Fiscal Year:	FY 2016	**Task Last Updated:**	FY 11/06/2015
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		
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PI Organization Type:	UNIVERSITY	**Phone:**	409-747-1943
Organization Name:	The University of Texas Medical Branch		
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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:**	01/06/2019
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	2	**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:**	
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	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):	Meyer-Baese, Anke Ph.D. (Florida State University) Moskal, Joseph Ph.D. (Falk Center for Molecular Therapeutics) Ullrich, Robert Ph.D. (University of Texas Medical Branch) Lichti, Cheryl Fae 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:	
Task Progress:	Although this grant has only been operational for approximately seven months, the Principal Investigator (P.I.) is happy to report significant progress. The official start date on the grant is listed as 01/06/2015, but funds did not arrive at University of Texas Medical Branch (UTMB) until ~03/22/2015. The P.I. had usable funds for this project starting approximately 04/01/2015. There have been major staffing changes to the project. The P.I. and Co-I (Dr. Robert L. Ullrich) are confident that these changes will enhance the project. In the resubmission of the proposal, the proteomics focus was shifted to targeted proteomics based on the transcriptomic data instead of broad based shotgun proteomics. The targeted proteomics can easily be performed with the P.I.'s ultra high-resolution 12T Fourier transform ion cyclotron mass spectrometer (FT-ICR MS). This change no longer warranted an expert in global proteomics. To enhance productivity, Dr. Cheryl F. Lichti has been added at 20% Effort. Dr. Lichti is highly qualified and has over 10 years of experience in proteomics, mass spectrometry instrumentation and is highly skilled in mass spectrometry data analysis. In the original budget, the P.I. had budgeted to bring in Dr. Lichti at 10% effort in years 3 and 4. The personnel change now allows Dr. Lichti to participate in the project from the beginning. Dr. Lichti is currently applying her expertise in proteomics data analysis to enhance the throughput and efficiency of the lipid analysis, which is a major advance over the manual identification used previously by the P.I. Two graduate students have joined this project: Brooke L. Barnette (Ph.D. student) and Shinji K. Strain (MD/Ph.D. student). Both of these students are highly advanced. Ms. Barnette joined the P.I.'s lab May of 2015 with a Master's Degree and a great deal of mass spectrometry experience. She already has the nano-LC chromatography for lipids interfaced to the 12T FT-ICR MS. She has optimized the lipid extraction from samples and moved to a much smaller sample size (20 micron tissue slices vs. 5 mm tissue punches) and has demonstrated reproducible, high sensitivity analysis of these samples on the 12T FT-ICR MS. She is also working with Dr. Lichti to develop enhanced data analysis of the global lipid profiling from the data that she is collecting on the 12T FT-ICR MS. Shinji K. Strain was in his third year of his Ph.D. in physics at Rice University (Houston) when he decided to pursue a degree in medicine. Mr. Strain came to UTMB's MD/Ph.D. program and joined the P.I.'s lab in July 2015. Mr. Strain's background in physics and instrumentation has allowed him to master the mass spectrometry instrumentation used in this project faster than any student the P.I. has ever encountered. His two years of medical school training has provided him with the biological/biochemical background to be a great asset in the interpretation of the biochemical mechanisms involved in the molecular changes in the irradiated vs. control samples in this project. The P.I. is FULLY confident that these two advanced graduate students can easily replace the TBA senior scientist (50% effort) in this project. They are both fully trained on the instrumentation and currently working on the project. The P.I. travelled to the NASA Space Research Laboratory (NSRL) at Brookhaven National Laboratory (BNL) in October, 2015 and was able to irradiate all the mice for this project. Mice were irradiated with HZE-irradiation with 600 MeV/n 56Fe ions (0.2 Gy), 1 GeV/n 16O (0.2 Gy), and 350 MeV/n 28Si (0.2 Gy) and 137Cs gamma rays (1 and 3 Gy). These mice have been received at UTMB in good health from Brookhaven Laboratory Animal Facilities (BLAF) and the first samples will be taken for analysis beginning on 11/16/2015. The progress on the specific aims for this project is: Specific Aim 1. Determine the microenvironmental changes in hepatic lipids by MALDI-IMS after HZE-irradiation with 600 MeV/n 56Fe ions (0.2 Gy), 1 GeV/n 16O (0.2 Gy) and 350 MeV/n 28Si (0.2 Gy) and 137Cs gamma rays (1 and 3 Gy). All irradiations HZE and gamma on all mice have been completed. First time point sample collection will begin 11/16/2015. Specific Aim 2. Determine transcriptional changes in the hepatic microenvironment of HZE- and gamma-irradiated samples, compared to controls. Transcriptional analysis will begin when enough samples have been collected to establish a full chip for efficient analysis. 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 The lipid extraction methodology has been optimized. The nano-LC chromatographic separation has been optimized and interfaced to the 12T FT-ICR MS. Data collection has been demonstrated and reproducibility established with control samples. The assay for global analysis is fully functional and ready for application as soon as samples are produced (beginning 11/16/2015). 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. New data analysis regimes have been under evaluation and progress has been made on efficient lipid identification and quantification which greatly surpass previous methodology used by the P.I. In summary, the project is on-track and on-schedule.
Bibliography Type:	Description: (Last Updated: 04/10/2021)