Fiscal Year:	FY 2014	**Task Last Updated:**	FY 08/31/2015
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		
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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:**	
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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 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 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 irradiations. To expand on these results and to address the overall goal of this NSCOR a series of coordinated activities will 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 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 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). 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. We have 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. Publication listed in Bibliography section.
Project 1 publications in process:

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. Submitted April 2014.

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 Investigation. Submitted June 2014.

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

Task Progress:	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. See Bibliography for publication in press. Project 3. Pathogenesis of radiation-induced hepatocellular carcinoma (project leader, Drs.Robert L. Ullrich and Yongjia Yu). 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. We have found that HZE radiations induce a significant increase in the frequency of hepatocellular carcinomas (HCC) in certain mouse strains in comparison to gamma rays (see project 1). The underlying mechanisms remain unclear, but this observation is likely to reflect both quantitative as well as qualitative differences in high LET effects. To study the pathogenesis of HZE-induced HCC, we have been pursuing three specific aims for Project 3: 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. Project 4 has been eliminated due to insufficient progress. [Ed. note: compiled from NSCOR FY2014 annual report]
Bibliography Type:	Description: (Last Updated: 06/10/2025)
Articles in Peer-reviewed Journals	Kantara C, O'Connell M, Sarkar S, Moya S, Ullrich R, Singh P. "Curcumin promotes autophagic survival of a subset of colon cancer stem cells, which are ablated by DCLK1-siRNA." Cancer Res. 2014 May 1;74(9):2487-98. http://dx.doi.org/10.1158/0008-5472.CAN-13-3536 ; PubMed PMID: 24626093; PubMed Central PMCID: PMC4013529 , May-2014
Articles in Peer-reviewed Journals	Genik PC, Vyazunova I, Steffen LS, Bacher JW, Bielefeldt-Ohmann H, McKercher S, Ullrich RL, Fallgren CM, Weil MM, Ray FA. "Leukemogenesis in heterozygous PU.1 knockout mice." Radiation Research. 2014 Sep;182(3):310-5. Epub 2014 Jul 30. http://dx.doi.org/10.1667/RR13738.1 ; PubMed PMID: 25076114 (Ed. note: previously reported in June 2015 as Accepted) , Sep-2014