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TITLE: Defining Hepatocellular Carcinoma Subtypes and Treatment Responses in Patient-Derived Tumorgrafts

PRINCIPAL INVESTIGATOR: Daniel Siegwart, Ph.D.

RECIPIENT: University of Texas Southwestern Medical Center at Dallas
Dallas, TX 75390-9020

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Daniel Siegwart, Hao Zhu, Amit Singal, Adam Yopp, Akbar Waljee

E-Mail: daniel.siegwart@utsouthwestern.edu

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

UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX 75390-9020

Veteran's Education and Research Association of Michigan (VERAM) 2215 Fuller Rd Rear
Ann Arbor, MI 48105-23032

8. PERFORMING ORGANIZATION REPORT NUMBER

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14. ABSTRACT
Hepatocellular carcinoma (HCC) is the 6th most common cancer and 3rd leading cause of cancer-related death worldwide. We know that HCC subtypes exist because clear clinical, radiographic, and histological differences between patients with HCC are observed. In this study we investigated distinct subtypes of HCC using a mouse-human chimeric Patient Derived Xenograft (PDX) approach. We have performed a large effort to implant more than 100 tumors from human HCC patients from Texas. We have established the protocol and the results have taught us that engraftment using a variety of transplantation techniques will result in a 25-30% engraftment efficiency for early stage surgical tumors. We have established eight new human HCC PDX models that will be highly relevant for therapeutic and biological studies. These represent North American HCCs, including some patients with intermediate/advanced stage HCC, which is a unique resource for the field.

15. SUBJECT TERMS
HCC, patient derived xenografts, siRNA, mouse models of cancer.

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

Hepatocellular carcinoma (HCC) is the 6th most common cancer and 3rd leading cause of cancer-related death worldwide. In the US, its incidence has doubled over the past two decades due to the growing number of patients with hepatitis C virus (HCV) and/or non-alcoholic steatohepatitis (NASH) (El-Serag, 2004, 2012). We know that HCC subtypes exist because clear clinical, radiographic, and histological differences between patients with HCC are observed (Yopp et al., 2015). In this study we proposed to investigate distinct subtypes of HCC using a mouse-human chimeric Patient Derived Xenograft (PDX) approach. We aim to analyze and functionalize early and advanced stage HCC tumors with a large and representative cohort of patient derived xenograft (PDX) models. Our hypothesis is that HCC is poorly understood because tissue has been obtained from early HCC but not advanced cases. Biological subclasses of HCCs that behave differently in terms of natural history, prognosis and treatment response have not been categorized and/or functionally analyzed. Our team will use human-mouse PDX models to uncover novel biology and establish a platform to study experimental therapeutics.

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

HCC, patient derived xenografts, siRNA, mouse models of cancer.

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
For reference, the complete Statement of Work (SOW) is presented below with detail of Aims, Major Tasks, and Subtasks with Anticipated time lines. The column titled “Progress” indicates portion of the Major Task and related Sub-tasks completed.

Site 1:	UT Southwestern Medical Center	**Site 2:**	Ann Arbor Veterans Affairs Healthcare System
	5323 Harry Hines Blvd		2215 Fuller Rd
	Dallas, TX 75390		Ann Arbor, MI 48105
	Initiating PI: Dr. Hao Zhu Partnering PIs: Drs. Amit Singal; Adam Yopp; Daniel Siegwart		Partnering PI: Dr. Waljee

Specific AIM 1: Determine if early vs. advanced HCCs have distinct cell-intrinsic biology in PDX engraftment assays	**Timeline in months**	**Site 1** (Initiating PI)	**Site 2** (Partnering PI)	**Progress (*Percent Complete or Completion Date***
Major Task 1: Expand and characterize PDX models derived from surgical and biopsy HCC specimens				

Pre-task: Allow time to receive the regulatory approval for animal use (IACUC and DoD ACURO)	1-3	Drs. Yopp, Singal, and Zhu		100 % complete November 2016
Pre-task 2: Allow time to receive the regulatory approval for the Human Anatomical Substance use (IRB and DoD HRPO).	1-3	Drs. Yopp, Singal, and Zhu		100 % complete November 2016
Subtask 1: Continue to implant 40 surgical HCC specimens in the subcutaneous space and livers of NSG mice	0-12	Drs. Yopp and Zhu		100% complete Sep 2018
Subtask 2: Continue to implant 25 biopsy samples from intermediate and advanced HCC cases in the subcutaneous space and livers of NSG mice	0-12	Drs. Yopp, Singal, and Zhu		100% complete Sep 2018
Subtask 3: Harvest primary PDX tumors, establish PDX bank, and passage into additional NSG mice	6-18	Drs. Yopp and Zhu		100% complete Oct 2018
Subtask 4: Characterize tumor architecture, histology, growth, invasiveness, and paraneoplastic features of tumors that engraft, and determine if the grafts resemble or deviate from original tumors (surgical or biopsy specimens)	6-24	Drs. Yopp and Zhu		100% complete Sept 2018
Subtask 5: Obtain genomic data from PDX grafts to determine if they resemble or deviate from original tumors (surgical or biopsy specimens)	12-30	Drs. Yopp, Singal, and Zhu		100% complete June 2018
Major Task 2: Compare biological and genetic features (stage, survival, progression) of early vs. non-early HCCs				
Subtask 1: Compare biological features of the tumors that engraft vs. those that do not, and determine if there is a difference between PDX made from early surgical or more advanced biopsy specimens	6-24	Drs. Yopp and Zhu		100% complete April 2019
Subtask 2: Compare patient clinical features (stage, survival, progression) of specimens that engraft versus not engraft and determine if engraftment can predict clinical outcomes	6-18	Drs. Singal,	Drs. Wajlee	100% complete October 2018
Subtask 3: Analyze genomic data to survey genetic landscape of PDX population that successfully engrafts and identify genetic drivers of engraftment	12-36	Drs. Singal and Zhu	Drs. Wajlee	100% complete October 2018

Milestone #1: Co-author manuscript on biology and genomics of HCC PDX models	12-24	Drs. Zhu, Singal, and Yopp	Drs. Wajlee	100% complete July 2019
Specific AIM 2: Determine the efficacy of small RNA therapeutics against the *LIN28B/LET-7* pathway in PDXs activating this oncogenic pathway	**Timeline**	**Site 1** (Initiating PI)	**Site 2** (Partnering PI)	
Major Task 1: Identify and deliver small RNAs to target PDX populations				
Subtask 1: Evaluate and optimize custom dendritic nanoparticle delivery to PDX tumors	0-12	Drs. Zhu and Siegwart		100% complete Dec 2018
Subtask 2: Formulate and optimize siRNA and microRNA containing dendritic nanoparticles to ensure that successful modulation of LIN28B and or LET-7 is achieved in PDX models.	6-24	Dr. Siegwart		100% Sept 2019
Subtask 3: Define HCC PDX models that overexpress MYC or LIN28B and those that suppress LET-7 family microRNAs	6-24	Drs. Singal and Zhu		Incomplete, discontinued
Subtask 4: Therapeutically deliver siRNAs or microRNAs in dendritic nanoparticles to mice harboring these PDX models	12-36	Dr. Siegwart		100% complete (performed in analogous models) June 2020
Major Task 3: Define response to small RNAs in target PDX populations				
Subtask 1: Determine response to small RNA therapies using luciferase and CT imaging	6-30	Dr. Siegwart		100% complete (performed in analogous models)
Subtask 2: Define histological response and intermediate markers of tumor biology (Ki67, apoptosis, necrosis)	12-36	Dr. Siegwart		75% complete (performed in analogous models)
Milestone #2: Co-author manuscript about therapeutic efficacy of small RNA therapy in HCC PDX models	24-36	Drs. Zhu and Siegwart		Not completed
Specific AIM 3: Define targeted therapy responders with HCC-PDX patient avatars and use to identify predictive biomarkers	**Timeline**	**Site 1** (Initiating PI)	**Site 2** (Partnering PI)	

Major Task 1: Define PDX models that show partial response, stable disease, and progressive disease to targeted therapies				
Subtask 1: Characterize tumors for growth, histology, vascular invasion, metastasis, proliferation and apoptosis after treatment	12-36	Drs. Zhu, Yopp, and Singal		100% complete Oct 2018
Subtask 2: Perform exome and RNA-expression sequencing for top responders and non-responders for each group to determine mechanistic basis of response	18-36	Drs. Singal and Zhu	Dr. Waljee	100% complete July 2019
Major Task 2: Establish predictive biomarkers for response to treatment				
Subtask 1: Use machine learning methods to identify clinical and genetic factors associated with response to targeted therapies	18-36	Drs. Yopp, and Singal	Dr. Waljee	100% complete Oct 2018
Subtask 2: Derive and internally validate predictive model using factors significantly associated with targeted therapy response	24-36	Dr. Singal	Dr. Waljee	100% complete July 2019
Milestone #3: Co-author manuscript on HCC PDX treatments and predictive modeling results	24-36	Drs. Zhu, Yopp, and Singal	Dr. Waljee	Will not continue July 2019

What was accomplished under these goals?

Specific AIM 1: Determine if early vs. advanced HCCs have distinct cell-intrinsic biology in PDX engraftment assays
Major Task 1: Expand and characterize PDX models derived from surgical and biopsy HCC specimens
Subtask 1: Implant surgical HCC specimens in the subcutaneous space and livers of NSG mice. This task has been completed by Drs. Singal, Yopp, and Zhu.
Subtask 2: Continue to implant 25 biopsy samples from intermediate and advanced HCC cases in the subcutaneous space and livers of NSG mice. This subtask has been completed by Drs. Singal, Yopp, and Zhu.
Subtask 3: Harvest primary PDX tumors, establish PDX bank, and passage into additional NSG mice. This task has been completed by Drs. Singal, Yopp, and Zhu.
Subtask 4: Characterize tumor architecture, histology, growth, invasiveness, and paraneoplastic features of tumors that engraft, and determine if the grafts resemble or deviate from original tumors (surgical or biopsy specimens). This subtask is complete.

Subtask 5: Obtain genomic data from PDX grafts to determine if they resemble or deviate from original tumors (surgical or biopsy specimens). This has been completed.

Major Task 2: Compare biological and genetic features (stage, survival, progression) of early vs. non-early HCCs

Subtask 1: Compare biological features of the tumors that engraft vs. those that do not, and determine if there is a difference between PDX made from early surgical or more advanced biopsy specimens
This has been completed by Drs. Singal, Yopp, and Zhu.

Subtask 2: Compare patient clinical features (stage, survival, progression) of specimens that engraft versus not engraft and determine if engraftment can predict clinical outcomes
This has been completed by Drs. Singal, Yopp, and Zhu.

Subtask 3: Analyze genomic data to survey genetic landscape of PDX population that successfully engrafts and identify genetic drivers of engraftment
Dr. Waljee's team considered a variety of gene selection methods, including (1) logistic regression model with lasso regularization, (2) logistic regression model with elastic net regularization, (3) nearest shrunken centroid (NSC) method, and (4) adaptive hierarchically penalized NSC (AHP-NSC). This task was completed.

Milestone #1: Co-author manuscript on biology and genomics of HCC PDX models
The manuscript has been published by Drs. Singal, Yopp, Waljee, and Zhu. Zhu M et al., Hepatology. 2020 Jan 3 (EPub ahead of print). Information from this project also contributed to a second manuscript, recently published at Hepatology by Drs. Singal, Zhu, and Yopp. These papers are listed in a below section.

Subtask 1: Compare biological features of the tumors that engraft vs. those that do not, and determine if there is a difference between PDX made from early surgical or more advanced biopsy specimens
This was completed by Drs. Singal, Yopp, Waljee, and Zhu.

Specific AIM 2 (Determine the efficacy of small RNA therapeutics against the LIN28B/LET-7 pathway in PDXs activating this oncogenic pathway).

Major Task 1: Identify and deliver small RNAs to target PDX populations

Subtask 1: Evaluate and optimize custom dendritic nanoparticle delivery to PDX tumors
This has been completed by Drs. Zhu and Siegwart.

Subtask 2: Formulate and optimize siRNA and microRNA containing dendritic nanoparticles to ensure that successful modulation of LIN28B and or LET-7 is achieved in PDX models.
This has been completed by Dr. Siegwart.

Subtask 3: Define HCC PDX models that overexpress MYC or LIN28B and those that suppress LET-7 family microRNAs
We did not find any PDXs that were overexpressing LIN28B, thus we have altered the targets for this subtask. Instead we have used an siRNA to target ANLN, which is a gene required for cytokinesis. We have previously shown in other work that this is a good therapeutic target for liver cancer. This work is a collaboration with Alnylam. We now have a few candidate siRNAs worked well in human cell lines. In the future, we are planning on using the HCC PDX lines to test the ANLN siRNAs in vivo, either in orthografts or in xenografts. This will require additional studies funded by other grants.

Subtask 4: Therapeutically deliver siRNAs or microRNAs in dendritic nanoparticles to mice harboring these PDX models
This was done by Dr. Siegwart. In a previous report, we described our discovery of hepatocyte-specific and Kuppfer cell-specific dendrimer lipid nanoparticles (DLNPs). We made the exciting observation that dendrimer chemistry can control cellular tropism within the liver. This has been completed using analogous models. We published two manuscripts concerning optimizing dendritic nanoparticles to deliver RNAs to the liver relating to this subtask and other aims/subtasks of the overall grant: (1) Cheng et al. Advanced Materials, 2018, 30, 1805308. (2) Zhou et al. Molecular Pharmaceutics, 2020, 17, 5, 1575-1585.

Major Task 3: Define response to small RNAs in target PDX populations

Subtask 1: Determine response to small RNA therapies using luciferase and CT imaging Drs. Zhu, Yopp, and Siegwart are working on this with ANLN siRNAs. We have candidate siRNA of ANLN that worked well in human cell lines. Dr. Siegwart has also determined responses using luciferase imaging for MYC and PD-L1 therapies in analogous HCC mouse models.
Subtask 2: Define histological response and intermediate markers of tumor biology (Ki67, apoptosis, necrosis) We have obtained ANLN siRNAs from Alnylam to perform these experiments, but at this point these cannot be completed without additional funding.
Specific AIM 3: Define targeted therapy responders with HCC-PDX patient avatars and use to identify predictive biomarkers There were not enough PDXs to do this. Discontinued.
Major Task 1: Define PDX models that show partial response, stable disease, and progressive disease to targeted therapies
Subtask 1: Characterize tumors for growth, histology, vascular invasion, metastasis, proliferation and apoptosis after treatment This was performed by Drs. Zhu, Yopp, and Siegwart. We have performed selected drug studies in the PDX models so this has been completed. We have also started testing experimental drugs that target telomere elongation. This is a drug developed by Jerry Shay at UTSW. So far, some PDXs have responded to these drugs when in combination with immunotherapy. We have added more PDX lines to test the telomere elongation targeting experimental drugs.
Subtask 2: Perform exome and RNA-expression sequencing for top responders and non-responders for each group to determine mechanistic basis of response This was performed by Drs. Zhu, Waljee, and Siegwart. This has not been completed because the numbers of PDXs and therefore responder/non-responder cohorts are too small for this type of analysis. This subtask has been discontinued.
Major Task 2: Establish predictive biomarkers for response to treatment
Subtask 1: Use machine learning methods to identify clinical and genetic factors associated with response to targeted therapies This has not been completed because we do not have enough responders and non-responders. This subtask has been discontinued.
Subtask 2: Derive and internally validate predictive model using factors significantly associated with targeted therapy response This has not been completed and will be discontinued.
Milestone #3: Co-author manuscript on HCC PDX treatments and predictive modeling results This has not been completed. Other work involving PDX models will be pursued and published in the near future.

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

Nothing to report during this period.

How were the results disseminated to communities of interest?

Several papers have been published.

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

Nothing to report.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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

The major impact at this point is that we have performed a large effort to implant 102 tumors from human HCC patients from Texas. We have established the protocol and the results have taught us how efficient this process will be. We have established 8 new human HCC PDX models that will be highly relevant for therapeutic and biological studies. These represent North American HCCs, including some patients with intermediate/advanced stage HCC, which is a unique resource for the field. We have found that increasing the rate of engraftment with partial hepatectomy or mouse models of chronic liver disease helps to make the growth and engraftment of the tumors more efficient. We will be able to use these models to evaluate experimental therapeutics, in the form of small molecules or small interfering RNAs.

Several outside groups have contacted us to test their therapies on our models. We will collaborate with them and share our reagents.

We demonstrated HCC can have variable tumor biology, showing some tumors are fast growing and others are indolent. We have shown this in mice and then demonstrated this is also true using clinical data in humans. This was first evaluated using local data combined in a multi-site retrospective study we led. Recently, we have similarly shown this to be true in a systematic review of the literature on tumor biology in HCC (Nathani et al, in press at Gut). The PDX and organoid models serve as a good system to evaluate biological drivers of tumor biology in the future.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

We have set up several collaborations with Cedars Sinai Medical Center and Baylor Medical Center, where labs have requested our PDX models.

What was the impact on society beyond science and technology?

Nothing to report

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants

Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

Changes in approach and reasons for change

Nothing to report

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

None

Changes that had a significant impact on expenditures

Nothing to report

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

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

None

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

· **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications.

1. Zhu M, Li L, Lu T, Yoo H, Zhu J, Gopal P, Wang SC, Porempka MR, Rich NE, Kagan S, Odewole M, Renteria V, Waljee AK, Wang T, Singal AG, Yopp AC, Zhu H. 2020. Uncovering biological factors that regulate hepatocellular carcinoma growth using patient derived xenograft assays. ***Hepatology***. Epub. PMID: 31899548.
2. Cheng Q, Wei T, Jia Y, Farbiak L, Zhou K, Zhang S, Wei Y, Zhu H, Siegwart DJ. 2018. Dendrimer-based lipid nanoparticles deliver therapeutic FAH mRNA to normalize liver function and extend survival in a mouse model of Hepatorenal Tyrosinemia Type I. ***Advanced Materials***. 30, 1805308.
3. Rich NE, John BV, Parikh, ND, Rowe I, Mehta N, Khatri G, Thomas SM, Anis M, Mendiratta-Lala M, Hernandez C, Odewole M, Sundaram LT, Konjeti VR, Shetty S, Shah T, Zhu H, Yopp A, Hoshida Y, Yao FY, Marrero JA, Singal AG. 2020. Hepatocellular carcinoma demonstrates heterogeneous growth patterns in a multi-center cohort of patients with cirrhosis. ***Hepatology***. Epub. PMID: 32017165.
4. Zhou K, Johnson LT, Xiong H, Barrios S, Minnig JT, Yan Y, Abram B, Yu X, Siegwart DJ. 2020. The hydrophobic domain structure of linear-dendritic poly(ethylene glycol) lipids affects RNA delivery of lipid nanoparticles." ***Molecular Pharmaceutics***, 17, 1575.

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers, and presentations.

Nothing to report

· **Website(s) or other Internet site(s)**

Nothing to report

· **Technologies or techniques**

These techniques have been described above and will be reported to the community when a manuscript is published. While PDX models of cancer are commonly generated, there are specific approaches that were optimized in the course of this project and they were described in Zhu et al, *Hepatology* 2019.

· **Inventions, patent applications, and/or licenses**

Nothing to report.

· **Other Products**

Data or databases: We continue to collect patient data in a clinical database.
Biospecimen collections: We have a human HCC biospecimen and PDX collection.
Research material: We have established live mice carrying human HCC PDXs.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Hao Zhu
Project Role: Lead PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-8417-9698
Nearest person month worked: 45
Contribution to Project: Direct the project, design the experiments and objectives, organize personnel, report progress to the DOD.

Name: Lin Li
Project Role: Senior Research Associate)
Researcher Identifier (e.g. ORCID ID): none
Nearest person month worked: 45
Contribution to Project: implantation of HCC specimens, passage of engrafted PDXs, storage of PDX engrafts.

Name: Daniel Siegwart
Project Role: Co-PI
Researcher Identifier (ORCID ID): 0000-0003-3823-1931
Nearest person month worked: 45
Contribution to Project: Co-planned and co-directed research activities. Worked on 5A2-SC8 synthesis and purification. Worked on nanoparticle delivery optimization to liver tumors.

Name: Qiang Cheng
Project Role: Senior Research Associate
Researcher Identifier (e.g. ORCID ID): none
Nearest person month worked: 45
Contribution to Project: Developed nanoparticle delivery carriers with an improved ability to deliver RNAs to the liver. Assisted with 5A2-SC8 experiments.

Name: Adam Yopp
Project Role: Co-PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 45
Contribution to Project: Design and conducted experiments, participated in co-PI conference calls to organize personnel and direct project.

Name: Min Zhu
Project Role: Senior Research Associate

Researcher Identifier (e.g. ORCID ID): none
Nearest person month worked: 45
Contribution to Project: implantation of HCC specimens, passage of engrafted PDXs, storage of PDX engrafts. inventory of HCC samples, preparation of genomic DNA libraries from HCC samples, data analysis, etc.

Name: Amit Singal
Project Role: Co-PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-1172-3971
Nearest person month worked: 45
Contribution to Project: Design experiments, participated in co-PI conference calls to organize personnel and direct project.

Name: Veronica Renteria
Project Role: Research coordinator
Researcher Identifier (e.g. ORCID ID): none
Nearest person month worked: 33
Contribution to Project: collection of HCC specimens

Name: Amanda Ellis
Project Role: Research assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 2.4
Contribution to Project: Ms. Ellis has performed administrative duties such as organizing meetings, regulatory policies, and served as liaison between AAVA and UTSW.

Name: Xianshi Yu
Project Role: Statistician
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Will be helping predict engraftment using both clinical and various predictor genes.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel

For Akbar Waljee, the following grant has become active:
UMHS-CGMH Waljee (Partner-PI) 06/01/2019-05/31/2020
Title: The genetic, environmental, and microbial determinant of IBD pathogenesis in Taiwan vs the U.S.
This joint project between CGMH and UMHS aims to better characterize IBD phenotypes and to identify potential risk factors by examining host genome, environmental exposures, and gut microbiota. Successful establishment of this pilot biorepository will provide the necessary preliminary data and available samples for an extramural grant application to perform more extensive analyses (e.g., host metatranscriptomics and serum metabolomics, fecal microbiota metagenomics/metatranscriptomics and metabolomics).

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

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

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

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