Fiscal Year:	FY 2015	**Task Last Updated:**	FY 02/16/2017
PI Name:	Ullrich, Robert Ph.D.		
Project Title:	NSCOR: NASA Specialized Center of Research on Radiation Carcinogenesis		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
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:	bullrich@utmb.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	409-747-1935
Organization Name:	University of Texas Medical Branch		
PI Address 1:	301 University Blvd		
PI Address 2:	Comprehensive Cancer Center, MS 1048		
PI Web Page:			
City:	Galveston	**State:**	TX
Zip Code:	77555-5302	**Congressional District:**	14
Comments:	NOTE: PI moved to UTMB from Colorado State University in late 2008 (6/2009)		
Project Type:	Ground	**Solicitation / Funding Source:**	2008 NSCOR Space Radiation NNJ08ZSA003N
Start Date:	06/01/2009	**End Date:**	09/30/2015
No. of Post Docs:	2	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**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: End date changed to 9/30/2015 (from 5/31/2015) per NSSC information (Ed., 6/1/15) NOTE: End date changed to 5/31/2015 per NSSC information (Ed., 3/3/14)		
Key Personnel Changes/Previous PI:	none		
COI Name (Institution):	Le Beau, Michelle (University of Chicago) Bacher, Jeff (Promega Corporation) Yu, Yongjia (University of Texas Medical Branch) Story, Michael (University of Texas Southwestern Medical Center at Dallas) Bedford, Joel (Colorado State University) Weil, Michael (Colorado State University) Ray, F (Colorado State University) Ding, Lianghao (University of Texas Southwestern Medical Center at Dallas) Xie, Yang (University of Texas Southwestern Medical Center)		
Grant/Contract No.:	NNX09AM08G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

The goal of this NASA Specialized Center of Research (NSCOR) is to provide the information required to develop a rational scientific basis for estimation of risks for carcinogenesis in humans from exposure to radiation during space flight. Previous results from this Program found an unexpectedly low RBE (relative biological effectiveness) value for acute myeloid leukemia (AML) induction by 1 GeV 56Fe ions. Systematic cytogenetic analyses suggested both microdosimetric factors related to the track structure of 1 GeV 56Fe ions and biological factors could account for this observation. In addition, these studies found an unexpected increase in hepatocellular carcinoma (HCC) at doses as low as 0.1 Gy of 1 GeV 56Fe ions but very little, if any, increase following gamma-ray exposure. These data suggest that processes associated with expansion and progression of initiated cells may play a more prominent role in HCC. If this is the case, it is possible that there are qualitative differences as well as quantitative in the effects of HZE (high energy) irradiations. To expand on these results and to address the overall goal of this NSCOR a series of coordinated activities will be conducted in 5 Projects and 3 Cores aimed at: (1) providing quantitative animal tumorigenesis data on the relative effectiveness of specific HZE particles and SPE (solar particle event) protons compared with gamma-rays in mouse models of AML and HCC; (2) providing a better understanding of the impact of radiation exposure on the processes involved in the initiation and in the progression of initiated cells toward the neoplastic phenotype; 3) delineating potential differences between low LET (linear energy transfer) radiation and high LET radiation such as those encountered in space travel on these processes; 4) developing links between animal data and radiation-induced effects for AML in humans; and (5) developing biologically-based modeling approaches which are critical to link these biological effects to risks in humans.
Program Overview: The Radiation Carcinogenesis NSCOR was initiated in June 2009 and builds upon results obtained in its predecessor, the Leukemogenesis NSCOR. The Radiation Carcinogenesis NSCOR consists of four projects supported by three cores. The projects and cores are briefly described below.

Project 1. Dose response relationships for induction of AML and HCC as a function of radiation quality (project leader, Dr. Robert. L. Ullrich). This project is designed to compare the effects of irradiation with gamma-rays, select HZE particles, and protons on the induction of AML and hepatocellular carcinoma (HCC) using the C3H murine model.

Project 2. Mechanisms of radiation leukemogenesis (project leader, Dr. Michael M. Weil). The goal of Project 2 is to better understand how radiation leads to AML in a murine model and to generate data for the development of a biologically based model that can be used to predict AML risks from various HZE or high energy proton exposures.

Project 3. Pathogenesis of radiation-induced hepatocellular carcinoma (project leader, Dr. Robert L. Ullrich). The overall hypothesis of this project is that the dose response is likely to reflect both quantitative as well as qualitative differences in high LET effects. This overall hypothesis will be tested in 3 specific aims:

1. Quantify the frequency and progression of preneoplastic foci (including both hyperplastic and dysplastic foci) in livers of C3H/HeNCrl mice irradiated with either 137Cs gamma-rays or HZE ions.

2. Examine irradiated liver for evidence of increased oxidative damage and alterations in the regulation of inflammatory processes.

3. Determine tumorigenic effects following HZE and gamma-ray irradiation in murine models of hepatocellular carcinoma in which secondary “promoting” events play a significant role.

Project 4. Molecular and cytogenetic targets in murine and human AML. (Project leader, Dr. Michelle Le Beau). This project is designed to develop a cytogenetic and molecular profile of human radiation-induced AML, leading to an understanding of the key events and genetic pathways involved in the pathogenesis of this disease.

Core A (Core Director, Dr. F. Andrew Ray). The Biology Core facilitates the distribution of irradiated and control animals, tissues, cells, and other biological samples to investigators. This core is also responsible for conducting the irradiations required at the various sites for all projects.

Core B (Core Director, Dr. Michael Story). The Genomics and Biostatistics core provides appropriate genomic analyses, innovative statistical modeling, simulations, and data analyses for the projects.

Core C (Core Director, Dr. Robert Ullrich). The Administrative Core provides administrative, fiscal, and management support for the Radiation Carcinogenesis NSCOR. This core also oversees the overall scientific conduct of the NSCOR and facilitates interactions between projects, core leaders, and project investigators as well as interactions with the internal and external advisors.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

This work will provide basic information on mechanisms of carcinogenesis as well as mechanisms specific to radiation-induced cancer.

Project 1. Dose response relationships for induction of AML and HCC as a function of radiation quality (project leader, Dr. Robert. L. Ullrich).
We completed analysis of the incidence of acute myeloid leukemia (AML) and hepatocellular carcinoma (HCC) as a function of dose in the gamma ray, 1972SPE proton, 600 MeV/n 56Fe, and 300 MeV/n 28Si groups and the data for the 600 MeV/n 56Fe and 300 MeV/n 28Si groups were published (Weil et al., 2014). While the dose responses for AML are slightly different than in our previous studies using 1 GeV/n 56Fe ions obtained in an earlier NSCOR, they confirm a relatively low RBE for induction of AML (<5). Data for HCC were also quite similar to our previous studies with 1 GeV/n 56Fe ions, confirming a very high RBE (>60) for induction of HCC.

In addition, we analyzed the frequency of metastases in each of these groups. There were significantly more metastases in the Si and Fe groups suggesting that in addition to qualitative effects, there are also qualitative differences in effects of Si and Fe ions when compared with gamma ray or protons. Studies examining effects of low dose rate protons and fractionated 600 MeV 56Fe ions on the induction of AML and HCC were also completed.

Project 2. Mechanisms of radiation leukemogenesis (project leader, Dr. Michael M. Weil).

Project 2 focused on unraveling the events that lead to radiation-induced leukemia (rAML) in a murine model. We took

Task Progress:	advantage of mice heterozygous for a Sfpi1 knockout allele on rAML susceptible and resistant backgrounds. The experimental designs and results are published in Genik et al., 2014. In the mouse, as in humans, rAML is associated with recurrent, large chromosomal deletions. In mice the radiation-induced deletion occurs on chromosome 2 and the critical gene in the deleted region is Sfpi1 (PU.1 in human nomenclature). The remaining allele of Sfpi1 is mutated in leukemias at codon 235, with a recurrent C to T transition resulting in R235C being the most common event. We found that this mutation is spontaneous, not radiation-induced. We also found that the Sfpi1 codon 235 mutation is not a rate limiting step in radiation leukemogenesis, suggesting it is present around the time of irradiation. In addition, we found evidence that loss of at least one other gene in the deleted region was required for leukemogenesis. In further work, we found that the Sfpi1 codon 235 mutation does occur spontaneously in hematopoietic cells in unirradiated C3H mice that are susceptible to rAML, but not in C57BL/6 mice that are resistant. Furthermore, the frequency of the mutation is age dependent and corresponds to the age at exposure risk for rAML. These results are significant to the NASA program because they support a hypothesis by Nori Nakamura (Radiat Res 2005; 163:258-265) that only some individuals are susceptible to radiation-induced leukemias, and those individuals carry cells with a pre-leukemic mutation at the time of radiation exposure. Radiation acts on the pre-leukemic cells by inducing additional mutations (e.g., a recurrent chromosomal deletion) that complete the transformation pathway. If the human correlates to the pre-leukemic mutation in Sfpi1 codon 235 and radiation-induced chromosome 2 deletion can be identified it will be possible to screen astronauts for pre-leukemic cells prior to missions, thus reducing their risk of leukemia. Based on recent results from large scale genome sequencing projects, the likely candidates are spontaneous TP53 mutations and deletions involving chromosomes 5 and/or 7. [Ed. note 2/1/2017: compiled from NSCOR FY2015 final progress report]
Bibliography Type:	Description: (Last Updated: 06/10/2025)
Articles in Peer-reviewed Journals	Weil MM, Ray FA, Genik PC, Yu Y, McCarthy M, Fallgren CM, Ullrich RL. "Effects of 28Si ions, 56Fe ions, and protons on the induction of murine acute myeloid leukemia and hepatocellular carcinoma." PLoS One. 2014 Aug 15;9(7):e104819. eCollection 2014. http://dx.doi.org/10.1371/journal.pone.0104819 ; PubMed PMID: 25126721 ; PubMed Central PMCID: PMC4134239 , Aug-2014
Articles in Peer-reviewed Journals	Kantara C, O'Connell MR, Luthra G, Gajjar A, Sarkar S, Ullrich RL, Singh P. "Methods for detecting circulating cancer stem cells (CCSCs) as a novel approach for diagnosis of colon cancer relapse/metastasis." Lab Invest. 2015 Jan;95(1):100-12. Epub 2014 Oct 27. http://dx.doi.org/10.1038/labinvest.2014.133 ; PubMed PMID: 25347154; PubMed Central PMCID: PMC4281282 , Jan-2015
Articles in Peer-reviewed Journals	Christofidou-Solomidou M, Pietrofesa RA, Arguiri E, Schweitzer KS, Berdyshev EV, McCarthy M, Corbitt A, Alwood JS, Yu Y, Globus RK, Solomides CC, Ullrich RL, Petrache I. "Space radiation-associated lung injury in a murine model." Am J Physiol Lung Cell Mol Physiol. 2015 Mar 1;308(5):L416-28. Epub 2014 Dec 19. http://dx.doi.org/10.1152/ajplung.00260.2014 ; PubMed PMID: 25526737; PubMed Central PMCID: PMC4346772 , Mar-2015
Articles in Peer-reviewed Journals	Barcellos-Hoff MH, Blakely EA, Burma S, Fornace AJ Jr, Gerson S, Hlatky L, Kirsch DG, Luderer U, Shay J, Wang Y, Weil MM. "Concepts and challenges in cancer risk prediction for the space radiation environment." Life Sci Space Res. 2015 Jul;6:92-103. http://dx.doi.org/10.1016/j.lssr.2015.07.006 , Jul-2015
Articles in Peer-reviewed Journals	Fleenor CJ, Higa K, Weil MM, DeGregori J. "Evolved cellular mechanisms to respond to genotoxic insults: Implications for radiation-induced hematologic malignancies." Radiat Res. 2015 Oct;184(4):341-51. Review. http://dx.doi.org/10.1667/RR14147.1 ; PubMed PMID: 26414506; PubMed Central PMCID: PMC4617554 , Oct-2015
Articles in Peer-reviewed Journals	Nia AM, Shavkunov A, Ullrich RL, Emmett MR. "137Cs γ ray and 28Si irradiation induced murine hepatocellular carcinoma lipid changes in liver assessed by MALDI-MSI combined with spatial shrunken centroid clustering algorithm: A pilot study." ACS Omega. 2020 Oct 6;5(39):25164-74. https://doi.org/10.1021/acsomega.0c03047 ; PMID: 33043195; PMCID: PMC7542585 , Oct-2020
Articles in Peer-reviewed Journals	Ding LH, Yu Y, Edmondson EF, Weil MM, Pop LM, McCarthy M, Ullrich RL, Story MD. "Transcriptomic analysis links hepatocellular carcinoma (HCC) in HZE ion irradiated mice to a human HCC subtype with favorable outcomes." Sci Rep. 2021 Jul 7;11(1):14052. https://doi.org/10.1038/s41598-021-93467-3 ; PMID: 34234215; PMCID: PMC8263559 , Jul-2021
Articles in Peer-reviewed Journals	Ding LH, Fallgren CM, Yu Y, McCarthy M, Edmondson EF, Ullrich RL, Weil MM, Story MD. "Orthologs of human circulating miRNAs associated with hepatocellular carcinoma are elevated in mouse plasma months before tumour detection." Sci Rep. 2022 Jun 28;12:10927. https://doi.org/10.1038/s41598-022-15061-5 ; PMID: 35764780; PMCID: PMC9240017 , Jun-2022