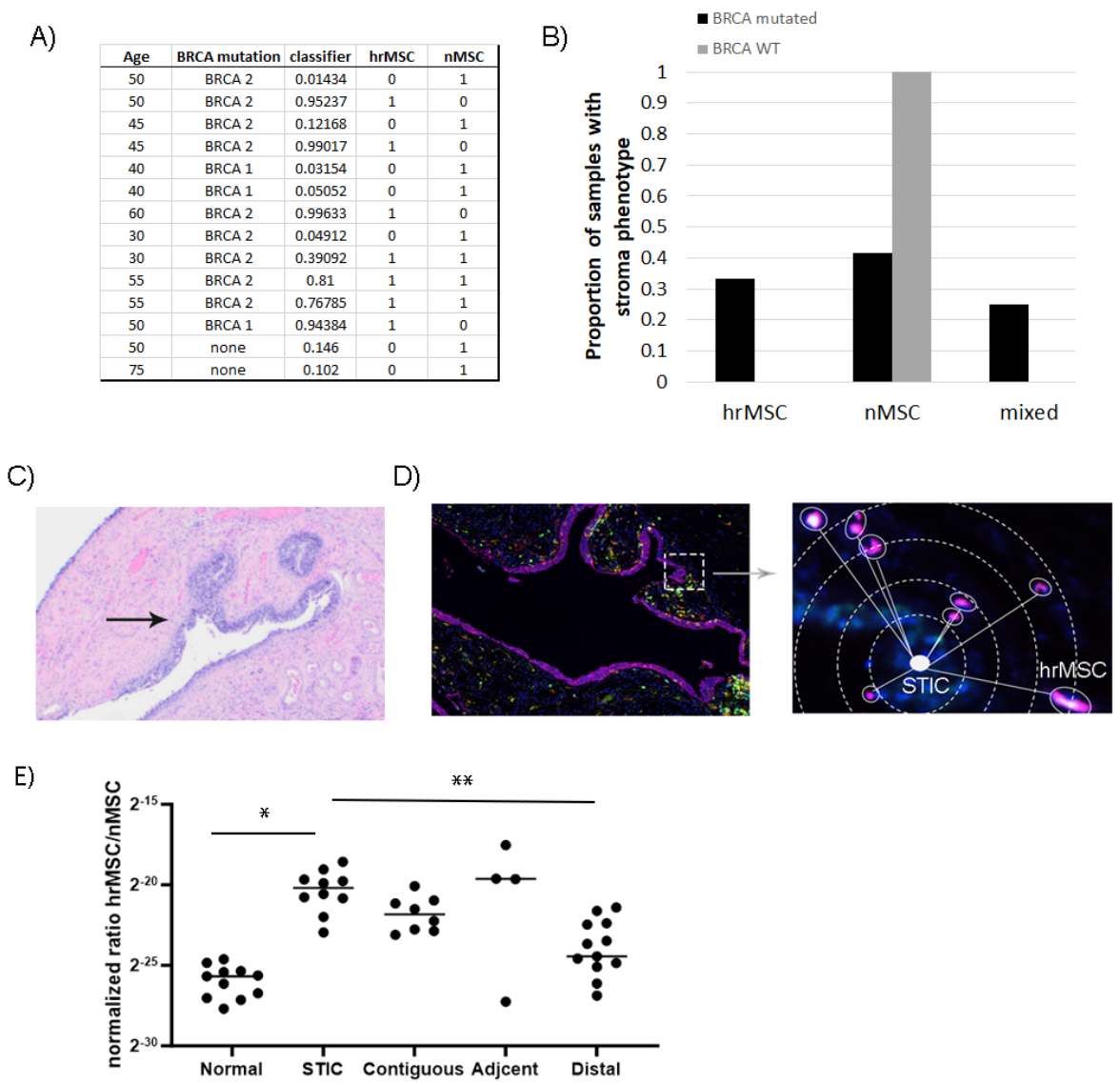


Figure 1. Analysis of hrMSCs within fallopian tubes. A) List of patient samples and the characteristics of the MSC abundance. Age and BRCA carrier status are displayed. The CA-MSC classifier was run on all isolated MSCs, a score of >0.96 indicates a high risk or cancer-promoting phenotype and a score of <0.3 indicates a normal MSC. If hrMSCs or nMSCs were detected, '1' is noted. If both hrMSCs and nMSCs were detected, a '1' is noted in each column and the sample is labeled 'mixed'. B) Quantification of the proportion of BRCA mutated vs BRCA wildtype fallopian tubes that contain hrMSCs vs nMSC or a mixed population. C) H&E of fallopian tube demonstrating a STIC (black arrow). D) Vectra imaging of a fallopian tube with a STIC lesion and spatial quantification of hrMSCs surrounding the STIC (second panel). E) Quantification of the ratio of hrMSC to normal MSCs in regions surrounding STIC or normal fallopian tube epithelium (normal: stroma in normal fallopian tube. STIC: stroma underlying STIC regions. Contiguous: stroma underlying 20 cells surrounding STIC

regions. Adjacent: stroma underlying cells <2mm from STIC lesion. Distal: stroma underlying cells <2cm from STIC region.

Milestone (s) Achieved: Complete quantification and spatial mapping of hrMSCs in standard and high risk FTs. Submit manuscript 1. Timeline: 20-24 months.

We have successfully started our sample acquisition and processing. We have collected and quantified the presence of hrMSCs in 32 samples. We have obtained all the necessary material for the proposed single cell sequencing and have completed the Vectra analysis. We are currently preparing the manuscript and anticipate submitting within 1-2 months.

Aim 2. Assess the acquisition of malignancy-associated molecular changes in hrMSC-marked epithelium.

Major Task 2: Characterize RNA expression and DNA methylation changes in hrMSC associated epithelium

Subtask 1: Analyze histologic changes in epithelium associated with hrMSC. Timeline: 18-24 months.

We have obtained FFPE sections from 15 standard risk and 18 high risk patients without pathologic epithelial lesions. We have now meet our goal of N=12 per group.

Subtask 2: Assess the RNA expression profile of 1833-malignancy related genes in epithelium associated with hrMSCs using the Nanostring digital spatial profiler. Timeline: 24-36 months.

We have successfully piloted this technology and can reliably segment the fallopian tube epithelium for digital spatial profiling. As demonstrated in Figure 2A, we are able to define selected regions of interest from the fallopian tube section (yellow box) and within that region of interest, select the epithelial cells (based on panCK positive stain) and the associated stromal cells (negative for pan CK and negative for CD45). We have collected DSP data from 18 samples at this point and are in the process of analyzing the data.

Subtask 3: Determine the DNA methylation profile of epithelium associated with hrMSCs after laser capture microdissection. Timeline: 24-30 months.

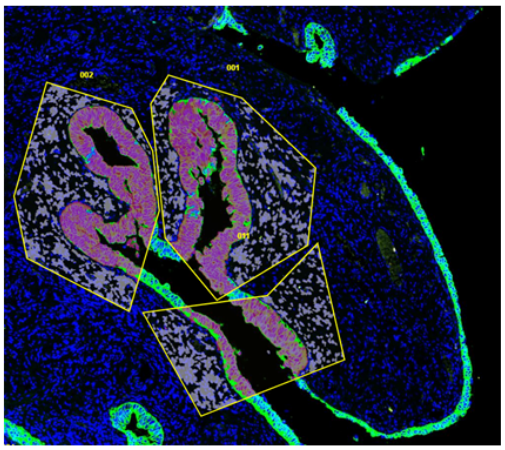
We have successfully optimized laser capture microdissection (LCM) on fallopian tube FFPE samples. We have performed LCM on 6 samples thus far with ongoing collection.

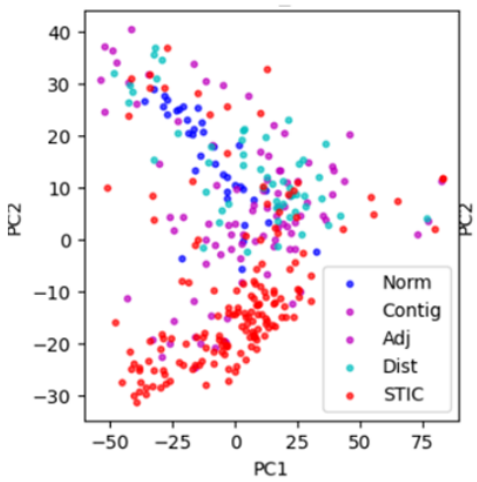
Subtask 4: Analyze DNA methylation data from subtask 3 and compare data to STIC and invasive cancer profiles. Timeline: 30-32 months.

The pipeline is set up for this analysis once subtask 3 is completed.

Subtask 5: Identification of DNA methylation biomarkers shared by hrMSC-marked epithelia and STIC lesion. Timeline: 32-36 months.

This subtask is dependent on the completion of subtask 3 and 4. We have all the necessary tools and expertise to perform this analysis once subtasks 3 and 4 are complete.





yellow box=selected region of interest
pink mask within yellow box=panCK+ epithelial cells
gray mask within yellow box=CD45- stromal cells

Figure 2. Digital spatial profiling. Graphic of region of interest selection and identification of epithelium and stroma within the selected region of interest. PCA plot of the different ROIs in normal vs STIC lesions.

Milestone (s) Achieved: Identification of molecular changes in epithelium with cancer supportive stroma. Biomarker identification based on changes in hrMSC associated epithelium. Submit manscript two. Timeline: 36-40.

We have accomplished the optimization of digital spatial profiling on fallopian tube FFPE samples and LCM of these same samples and have started processing samples. These techniques are critical to the success of this aim and achieving these milestones. We are on track for completing these milestones in the proposed timeline.

Aim 3. Assess the impact of hrMSCs on epithelial precursor lesion transformation.

Major Task 3: Determine how hrMSCs support epithelial cell transformation.

Subtask 1: Determine if hrMSCs alter epithelial cell growth. Timeline: 36-40 months.

We have determined the impact of hrMSCs on primary fallopian tube epithelial cell growth. We have successfully grown both primary patient hrMSCs and fallopian tube epithelium. We demonstrate that hrMSCs increase the growth of fallopian tube epithelial cells under both 2D culture and spheroid/non-adherent conditions (Figure 3A).

Subtask 2: Determine if hrMSCs induce genomic changes in epithelial cells. Timeline 36-46 months.

We also have investigated the impact of hrMSCs on genomic changes in primary patient fallopian tube epithelial cells. We demonstrate that hrMSCs (compared to matched normal MSCs derived from the

same patient) induce significant DNA damage in fallopian tube epithelial cells. Using qH2AX and 53BP1 as markers of DNA damage, Figure 3B illustrates that hrMSCs increase the number of 53BP1 foci in co-culture epithelial cells. 53BP1 accumulates at sites of DNA double strand breaks to facilitate nonhomologous end-joining. Additionally, hrMSCs increase the intensity of gH2A in co-cultured epithelial cells. gH2AX is an early response to DNA double-strand breaks and serves as another piece of evidence that hrMSCs are inducing DNA damage in epithelial cells.

Subtask 3: Asses the hrMSC-induced methylation changes in the organoid system. Timeline 36-40 months.

We have not begun to assess methylation changes in this system yet. The organoid co-culture system has been established and we have validated methods for assessing DNA methylation so we are fully prepared to perform these experiments.

Subtask 4: Determine if hrMSCs lead to epithelial cell tumor initiation. Timeline 3-46 months.

ACURO approval has been approved. We demonstrate that long term co-culture of hrMSCs with FTE results in full malignant transformation of FTE. We demonstrate that only FTE co-cultured with hrMSCs and not normal MSCs or FTE grown alone or hrMSCs grown alone initiate tumors in 3 of 6 tumors. We resected these tumors and demonstrate the isolated human epithelial cells have behavior characteristic of tumor cells including increased proliferation and chemotherapy resistance. Additionally, verifying full malignant transformation, these isolated cells initiate secondary tumors.

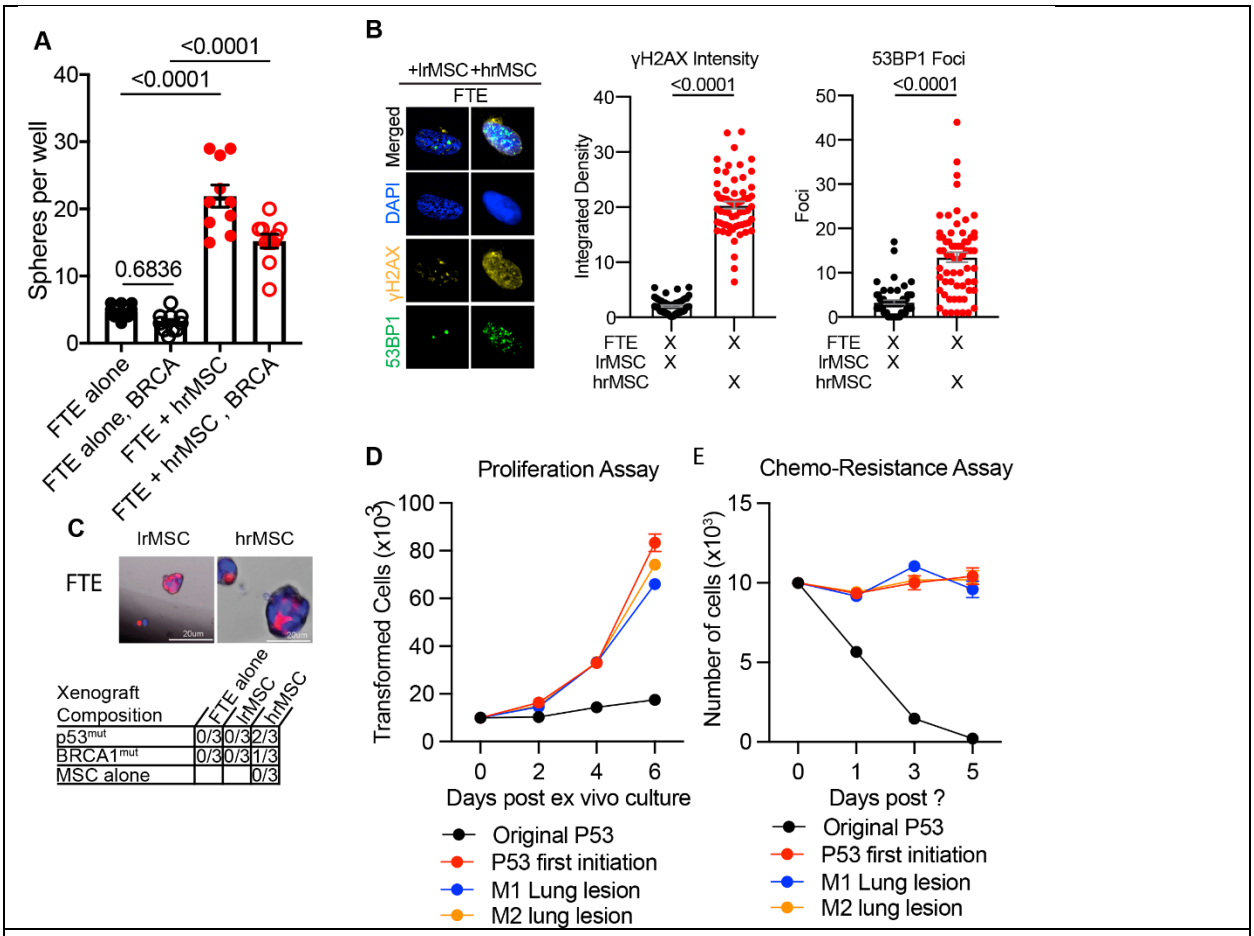


Figure 3. hrMSCs induce fallopian tube epithelial (FTE) cell malignant transformation. A) hrMSCs increase the growth of FTE under sphere conditions. Growth of FTE derived from wild type or BRCA carrier patients have enhanced proliferation under spheroid conditions when grown with hrMSCs. B) hrMSCs induce DNA damage in FTE. hrMSCs co-cultured with FTE induce DNA damage as measured by gH2AX intensity and 53BP1 foci formation. normal MSC (nMSC) co-culture is used as a comparison. C) long-term co-culture of hrMSC with FTE followed by injection into NSG mice results in tumor initiation in 3/6 xenografts. D) Isolation of human epithelium which initiated tumors demonstrate increased proliferation and chemotherapy resistance when grown ex vivo.

<u>Milestone (s) Achieved: Define the impact of hrMSCs on epithelial transformation. Manuscript 3 submission and new grant applications base upon preliminary data.</u> Timeline 46-48 months.

We have begun to perform the critical experiments necessary to achieve these milestones. We have demonstrated hrMSCs enhance epithelial cell proliferation and that hrMSCs induce epithelial cell DNA damage. Most importantly, we demonstrate long-term co-culture with hrMSCs induces full malignant transformation in FTE.

<u>Training and professional development:</u>

This work provided a post-doc, Dr. Huda Atiya, with significant one-on-one training with her mentor, Dr. Lan Coffman. This work also enhanced the professional development of Dr. Atiya and facilitated collaborations with our co-investigators Dr. Soong, Dr. Pisanic and Dr. Bao. This work was presented at the 2022 and 2023 annual Hillman Scientific Retreat.

Result dissemination:

Nothing to report

Plan for next reporting period:

We plan to complete the remainder of Aim 1 and Aim 3. We plan to disseminate our results once published by working with the Hillman Cancer Center public relations team to create press releases to inform the community of our work.

4 IMPACT:

Our results have impacted our knowledge of the stromal support of ovarian cancer initiation. We have made significant strides in understanding how stromal cells have a cancer supportive phenotype prior to cancer initiation and may plan a critical role in cancer formation.

Impact on other disciplines:

This work will impact other disciplines as these findings are likely generalizable to other cancer types and represent a novel mechanism of stromal driven tumor initiation.

Impact on technology transfer:

Nothing to report

Impact on society beyond science and technology:

Nothing to report

5 CHANGES/PROBLEMS:

Changes in approach and reasons for change:

No significant changes were made to the approach

Problems or delays and actions or plans to resolve them:

No significant delays.

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

No changes were made.

6 PRODUCTS:

Publications, conference papers and presentations:

Poster presentation at the 2022 Hillman Scientific Retreat

7 PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project:

Name:	**Lan Coffman**
Project Role:	PI
Researcher Identifier (ORCID ID)	0000-0002-3753-1652
Nearest person month worked:	1.2
Contribution to Project:	Dr. Coffman has been overseeing the experimental design and data interpretation. She has also managing the contributions of the collaborating investigators.
Funding Support	NA
Name:	**Huda Atiya**
Project Role:	Post-doctoral fellow

Researcher Identifier (ORCID ID)	0000-0001-9850-102X
Nearest person month worked:	3.45
Contribution to Project:	Dr. Atiya has been performing the proposed experiments'
Funding Support	NA
Name:	**Thomas Pisanic**
Project Role:	Co-investigator
Researcher Identifier (OCID ID)	0000-0001-5796-0836
Nearest person month worked:	1CM
Contribution to Project:	Dr. Pisanic has been contributing to experimental design/planning and assay optimization.

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

See attached OS document for the PI

What other organizations were involved as partners?

Organization Name: Johns Hopkins University

Location of Organization: (if foreign location list country) Baltimore, Maryland

Partner's contribution to the project (identify one or more)

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);

Dr. Pisanic oversees all aspects of the DNA methylation assays and guides associated staff on the corresponding data analyses, as needed. He will also aid in the training and supervision of personnel involved in the epigenetic aspects of the proposed work. Lastly, he will aid in the bioinformatic analysis and interpretation of scRNA-seq data.

8 SPECIAL REPORTING REQUIREMENTS:

None

9 APPENDICES:

None

PHS OTHER SUPPORT
For All Application Types – DO NOT SUBMIT UNLESS REQUESTED

Name of Individual: Coffman, LG
Commons ID: COFFMANLAN

Other Support – Project/Proposal

ACTIVE

Title: NCI NCTN-Network Lead Academic Participating Site at UPMC Hillman Cancer Center

Major Goals: The goal of the National Clinical Trials Network (NCTN) Lead Academic Participating Site at UPMC Hillman Cancer Center, is to increase our level of participation in conceptualization, development, activation, performance, and reporting of the late-phase clinical trials of the NRG Oncology, ECOG-ACRIN, and Alliance for Clinical Trials in Oncology Network Groups.

Status of Support: Active

Project Number: UG1 CA233184

Name of PD/PI: Brufsky, Adam

Source of Support: NIH/NCI

Contracting/Grants Officer: Margaret M Mooney, mooneym@mail.nih.gov

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 03/01/19-02/28/25

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
03/01/23-02/28/24	0.60 calendar months
03/01/24-02/28/25	0.60 calendar months

Title: Targeting Stromal to Tumor Cell Mitochondrial Transfer in Ovarian Cancer Metastasis (OC200282)

Major Goals: The goal of this proposal is to understand the mechanism and impact of CA-MSC to cancer cell mitochondrial transfer on ovarian cancer metastasis

Status of Support: Active

Project Number: W81XWH-21-1-0371

Name of PD/PI: Coffman, Lan

Source of Support: DOD

Contracting/Grants Officer: Chris Baker christopher.l.baker132.civ@mail.mil
Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 05/15/21 – 11/14/23 (NCE)

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
05/15/23-11/14/23	0.60 calendar months

Title: Defining the impact of stromal aging on ovarian cancer initiation

Coffman, Lan
Major Goals: The goal of this proposal, in direct response to the request for application, is to define the impact of aging on interactions between stromal cells and cancer initiating cells (CIC) that drive ovarian cancer formation.

Status of Support: Active

Project Number: U01 AG077923

Name of PD/PI: Coffman, Lan

Source of Support: NIH

Contracting/Grants Officer: Jillian Morris morrisjil@mail.nih.gov
Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 09/30/21-05/31/26

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
09/30/23-05/31/24	1.20 calendar months
09/30/24-05/31/25	1.20 calendar months
09/30/25-05/31/26	1.20 calendar months

Title: EZH2-mediated epigenetic reprogramming of ovarian cancer stroma

Major Goals: The goal of this research is to understand how ovarian cancer reprograms normal MSCs into CA-MSCs to support ovarian cancer and to develop strategies to block or reverse CA-MSC reprogramming as a new way to fight this disease

Status of Support: Active

Project Number: RSG-21-113-01-MM

Name of PD/PI: Coffman, Lan

Source of Support: American Cancer Society

Contracting/Grants Officer: greta.mcshan@cancer.org

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 1/1/22 – 12/31/25

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
01/01/23 – 12/31/23	2.40 calendar months
01/01/24 – 12/31/24	2.76 calendar months
01/01/25 – 12/31/25	2.76 calendar months

Title: Stromal biomarkers for enhanced detection of early-stage ovarian cancer
Major Goals: Aim 1: Define the extent of the stromal field effect relative to STIC location and identify stroma-specific DNA methylation changes associated with STIC lesions. Aim 2: Design locus-specific assays for the top regions of STIC-stroma-specific DNA methylation and preliminarily assess their performance in liquid biopsies.

Status of Support: Active

Project Number: DB3 / 204110216.2

Name of PD/PI: Coffman, Lan

Source of Support: The Honorable Tina Brozman Foundation

Coffman, Lan
Contracting/Grants Officer: Beverly Wolfer (bwolfer@tinaswish.org)

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 1/1/22 – 12/31/23

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
01/01/23 – 12/31/23	1.2 calendar months

Title: Regulation of mitochondrial redox homeostasis and signaling in metastatic ovarian cancer

Major Goals: The proposal will test the hypothesis that mitochondrial redox signaling is an important regulator of survival adaptations in response to matrix detachment, and that two key mitochondrial proteins, SIRT3 and Sod2, are required for the initiation and regulation of mitochondrial redox signaling in anchorage-independence.

Status of Support: Active

Project Number: R01 CA242021
Name of PD/PI: Hempel, Nadine

Source of Support: NCI

Contracting/Grants Officer: Joseph Allen; joe.gipson@nih.gov

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 07/01/21-03/31/25

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
07/01/23-03/31/24	0.12 calendar months
07/01/24-03/31/25	0.12 calendar months

Title: The DOD Omics Consortium to Study the Origins of Ovarian Cancer (DOCSOOC)

Major Goals: The goal of this proposal is define the evolution of ovarian cancer precursor lesions though multiple ‘omics approaches to develop novel strategies for early detection of ovarian cancer.

Status of Support: Active

Project Number: OC210403

Name of PD/PI: Ronald Drapkin, site PI: Lan Coffman

Source of Support: DOD

Contracting/Grants Officer: Jason Kuhns; jason.d.kuhns.civ@mail.mil

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 8/15/22-7/31/2026

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
8/15/23-7/31/2024	.60 calendar months
8/15/24-7/31/2025	1.20 calendar months
8/15/25-7/31/2026	1.20 calendar months

Coffman, Lan
Title: Stromal Drivers of Ovarian Cancer initiation

Major Goals: The goal of this proposal is to define how cancer-supportive stromal cells contribute to high grade serous ovarian cancer initiation to improve early diagnosis and therapeutic strategies.

Status of Support: Active

Project Number: OC210139

Name of PD/PI: Coffman, Lan

Source of Support: DOD

Contracting/Grants Officer: Abigail Strock; abigail.l.strock.civ@health.mil

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 09/30/22-09/29/2026

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
09/30/23-09/29/2024	1.20 calendar months
09/30/24-09/29/2025	1.80 calendar months
09/30/25-09/29/2026	1.80 calendar months

Title: Environmental pollutants contributing to the pathogenesis of small cell carcinoma of the ovary, hypercalcemic type in western Pennsylvania

Major Goals: Determine the impact of environmental pollutants on the development of small cell carcinoma of the ovary, hypercalcemic type.

Status of Support: Active

Project Number: 5P30CA047904-34
Name of PD/PI: Dr. Taylor

Source of Support: NCI

Contracting/Grants Officer: Coleen Cassidy @ cmc215@pitt.edu

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 01/01/23 – 12/31/2023

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
01/01/23 – 12/31/2023	.12 calendar months

Title: TLS-inducing Therapeutic in HGSOC
Major Goals: Identify critical factors that impact TLS development to leverage as novel immunotherapeutics in ovarian cancer.
Status of Support: Active

Project Number: SRA00003213

Name of PD/PI: Bruno, Tullia

Source of Support: UPMC

Contracting/Grants Officer: Long Nguyen; nguyen1@mail.nih.gov

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Coffman, Lan
Project/Proposal Start and End Date: 03/01/23 – 02/28/2024

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
03/01/23 – 02/28/2024	.12 calendar months

Title: HCC Ovarian Cancer SPORE

Major Goals: The goal of the UPMC HCC Ovarian Cancer SPORE is to improve the outcomes of patients with ovarian cancer.

Status of Support: Active

Project Number: P50CA272218-01A1

Name of PD/PI: Ronald Buckanovich; Robert Edwards

Source of Support: NIH/NCI

Contracting/Grants Officer: McGraw, Michael R., Michael.mcgraw2@nih.gov,

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 07/01/2023-06/30/2028

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
07/01/2023-06/30/2024	2.40 calendar months
07/01/2024-06/30/2025	2.40 calendar months
07/01/2025-06/30/2026	2.40 calendar months
07/01/2026-06/30/2027	2.40 calendar months
07/01/2027-06/30/2028	2.40 calendar months

Title: Tubal Immune Milieu and Tumor Precursor Evolution in the Development of High-Grade Serous Carcinoma

Major Goals: We hypothesize that TP53-mutated tubal epithelial lesions (ESPs, STIC, HGSC) are associated with an increasingly proinflammatory stromal phenotype, higher TP53 mutational burden and pathogenicity as tubal lesions advance with atypia, and that disruption of host T cell immune response accelerates the progression of TP53-mutated lesions into carcinoma. Using fallopian tubal tissue collected from women and transgenic mouse models, we will (1) examine TP53 mutational burden and profiles via Duplex Sequencing in benign and histologically abnormal fallopian tubes from human; (2) define stromal immune phenotypes in benign and histologically abnormal fallopian tubes from human and mouse models using multiplex immunofluorescence studies, RNA-based multiplex and digital spatial profiling.

Status of Support: Active

Project Number: Pending

Name of PD/PI: Soong, T. Rinda

Source of Support: US Army/DOD

Contracting/Grants Officer: Pending

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 09/30/23-09/29/27

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Coffman, Lan

Year	Person Months
09/30/23-09/29/24	0.60 calendar months
09/30/24-09/29/25	0.60 calendar months
09/30/25-09/29/26	0.60 calendar months
09/30/26-09/29/27	0.60 calendar months

COMPLETED:

Title: Targeting Tumor Desmoplasia to Enhance Immunotherapy
Major Goals: The role of tumor desmoplasia is controversial. This collaborative project will develop key data on the importance of CA-MSC in the generation of the immunosuppressive OvCa TME. Furthermore, these studies will evaluate the role of clinically relevant therapeutics in increasing the activity of immune checkpoint therapy. As such, these drugs could be directly translated into the clinic to increase the activity of these game-changing therapies.
Status of Support: Completed

Project Number: OCRFA-CRDG 2019

Name of PD/PI: Buckanovich, Ronald

Source of Support: Ovarian Cancer Research Fund Alliance

Contracting/Grants Officer: Emily Hickey, pcsupport@altum.com

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 01/01/2019 – 12/31/2021

Total Award Amount (including Indirect Costs):

Effort: 0.48 CM

Title: Defining the Formation and Function of Carcinoma-Associated Mesenchymal Stem Cells in the Ovarian Cancer Microenvironment
Major Goals: The goal of this project is to understand where CA-MSCs come from and how they function to enhance tumor growth thus providing clues necessary to developing treatments to block the cancer- promoting effects of these cells.

Status of Support: Completed

Project Number: 7K08CA211362-02

Name of PD/PI: Coffman, Lan

Source of Support: NIH

Contracting/Grants Officer: Susan Lim, lims@mail.nih.gov
Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 09/15/2016 – 02/28/2022

Total Award Amount (including Indirect Costs):
Effort: 7.20 calendar months

Title: Targeting the formation of carcinoma-associated mesenchymal stem cells to prevent the establishment of the ovarian cancer microenvironment
Major Goals: To inhibit the epigenetic reprograming of ovary MSCs into CA-MSCs thus preventing the formation of the TME and establishment of invasive ovarian cancer.

Status of Support: Completed

Project Number: RSG 2017-19 Rising Star Grant

Name of PD/PI: Coffman, Lan

Source of Support: The Honorable Tina Brozman Foundation

Coffman, Lan
Contracting/Grants Officer: Beverly Wolfer, bwolfer@tinaswish.org

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 11/01/2017 – 10/31/2019

Total Award Amount (including Indirect Costs):

Effort: 0.84 calendar months

Title: Investigating the Role of Carcinoma-Associated Mesenchymal Stem Cells in Ovarian Cancer Metastasis

Major Goals: To the role of CA-MSCs in ovarian cancer metastasis

Status of Support: Completed

Project Number: #19-18 2018 Research Grant Coffman

Name of PD/PI: Coffman, Lan

Source of Support: Mary Kay Foundation

Contracting/Grants Officer: Michal Lunceford, president

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 07/01/2018 – 06/30/2020

Total Award Amount (including Indirect Costs):

Effort: 1.80 calendar months (concurrent with K08)

Title: University of Pittsburgh Competitive Medical Research Fund
Major Goals: To understand the role of CA-MSCs in the promotion of ovarian cancer metastasis and the formation of the metastatic niche to improve treatment of ovarian cancer.

Status of Support: Completed

Project Number: CMRF Coffman

Name of PD/PI: Coffman, Lan

Source of Support: University of Pittsburgh

Contracting/Grants Officer: Selena Crawford, CMRF coordinator

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 07/01/2018 – 06/30/2020

Total Award Amount (including Indirect Costs):

Effort: 2.40 calendar months

Title: Investigating the impact of carcinoma-associated mesenchymal stem cells on the formation and function of the immune tumor microenvironment in ovarian cancer.

Major Goals: To determine the impact of CA-MSCs on immune cell recruitment and TLS formation within the ovarian tumor microenvironment

Status of Support: Completed

Project Number: HCC Development Pilot

Name of PD/PI: Coffman, Lan

Source of Support: Hillman Cancer Center

Coffman, Lan
Contracting/Grants Officer: Moria Hitchens; hitchensm2@upmc.edu

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 7/1/19-8/30/20

Total Award Amount (including Indirect Costs):

Title: Omics Consortium to Study the Origins of Ovarian Cancer

Major Goals: To develop the consortium infrastructure and a multi-institutional research team of scientists, clinicians, and ovarian cancer consumer advocates to establish new collaborations, initiate a research and communication plan, and formalize the organizational structure

Status of Support: Completed

Project Number: W81XWH-18-OCRP-OMCDA

Name of PD/PI: Coffman, Lan

Source of Support: DOD

Contracting/Grants Officer: N/A

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 6/1/19-5/31/21

Total Award Amount (including Indirect Costs):

Effort: 0.24 calendar months

Title: CCSG - Development
Major Goals: The goal of this award is to support the development and scientific mission of the cancer center
Status of Support: Completed
Project Number: P30 CA047904

Name of PD/PI: Coffman, Lan

Source of Support: NCI

Contracting/Grants Officer: Michael A. Marino, (301) 594-4330, mmarino@mail.nih.gov

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 08/01/17-04/30/20

Total Award Amount (including Indirect Costs):

Effort: 1.20 calendar months

Title: Phase I trial of ribociclib (ribociclib (LEE-011)) with platinum-based chemotherapy in recurrent platinum sensitive ovarian cancer
Major Goals: Determine the maximal tolerated dose of ribociclib in combination with carboplatin and taxol in platinum sensitive recurrent ovarian cancer

Status of Support: Completed

Project Number: Investigator initiated clinical trial

Name of PD/PI: Coffman, Lan

Source of Support: Novartis

Contracting/Grants Officer: John Sabo, john.sabo@novartis

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Coffman, Lan
Project/Proposal Start and End Date: 07/13/2018-12/31/2022

Title: Determine the effects of ALKS 4230 vs. recombinant IL-2 on immune cells in the tumor microenvironment in cancer patients
Major Goals: To determine the role of ALKS 4230 on the anti-cancer immune response in novel human models
Status of Support: Completed
Project Number: Effects of ALKS

Name of PD/PI: Bruno, Tullia

Source of Support: Alkermes, Inc

Contracting/Grants Officer: Alkermes, Inc

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 12/02/19-12/01/22

Total Award Amount (including Indirect Costs):

Effort: .12 calendar months

Title: Targeting stromal to cancer cell mitochondrial transfer in ovarian cancer metastasis
Major Goals: The goal of this proposal is to block CA-MSC to cancer cell mitochondrial transfer to inhibit ovarian cancer metastasis

Status of Support: Completed

Project Number: HCC Development Pilot

Name of PD/PI: Coffman, Lan

Source of Support: HCC

Contracting/Grants Officer: N/A

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 01/01/21-12/31/22

Total Award Amount (including Indirect Costs):

Title: Determining the Impact of Stromal: Immune Interactions in the Ovarian Cancer Tumor Microenvironment
Major Goals: The goal of this project is to define the stromal and immune interactions which modulate the immune microenvironment in ovarian cancer.

Status of Support: Completed

Project Number: CR13797

Name of PD/PI: Bruno, Tullia

Source of Support: Cancer Research Institute

Contracting/Grants Officer: grants@cancerresearch.org

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 07/01/21 - 06/30/23

Total Award Amount (including Indirect Costs):

Title: Targeting Tumor Desmoplasia to Enhance Immunotherapy

Coffman, Lan
Major Goals: This collaborative project will develop key data on the importance of CA-MSC in the generation of the immunosuppressive OvCa TME.

Status of Support: Completed

Project Number: OCRFA- 905993

Name of PD/PI: Ronald J. Buckanovich

Source of Support: Ovarian Cancer Research Fund Alliance

Contracting/Grants Officer:

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 1/1/22 – 12/31/23 (NCE)
Total Award Amount (including Indirect Costs):

PENDING:
Title: Defining the mechanism of stromal mediated iron dysregulation in ovarian clear cell cancer

Major Goals: The goal of this proposal is to identify the mechanism by which enMSCs dysregulate cancer cell iron homeostasis and determine the potential to therapeutically target this pathway in OCCC. Specific Aims: Aim 1: Define the mechanism by which CD10 loss enables enMSCs to export iron and support OCCC growth. Aim2: Delineate the mechanism of iron dysregulation in OCCC cells. Aim3: Utilize labile iron-specific drug release to therapeutically target OCCC

Status of Support: Pending

Project Number: 1R01CA288837-01

Name of PD/PI: Coffman, Lan

Source of Support: NCI/NIH

Contracting/Grants Officer: Chen, Scott A. chensc@mail.nih.gov,

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 04/01/24-03/31/29

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
04/01/24-03/31/25	3.60 calendar months
04/01/25-03/31/26	3.60 calendar months
04/01/26-03/31/27	3.60 calendar months
04/01/27-03/31/28	3.60 calendar months
04/01/28-03/31/29	3.60 calendar months

Title: Hub for Endometriosis Research (HER): Interdisciplinary Strategies Leading to Improved Understanding of Endometriotic Disease and Diagnosis

Major Goals: The University of Pittsburgh proposes to create a highly interdisciplinary Hub for Endometriosis Research (HER) that combines the existing strengths of biomedical/engineering research with the clinical and basic science expertise, reproductive physiology research at the Magee-Womens Research Institute (MWRI) and high-volume clinical excellence at the University of Pittsburgh Medical Center (UPMC) Magee-Womens Hospital (MWH) Chronic Pelvic Pain and Endometriosis Center (CPPEC) to advance innovative approaches for the early and accurate noninvasive diagnosis of endometriosis and to enhance our understanding of the endometriosis pathophysiology and disease progression. We propose here a Focused Program Award strategy to address the challenges of detecting EM early and accurately through the following goals: i) the development of novel, noninvasive diagnostic tools (Projects 1-3) and ii) an enhanced mechanistic understanding of the disease, its progression, and associated diseases/conditions (Projects 3-5). In addition to

Coffman, Lan
improving EM detection, a related goal and outcome is to enable future development of novel targeted therapies using foundational research and bioengineered models to improve our understanding of EM pathogenesis and progression (Projects 4-5).

Status of Support: Pending

Project Number: Pending

Name of PD/PI: David Vorp

Source of Support: DOD

Contracting/Grants Officer: USAMRAA Representative; support@grant.gov;

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 08/01/2024 – 07/31/2028

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
08/01/2024 – 07/31/2025	0.60 calendar months
08/01/2025 – 07/31/2026	0.60 calendar months
08/01/2026 – 07/31/2027	0.60 calendar months
08/01/2027 – 07/31/2028	0.60 calendar months

Title: Investigating Physico-Chemical Properties of Mesenchymal Stromal Cells as Biophysical Markers for Early Detection of Ovarian Cancer

Major Goals: Define how MSCs alter the physical components of the fallopian tube where ovarian cancer starts.

Status of Support: Pending

Project Number: Pending

Name of PD/PI: Lan Coffman

Source of Support: Tina's Wish

Contracting/Grants Officer: Pending

Primary Place of Performance: University of Pittsburgh, Pittsburgh, PA

Project/Proposal Start and End Date: 01/01/24-12/31/26

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year	Person Months
01/01/24-12/31/25	1.80 calendar months
01/01/25-12/31/26	1.80 calendar months

Overlap:

There is no overlap to report. Effort for Dr. Coffman will be adjusted to avoid overcommitment if needed to ensure active effort will not exceed 12.00 calendar months.

Signature: DocuSigned by: Lan Coffman 40818FC84AA74C2...

Date: 10-26-2023 | 1:48 PM EDT