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14. ABSTRACT

The goal of this project is to systematically characterize immune cell enrichment in the microenvironment of ovarian cancers and identify immune cell subsets that are prognostically relevant for patient care and/or can be used to develop more effective therapies targeting the tumor microenvironment. We compared the transcriptomes of primary tumors and omental metastases to elucidate if metastases have unique molecular characteristics that could be used as therapeutic targets or predictors of treatment success. We showed that biomarkers of clinical outcomes are different in primary tumors and metastases. Since biopsies of omental metastases are more accessible than primary tumors and increasingly used to determine the appropriate course of treatment for ovarian cancer patients, we generated an omental metastasis sample-based 8-gene signature as an independent risk factor for overall survival in ovarian cancer patients. We also identified different subsets of T cells in the epithelial and stromal tumor components in patient matched primary, metastatic, and recurrent ovarian cancer; conducted computational analyses of the imaging data; and identified correlations between patient survival and the presence of different T cell subsets in the epithelial and/or stromal tumor components.

15. SUBJECT TERMS
Ovarian cancer, tumor microenvironment, tumor progression, cancer-associated fibroblasts, immune infiltrates

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1. **INTRODUCTION:**

It is becoming increasingly clear that the tumor microenvironment plays an important role in tumor evolution, including the evolution of immune tolerance. In particular, cancer-associated fibroblasts (CAFs) are emerging as critical regulators of immune cell recruitment and function. CAFs physically hinder trafficking of functional immune cells to the tumor bed. CAFs are also a rich source of biologically active molecules that modify immune cell behavior and attract or repel certain immune cell types. While tumor progression is typically accompanied by the increased presence of CAFs, the configuration of pro-tumorigenic and anti-tumorigenic immune cell types during tumor progression is currently unknown. Our integrative approach is providing a comprehensive view of immune cell enrichment in the tumor microenvironment during tumor progression. Our major finding is that the presence of CAFs negates the beneficial effects of immune infiltrates on patient survival. In addition to identifying combinations of cell subsets that are prognostically significant for patient treatment with existing immunotherapies, our study could prove that immune cell infiltration can be effectively manipulated by targeting CAFs, which may provide a novel approach to immunotherapy. Our spatiotemporal quantitative map of individual immune cell subsets in matched primary, metastatic, and recurrent ovarian tumors could serve as a foundation for therapeutic targeting of the CAF/immune cell interface to develop more effective and less toxic therapies that selectively deplete the tumor-promoting stromal cell subsets in different stages of tumor progression.

KEYWORDS:

Ovarian cancer, tumor microenvironment, tumor progression, cancer-associated fibroblasts, immune infiltrates

ACCOMPLISHMENTS:

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

2.

Specific Aim 1 (specified in proposal)	Timeline	Percent Completed
Major Task 1 **Identify biomarkers and therapeutic targets in the tumor stroma by correlating stromal factors with clinical outcomes.**	**Months**	**Cedars-Sinai Medical Center**
Subtask 1 Normalize transcriptome data from 5 public Affymetrix-based ovarian cancer datasets and combine into one dataset with transcriptome and clinical information for 1,228 primary ovarian cancer samples.	1-2	100%
Subtask 2 Computationally (implementing the BASE algorithm) deduce hematopoietic cell type enrichment in human ovarian cancer samples using the ImmGen dataset (131 mouse hematopoietic	3-5	100%

cell types). Validate the enrichment of 22 major hematopoietic cell types using the LM22 dataset (leukocyte 547-gene signature that distinguishes 22 major human hematopoietic cell types).		
Subtask 3 Use statistical methods to associate enrichments in individual hematopoietic cell types (or specific groups of cell types) with distinct molecular and clinical phenotypes, such as the molecular subtype, chemosensitivity, metastasis, and survival.	6-7	90%
Subtask 4 Write and publish the computational part of the manuscript.	8-15	80%
Milestone Achieved Identified and validated association between immune cell enrichment and molecular and clinical parameters (molecular subtype, stromal content, overall survival, disease-free survival, and cisplatin sensitivity) in 1,228 primary ovarian cancer samples.	*15*	
Specific Aim 2 (specified in proposal)	**Timeline**	**Site 1**
Major Task 2 **Validate the identified stromal factors and generate a spatiotemporal map of stromal activity associated with tumor progression and chemoresistance.**	**Months**	**Cedars-Sinai Medical Center**
Subtask 1 Amend approved IRB 44852 protocol for local approval and send related material for DoD's approval.	Upon award notice	100%
Subtask 2 Design an immune cell panel for multi-color flow cytometry/immunohistochemistry (IHC)/immunofluorescence (IF); purchase reagents; plan experiments.	1-30	70%
Subtask 3 Prospectively collect surgically isolated matched primary and metastatic ovarian cancer samples from 40 patients. Process tissues in 4 ways: 1) disaggregate into viable single-cell suspensions for flow cytometry; 2) fix in formalin/embed in paraffin (FFPE) for IHC; 3) snap freeze for IF; 4) grow fresh omental metastasis tissue (5-10 patients) in culture for isolation of carcinoma-associated fibroblasts (CAFs).	1-30	30%
Subtask 4 Isolate and culture CAFs from metastasis samples from 5-10 patients.	1-12	10%
Subtask 5 Conduct multi-color flow cytometry and multi-color IHC or IF on prospectively collected samples from 40 patients or on an existing tissue microarray (TMA) of patient-matched primary, metastatic, and recurrent cancer samples from 42 patients.	1-30	60%

Subtask 6 Acquire images from TMAs and process for image analysis.	3-30	100%
Subtask 7 If ambiguous results are obtained with TMA, validate IHC and IF data on full tumor sections.	1-36	5%
Subtask 8 Analyze data from multi-color flow cytometry and multi-color IHC or IF and correlate with stromal content and clinical parameters, including debulking status, cisplatin sensitivity, disease-free survival, and overall survival.	3-36	30%
Milestone Achieved Obtained a detailed spatiotemporal map of immune cell subsets in primary and metastatic tumor samples and correlated data with stromal content and clinical parameters, including debulking status, cisplatin sensitivity, disease-free survival, and overall survival. Identified actionable immune biomarkers and therapeutic targets.	*36*	
Specific Aim 3 (specified in proposal)	**Timeline**	**Site 1**
Major Task 3 **Demonstrate that targeted ablation of stromal cell subsets impedes tumor progression**.	**Months**	**Cedars-Sinai Medical Center**
Subtask 1 Amend approved IACUC 5318 protocol for local approval and send related material for DoD's approval.	Upon award notice	Dr. Sandra Orsulic
Subtask 2 Purchase FVB mice, drugs and reagents; design a panel of mouse immunomarkers for multi-color flow cytometry and IHC/IF; select targeted stromal agents for treatment; plan experiments.	1-2	30%
Subtask 3 Implant FVB mice with mouse ovarian cancer cells. Treat mice with selected targeted stromal agents.	3-25	30%
Subtask 4 Collect and process tissues from experimental and control mice, including ascites, blood, tumor, spleen and lymph nodes, for multi-color flow cytometry and IHC or IF.	5-30	30%
Subtask 5 Conduct multi-color flow cytometry and multi-color IHC or IF on collected tissues from experimental and control mice, including ascites, blood, tumor, spleen and lymph nodes.	5-30	10%
Subtask 6 Analyze data using statistical methods; replicate experiments if necessary; prepare manuscripts.	5-36	10%
Milestone Achieved	*36*	

Tested the effect of stroma-targeted therapy on immune response. Identified potential immunomodulators for cancer treatment.		

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

1) major activities

Our activities focused on finalizing Aim 1, analyzing the results, and preparing a manuscript describing the novel data in the context of recent studies published by other laboratories. We also focused on the analysis of transcriptomes of omental metastases with the goal of identifying gene signatures for prediction of overall survival. In Aim 2, we focused on the multi-color immunofluorescent analyses of different subsets of T cells in patient matched primary, metastatic, and recurrent ovarian cancer. We have started writing the manuscript describing these data. For Aim 3, we published one manuscript and continue to analyze the data from mouse studies.

2) specific objectives

Aim 1. We identified an association between immune cell enrichment and molecular and clinical parameters (molecular subtype, stromal content, overall survival, disease-free survival, and cisplatin sensitivity) in 1,154 primary ovarian cancer samples. We generated an 8-gene risk score formula for prediction of overall survival in ovarian cancer patients.

Aim 2. We generated a detailed spatiotemporal map of immune cell subsets in primary and metastatic tumor samples and correlated data with stromal content and clinical parameters. We also identified different subsets of T cells in the epithelial and stromal tumor components in patient matched primary, metastatic, and recurrent ovarian cancer; conducted preliminary analyses of the imaging data; and identified correlations between patient survival and the presence of different T cell subsets in the epithelial and/or stromal tumor components.

Aim 3. We continue to analyze tissues from mouse ovarian cancer models treated with stroma-targeted therapies.

3) significant results or key outcomes, including major findings, developments, or conclusions

Aim 1. Identify biomarkers and therapeutic targets in the tumor stroma by correlating stromal factors with clinical outcomes

Aim 1, major achievement #1. Different molecular subtypes of ovarian cancer are associated with different stromal cell subsets. The hypothesis for Aim 1 is that individual immune cell types associated with specific tumor states and clinical outcomes in ovarian cancer can be identified by superimposing transcriptomes of tumor samples with transcriptomes of isolated hematopoietic cell types. We proved that the presence of CAFs is correlated with a skewed proportion of immune cell subsets and showed that the mesenchymal molecular subtype of ovarian cancer is enriched for tolerogenic immune cell subsets (the data were described in our last progress report). We are currently finalizing the manuscript describing these data.

Aim 1, major achievement #2. Established an omental metastasis gene signature to predict survival in ovarian cancer patients. The Cancer Genome Atlas Project (TCGA) and other comprehensive molecular analyses of clinically-annotated ovarian cancer samples have greatly enriched our molecular understanding of the most common type of ovarian cancer, high grade serous ovarian carcinoma (HGSOC). This wealth of molecular data is currently used by investigators worldwide to identify novel therapeutic targets and delineate biomarkers of clinical outcomes in HGSOC. However, the TCGA molecular data have been derived from primary ovarian cancer samples located in the ovary. Such data may not be fully representative of HGSOC, which is characterized by widespread peritoneal metastases at the time of diagnosis and upon relapse. To effectively treat metastatic disease, it is important to understand the distinct molecular characteristics of metastases. We suspect that transcriptome of a metastasis to the peritoneum (the most common metastatic site in HGSOC patients) is probably more representative of disease progression and has a closer association with survival than the transcriptome of the primary tumor. Another reason to pursue potential biomarkers of clinical outcomes in omental metastases is that biopsies of omental metastases are more accessible than primary tumors and increasingly used to determine the appropriate course of treatment for ovarian cancer patients (neoadjuvant chemotherapy with secondary cytoreduction vs. primary cytoreduction followed by chemotherapy).

To elucidate if metastases have unique molecular characteristics that could be used as therapeutic targets or predictors of treatment success, we determined expression patterns in formalin-fixed paraffin-embedded (FFPE) samples of chemotherapy-naive omental metastases from 152 patients diagnosed with HGSOC. Using Cox stepwise regression analysis, we identified an 8-gene signature that significantly correlated with poor overall survival (OS) (selection threshold $P<0.01$). We generated the 8-gene-RNA-expression based formula to evaluate the risk score (risk score = -0.59222*[TJP2] -0.40721*[HSD17B12] +0.43703*[MME] -0.30525*[TXK] +0.71850*[BMI1] -0.77805*[BTG1] -0.37296*[SCL2A1] +0.23967*[LIF]) and showed that this risk score was significantly associated with poor OS (**Fig. 1A**). We validated the ability of the 8-gene risk score to predict poor OS in an independent validation dataset of metastatic samples (**Fig. 1B**). Interestingly, while the 8-gene risk score was associated with poor OS upon analyses of transcriptome data from metastatic samples (**Fig. 1A-B**), analyses of transcriptome data from primary cancer samples did not show association with OS (**Fig. 1C-D),** indicating that the 8-gene risk score is a metastasis-specific. To test if the 8-gene signature is an independent risk factor of OS, we conducted univariate and multivariate Cox regression analysis (**Table 1**). The 8-gene signature was significantly associated with OS in both univariable and multivariable model, indicating it is an independent risk factor. The age, FIGO stage, debulking status and BRCA status were associated with OS in the univariable Cox regression analysis, however, only the FIGO stage was associated with OS in the multivariable Cox regression analysis. In summary, the 8-gene signature and FIGO stage are independent risk factors for OS and the 8-gene signature has superior prediction power than FIGO stage (HR=5.513, $P=0.0021$ vs HR=1.783, $P=0.0134$).

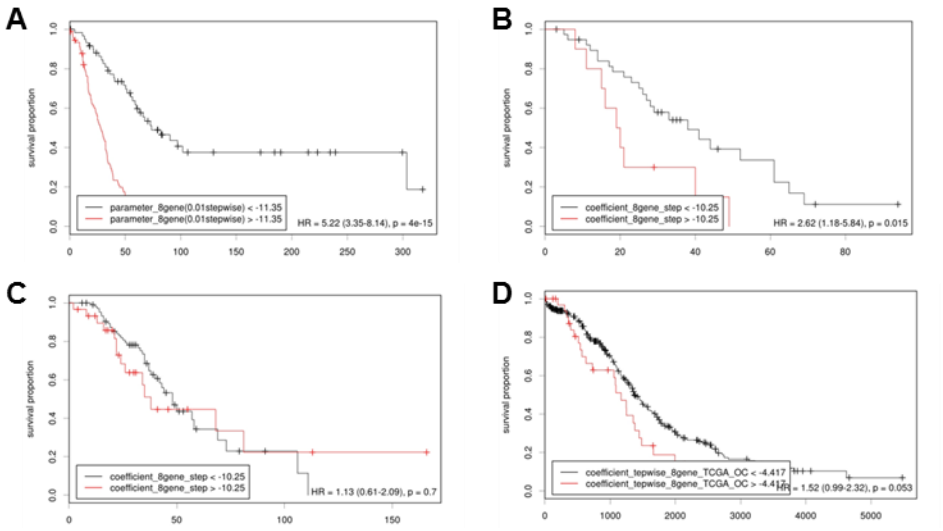

Fig. 1. Kaplan-Meier plots of OS in the low-risk versus high-risk group of HGSOC patients based on the 8-gene risk formula. (A) NanoString dataset of omental metastases (N=152). **B)** GSE9891 dataset of peritoneal metastases (N=52). **(C)** GSE9891 dataset of primary HGSOC (N=143). **(D)** TCGA dataset of primary HGSOC (N=378). X axis, months; Y axis, percent survival.

Table 1. Univariate and multivariate Cox regression analysis of HGSOC omental metastases (N=152).

Variables	Univariate model			Multivariate model		
	HR	95% CI of HR	*P* value	HR	95% CI of HR	*P* value
8-gene score (low vs. high)	5.205	3.338 to 8.117	**<0.0001**	5.513	3.337 to 9.106	**0.0021**
Age	1.025	1.009 to 1.042	**0.002**	1.012	0.995 to 1.029	0.1607
Stage	1.685	1.104 to 2.570	**0.0155**	1.783	1.128 to 2.819	**0.0134**
Debulking status	0.531	0.312 to 0.907	**0.0203**	0.601	0.339 to 1.068	0.0825
Brca mutation	0.632	0.421 to 0.949	**0.027**	/*		

*insufficient number of samples with BRCA information to fit into the multivariate model

Aim 2. Generate a spatiotemporal map of stromal activity associated with tumor progression and chemoresistance.

Aim 2, major achievement #1. Generated data on the identity of cell types, extracellular matrix, and soluble factors involved in ovarian cancer progression and metastasis. We completed these studies (the data were described in our last progress report) and are currently drafting the manuscript describing the results of these analyses.

Aim 2, Major Achievement #2. Characterized spatial localization of T cell subsets associated with survival in HGSOC patients. Multiple studies have reported an uneven distribution of different immune cell types and/or different maturation stages of the same cell type in different parts of the tumor. These observations formed the basis for developing "immunoscores" as predictors of survival, metastasis, and therapeutic response. A recent anti-PD-1 clinical trial in melanoma has revealed that, in addition to immunomarkers, a mesenchymal gene signature strongly correlates with therapy resistance. Our group has shown that this gene signature is primarily expressed in cancer-associated fibroblasts (CAFs), suggesting that CAFs may contribute to therapy resistance through immunosuppression. However, mechanisms by which CAFs control immune responses in cancer are unclear. Our goal was to test the hypotheses that the accumulation of CAFs during tumor progression skews the immune infiltrate toward the immuno-suppressive profile and/or prevents access of immune cells to the tumor bed. To distinguish tumor and stroma infiltrated immunocytes in primary, metastatic and recurrent tumors from 42 HGSOC patients, we conducted multiplex immunofluorescence staining with antibodies against CD3, CD4, CD8, Foxp3 and Keratin 8/18 or α-SMA (**Fig. 2A**). Keratin 8/18 staining was present in epithelial tumor cells and was used to generate a tumor mask to identify infiltrated immunocytes in the tumor component. α-SMA staining was present in fibroblasts and was used to generate a stroma mask to identify infiltrated immunocytes (combinations of CD3, CD4, CD8, and FoxP3 markers) in the stromal component. None of the CD3+ cell, CD3+CD4+ cell, CD3+CD8+ cell, CD3+CD4+Foxp3+ cell and CD3+CD8+Foxp3+ cell infiltration density in the tumor mask and the stroma mask was associated with OS in primary HGSOC (data not shown). In metastases, high CD3+ cell infiltration density in the stroma mask (but not tumor mask) was associated with better OS (**Fig. 2B**). We showed that CD3+ cell infiltration density was higher in the stromal region than in the tumor region in primary, metastatic, and recurrent tumors (**Fig. 2C**). This is important because most previous studies have focused on immune cell density in the tumor bed while the role of immune cells in the stromal region is largely unknown. CD3+CD8+ cell infiltration density in both the tumor (**Fig. 2D**) and stroma masks (**Fig. 2E**) was associated with better OS in metastases. CD3+CD8+ cell infiltration density was higher in the stroma mask than in the tumor mask in primary, metastatic, and recurrent tumors (**Fig. 2F**). Neither immunosuppressive CD3+CD4+Foxp3+ cell nor immunosuppressive CD3+CD8+Foxp3+ cell infiltration density was associated with OS in metastases, suggesting that metastasized HGSOC progression largely depends on cytotoxic T cells, not immunosuppressive T cells (Treg). Our future studies will continue the systematic characterization of immune and CAF activity in the tumor microenvironment to predict both anticipated and unanticipated combinations of cell types that are prognostically significant for patient care and/or can be used to develop more effective and less toxic stroma-targeted therapies. The spatiotemporal view of stromal dynamics during ovarian cancer progression will assist in decisionmaking about the most appropriate therapy regimen for different stages of cancer progression.

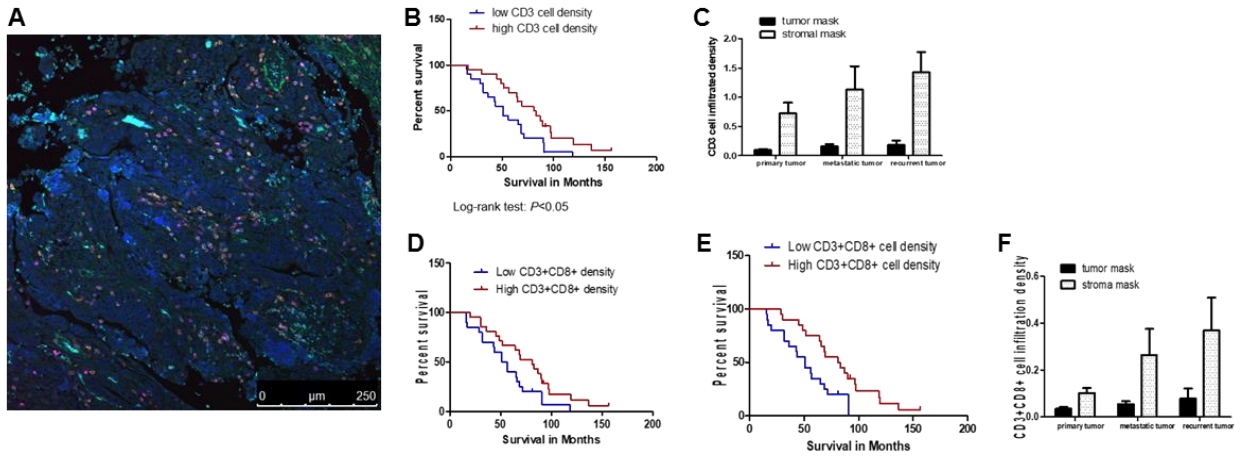

Fig. 2. (**A)** Example of multiplex immunofluorescence with antibodies against CD3, CD4, CD8, Foxp3 and Keratin 8/18 or α-SMA. **(B)** High CD3+ cell infiltration density in the stroma mask in metastases is associated with better OS. **(C)** CD3+ cell infiltration density is higher in the stroma mask than in the tumor mask in primary, metastatic, and recurrent tumors. **(D-E)** High CD3+CD8+ cell infiltration density in the tumor mask **(D)** and the stroma mask **(E)** in metastases is associated with better OS. **(F)** CD3+CD8+ cell infiltration density is higher in the stroma mask than in the tumor mask in primary, metastatic, and recurrent tumors.

Aim 3. Demonstrate that targeting CAFs improves the immune response to tumors.

Aim 3, major achievement #1. We published 1 research manuscript that establishes the basis of our experiments in targeting CAFs for improved immune response in our immunocompetent mouse model of ovarian cancer.

Jia D, Nagaoka Y, Katsumata M, **Orsulic S**. Inflammation is a key contributor to ovarian cancer cell seeding. Scientific Reports 2018; Aug 17;8(1):12394. doi: 10.1038/s41598-018-30261-8.

4) other achievements

Nothing to report.

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

Nothing to report.

b. How were the results disseminated to communities of interest?

Nothing to report.

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

For Aim 1, we will complete the manuscript and revise based on reviewers' suggestions. For Aim 2, we will complete the analyses and prepare a manuscript describing these data and the

relevance to clinical outcomes in ovarian cancer patients. For Aim 3, we will continue our experiments and analyses.

3. IMPACT:

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

Nothing to report.

b. What was the impact on other disciplines?

Nothing to report.

c. What was the impact on technology transfer?

Nothing to report.

d. What was the impact on society beyond science and technology?

Nothing to report.

4. CHANGES/PROBLEMS:

a. Changes in approach and reasons for change. No

b. Actual or anticipated problems or delays and actions or plans to resolve them.
There has been a change in personnel, which required the training of two new postdoctoral fellows. This caused delays in completing some experiments but should not affect the next grant period. Additionally, we were unable to obtain a sufficient number of surgical samples at our institution, which delayed one of the two planned experiments in Aim 2. We are in the process of obtaining IRB approval to collect surgical tissues from Israel (described in Significant Changes in Use or Care of Human Subjects).

c. Changes that had a significant impact on expenditures.
The delayed collection of surgical samples and the training of new postdoctoral fellows affected the number of experiments conducted and reduced overall expenditures.

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

e. Significant changes in use or care of human subjects. Yes.

We plan to collect surgical samples of patient-matched primary and metastatic tumors from Israel because our institution is increasingly switching to neoadjuvant therapy with secondary surgical cytoreduction, thus reducing the number of patients whose samples are useful for our project. We are in the process of seeking IRB approval to reflect this change in the site of sample collection.

f. Significant changes in use or care of vertebrate animals. No.

g. Significant changes in use of biohazards and/or select agents. No.

5. PRODUCTS:

Nothing to report.

a. Publications, conference papers, and presentations

i. Journal publications.

Jia D, Nagaoka Y, Katsumata M, **Orsulic S**. Inflammation is a key contributor to ovarian cancer cell seeding. Scientific Reports 2018; Aug 17;8(1):12394. doi: 10.1038/s41598-018-30261-8.

Books or other non-periodical, one-time publications. N/A

ii. Other publications, conference papers, and presentations.
Invited talk (acknowledged grant funding):
Sandra Orsulic, Tumor microenvironment: a gold mine of biomarkers and therapeutic targets. Department of Obstetrics and Gynecology Grand Rounds, David Geffen School of Medicine, UCLA. March 20, 2019

Invited manuscript (acknowledged grant funding):

Haro M and **Orsulic S**. A paradoxical correlation of cancer-associated fibroblasts with survival outcomes in B-cell lymphomas and carcinomas. Frontiers in Cell and Developmental Biology 2018 Aug 28;6:98. doi: 10.3389/fcell.2018.00098. eCollection

b. Website(s) or other Internet site(s). N/A

c. Technologies or techniques. N/A

d. Inventions, patent applications, and/or licenses. N/A

e. Other Products. N/A

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name:	Sandra Orsulic, PhD
Project Role:	PI
Nearest person month worked:	1.20
Contribution to Project:	Dr. Orsulic oversaw projects for all three specific aims, including experimental design, execution, and data analysis and interpretation. She submitted one invited manuscript and prepared presentations as well as the progress report.

Name:	Beth Karlan, MD
Project Role:	Collaborator
Nearest person month worked:	0.15
Contribution to Project:	Dr. Karlan advised on the translational aspects of the proposal and participated in experimental design.

Name:	Yael Raz, MD PhD
Project Role:	Postdoctoral Fellow
Nearest person month worked:	7.00
Contribution to Project:	Dr. Raz conducted experiments in Aims 1 and 2 and conducted data analyses.

Name:	Enes Taylan, MD
Project Role:	Postdoctoral Fellow
Nearest person month worked:	9.00
Contribution to Project:	Dr. Taylan conducted experiments in Aims 2 and 3 and conducted data analyses.

b. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? No

c. What other organizations were involved as partners? None

7. SPECIAL REPORTING REQUIREMENTS

a. COLLABORATIVE AWARDS: N/A

b. QUAD CHARTS: N/A

8. APPENDICES: N/A