Fiscal Year:	FY 2019	**Task Last Updated:**	FY 11/15/2018
PI Name:	Emmett, Mark Ph.D.		
Project Title:	Induction of Hepatocellular Carcinoma by Space Radiation: A Systems Biology Study of Causative Mechanisms		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cancer**:Risk of Radiation Carcinogenesis		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	mremmett@utmb.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	409-747-1943
Organization Name:	The University of Texas Medical Branch		
PI Address 1:	UTMB Cancer Research Center		
PI Address 2:	301 University Blvd, Rt. 1074		
PI Web Page:			
City:	Galveston	**State:**	TX
Zip Code:	77555-5302	**Congressional District:**	14
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2013-14 HERO NNJ13ZSA002N-RADIATION
Start Date:	01/07/2015	**End Date:**	01/06/2020
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	3	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
Contact Email:	lisa.c.simonsen@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: Extended to 1/6/2020 per NSSC information (Ed., 2/12/19)		
Key Personnel Changes/Previous PI:	November 2017 Report: Dr. Cheryl Lichti left UTMB (University of Texas Medical Branch) to take a position at Washington University, St. Louis. She is still a collaborator on the project, but is no longer a Co-Investigator and is not receiving salary support since 8/31/17. Ana Nia (MD/Ph.D. Graduate student, joined the project October 2017. November 2016 report: Dr. Joseph Moskal (Northwestern University) is no longer affiliated with academia nor involved with this project and is being removed as Co-I on the project. November 2015 report: Dr. Carol L. Nilsson (Co-I, 10% Effort) is no longer involved with the project. Dr. Cheryl F. Lichti has replaced Dr. Nilsson at 20% Effort. Two advanced graduate students, Brooke L. Barnette and Shinji K. Strain, will replace the TBA senior scientist (50% Effort).		
COI Name (Institution):	Ullrich, Robert Ph.D. (University of Texas Medical Branch)		
Grant/Contract No.:	NNX15AD65G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Exposure to high-energy heavy ions (HZE) during space travel is a health risk for astronauts. Even at low doses, exposure to HZE can lead to cancer. To better understand the molecular mechanisms of HZE-induced carcinogenesis we will use a mouse model of HZE-induced hepatocellular carcinoma to study microenvironment changes after exposure to low level HZE. A comprehensive systems biology approach consisting of transcriptomics, lipidomics, proteomics, and metabolomics with novel data analysis will be used to build detailed biological pathways and identify molecular mechanisms that drive carcinogenesis. This work will further our understanding of risk at a mechanistic level and allow the development of new models for estimating human risk.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	It is anticipated that there will be crosstalk between the molecular changes involved in HZE-induced hepatocellular carcinoma (HCC) and environmentally induced HCC seen on Earth. The Principal Investigator (PI) is actively collaborating with ground-based clinical researchers in HCC research. The computational methods being developed to analyze the vast omic data sets has the potential to revolutionize omic analyses.
Task Progress:	Year 4 Results: Project Setbacks/Modifications. Over the past four years, several challenges have arisen that have necessitated alternative research paths to be devised. Year 4 was no exception. The PI and Co-I have worked together to circumvent these unforeseen occurrences and believe that the research and data has benefited from these changes although these set-backs have slowed progress on the project. 4th Year Specific Aims Progress. Specific Aim 2. Determine transcriptional changes in the hepatic microenvironment of HZE- and gamma-irradiated samples, compared to controls. RNA sequencing (UTMB sequencing core) has been completed on all samples. Transcriptomic reads were aligned to the mouse genome and Star software was used to determine expression levels. Approximately 56,000 expressed genes have been identified in each sample. Data analysis has been done to calculate the statistical significance for each gene and to determine differentially expressed transcripts in response to HZE. The amount of data obtained from the low-read RNA sequencing is staggering. There are many methods to identify significantly altered transcripts and pathways involved in each treatment group. Our group has been working with both traditional statistical R package (EdgeR) software and Ingenuity Pathway Analysis (IPA) and devising new computational methods. The traditional methods data will be presented below in Specific Aim 3. The new computational approaches results will be presented in Specific Aim 4. Specific Aim 3. Determine comprehensive ultra high-resolution lipidomic alterations as well as high-resolution targeted proteomic microenvironment changes in hepatic tissue from tissue punches of HZE- and 137Cs gamma ray-irradiated animals as well as non-irradiated controls. Proteomic/Transcriptomic Results: Proteomic data was collected in the UTMB mass spectrometry core using Data Independent Analysis (DIA) on a Sciex 5600 Triple-TOF MS. DIA comprehensively and repeatedly samples every peptide within a protein digest (even low abundant peptides). DIA accommodates targeted data mining. If a new protein becomes of interest in the future the data can be re-mined without requiring additional analysis by MS. Ingenuity Pathway Analysis (IPA): IPA analysis predicts biological pathways that are affected by the differential expression of transcripts and proteins. Both transcriptomic and proteomic data was used to predict biological pathway changes with IPA in response to irradiation with gamma and HZE ions as compared to non-irradiated control. Pathways were identified for each time point that are key in describing the molecular mechanisms of the effects of HZE irradiations. Specific Aim 4. Correlate large ‘omic datasets by use of Ingenuity Pathways’ Knowledge based software and unique algorithms developed by our collaborators to construct biological pathways that elucidate molecular mechanisms of HCC carcinogenesis induced by HZE irradiation. After several different filtering steps, analysis is performed on a more manageable list of genes/transcripts, and different combinations of pairwise comparisons are used to identify transcripts that are significantly affected by different treatments. Multilevel modeling has been rarely implemented in the context of transcriptomic and lipidomic data. One focus is to use multilevel modeling on individual genes that have shown a significantly different behavior across different experimental parameters. Our goal is to identify a list of genes (using different computational approaches) and then perform a multilevel analysis. Multilevel models can allow for dynamic analysis of all data points, regardless of their behavior patterns. We believe this will provide further insight into future gene expression data based on different parameters. We hope to be able to extend the same type of analysis to the lipidomic data sets as well. These analyses are unique in that they are purely mathematically based and thus are not influenced by any external bias. The two key computational methodologies being used are: Self Organizing Maps (SOM) and Modularity Analysis. Presentations: During this year, there were three presentations on data from this work. 1) 29th Annual NASA Human Research Program Investigators’ Workshop, January 22-25, 2018, Galveston, TX, Brooke L. Barnette*, Anna M. Nia, Shinji K. Strain, Cheryl F. Lichti, Yongjia Yu, Robert L. Ullrich, and Mark R. Emmett, An Integrated Omics Approach to Define the Molecular Mechanisms of Hepatocellular Carcinoma (HCC) Induced by Low Dose, High-Energy, High charge Ions (HZE). *Oral presentation by my graduate student Brooke L. Barnette 2) 66th Annual American Society for Mass Spectrometry Conference (ASMS), June 3-7, 2018. San Diego, CA. Brooke L. Barnette, Anna M. Nia, Shinji K. Strain, Cheryl F. Lichti, Yu Yongjia, Robert Ullrich, Mark R. Emmett, An Integrated Omics Approach to Define the Molecular Mechanisms of Galactic Cosmic Ray Induced Hepatocellular Carcinoma. Poster Presentation. 3) 66th Annual American Society for Mass Spectrometry Conference (ASMS), June 3-7, 2018. San Diego, CA. Anna M. Nia, Brooke L. Barnette, Shinji K. Strain, Cheryl F. Lichti, Yu Yongjia, Robert Ullrich, Mark R. Emmett, Computational Mathematics Assimilation of Large Multi-Omics Datasets. Poster Presentation. Publications:

	1) Identification of Multiple Pathways: RNA-Seq Analysis of Livers from 56Fe Ion Irradiated Mice, Anna M. Nia, Tianlong Chen, Brooke L. Barnette, Robert L. Ullrich, Mark R. Emmett, and Suresh K. Bhavnani, to be submitted to BMC Bioinformatics, November 2018. Summary of Project Status: Despite several major setbacks, the massive multi-omic data sets are now producing informative data. The first of many manuscripts will be submitted this month. The advances in the computation reduction methods is exciting and the PI expects the Modularity based analysis to be a leap forward in multi-omics analysis. The PI and Co-I are equally excited about the prospects of identifying specific countermeasure therapeutic targets based on the multi-omics pathway analysis coupled with specific lipid/protein targeting. Additional data analysis and metabolite assays would further validate these targets.
Bibliography Type:	Description: (Last Updated: 04/10/2021)
Articles in Other Journals or Periodicals	Nia AM, Chen T, Barnette BL, Ullrich RL, Emmett MR, Bhavnani SK. "Identification of Multiple Pathways: RNA-Seq Analysis of Livers from 56Fe Ion Irradiated Mice." Submitted to BMC Bioinformatics, November 2018 , Nov-2018