Fiscal Year:	FY 2011	**Task Last Updated:**	FY 05/16/2011
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
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No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
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No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
Contact Monitor:	Cucinott1a, Francis	**Contact Phone:**	281-483-0968
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	none		
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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 involves irradiating large numbers of mice with 350 MeV 28Si ions, 600 MeV 56Fe ions, 1 GeV 56Fe ions, 137Cs gamma-rays, or protons (acute and low dose rate exposures mimicking the 1972 Solar Particle Event), and monitoring these mice for morbidity until they are 800 days of age. The mice are being necropsied and any tumors that arise characterized by histopathology. Because of the monitoring period, the immediate goal at the start of funding was to begin irradiating mice at NSRL as quickly as possible. To date, 3,800 mice have been irradiated. For Project 2 we are developing experiments that will identify the leukemia initiating cell, determine the mechanism(s) leading to PU.1 loss, and determine the role of microsatellite instability in radiation-induced AML leukemogenesis. We are engineering a panel of mice with different sized chromosome 2 deletions encompassing PU.1 and various adjacent genes. A multiplex for detection of microsatellite mutations in C3H mice has been constructed to test AML and HCC samples for evidence of MSI at the single cell level. The multiplex consists of five endogenous polyA mononucleotide repeats, including mBat-55d, mBat-56g, mBat-56j, mBat-57d, and mBat-59j. Similar assays have been developed for CBA and C57BL/6 strains, allowing us to compare MSI status in mice from any of these backgrounds. The software for analyzing MSI results has been improved to accommodate the need for high sample throughput and is now mostly automated. We are also examining mismatch repair (MMR) expression. Quantitative RT-PCR assays have been developed for Msh2, Msh3, Msh5, Msh6, Mlh1, and Pms2 genes along with a panel of mouse reference genes ActB, B2m, Gapdh, Hmbs,

Task Progress:	Hprt1, Rp113a, Sdha and Tbp. In addition, immunofluorescence assays for mouse Msh2, Msh3, Msh6 and Mlh1 are currently being optimized to test bone marrow and spleen samples for MMR protein expression. In the fall of 2010, 60 mice were irradiated for Project 3 which is designed to examine the pathogenesis of heavy ion induced hepatocellular carcinoma. Our original design was to perform serial sacrifice studies for liver tissue analysis at 6, 9, and 12 months after irradiation following 3 Gy of gamma rays or 0.1 Gy of 1 GeV Iron based on our previous studies. Surprisingly, we are observing liver tumors much earlier than expected. As a result we added a sacrifice time point at 3 months post irradiation. Based on our results we may add a 1 month time point. Below is a list of dates for serial sacrifice. The goal of Project 4 is to develop a cytogenetic and molecular profile of human radiation-induced AML, and to elucidate the key events and genetic pathways involved in the pathogenesis of this disease. To this end, we are profiling the genetic alterations in radiation-induced t-AML by (1) Cytogenetic analysis; (2) High-density SNP array analysis of copy number alterations (CNAs) and loss of heterozygosity; (3) Gene expression profiling; (4) Analysis of promoter methylation; and (5) miRNA expression profiling. To identify somatically acquired genetic CNAs in RT-induced t-AML, we are using a combination of high resolution copy number analysis using the Affymetrix Genome-Wide human SNP Array 6.0 platform (resolution of <5 kb), and targeted resequencing. Importantly, matched germline samples are available for most patients, allowing us to determine definitively if a CNA identified is somatically acquired. To date, we have extracted and hybridized DNA from 8 RT-induced t-AMLs. Analysis of recurrent CNAs by GISTIC identified several amplified (21q22.2) or deleted (5p13.3; 5q31.1 and 17p11.2) regions. Core A personnel started large scale mouse irradiations at the earliest possible time after notification that the NSCOR had been funded. The first groups of mice were irradiated in November 2009 at the NSRL facility at BNL. As of March 2011, 3,800 mice have been irradiated and are currently being monitored daily for AML and HCC at UTMB Galveston. 350 MeV 28Si, 600 MeV 56Fe, 1GeV 56Fe, 137Cs gamma-Rays, and unirradiated controls were all irradiated at the NSRL facility at the Brookhaven National Laboratory. 100 mice will be irradiated with Acute Protons this May. An additional 500 C3H mice will be irradiated with 350 MeV 28Si in the spring of 2012, thus completing the acute irradiations for Project 1 tumorigenicity studies. This year core B concentrated on concluding the expression analysis of radiation-induced AML samples. While we analyzed the data based upon both bone marrow cells and CD34+ cells last year, the final pathology had not been concluded. Interestingly, a handful of samples changed designation which meant the gene expression analysis and the aCGH had to be done. We now consider the pathology final as well as the genomic analysis. In addition to the gene expression and aCGH analysis we re-examined earlier data on DNA methylation where the Nimblegen methylation platform was used. Interestingly, there was little overall change in the gene expression data. AML and CD34+ or bone marrow cells all segregated into clusters of like samples. Some specific genes did drop out of our analysis as being differentially expressed. This was predominantly because the probes were no longer considered as valid for their gene target. This was especially true for genes associated with mis-match repair. While there were individual genes within the mis-match repair family differentially expressed, overall the pathway itself was not differentially expressed. Pu.1 is seen modestly upregulated even though one copy of the gene has been eliminated through chromosomal loss. The aCGH analysis reveals 3 very modest regions as minimally deleted which affect a handful of genes including Pu.1 for which we are investigating. Other than the massive deletion of one copy of chromosome 2 was expected, and seen, there are few other chromosomal rearrangements to speak of. The methylation data was re-examined because of the more robust analysis tools available now that we did not have originally. Although there is nothing that stands out as far as specific genes whose promoters are methylated, we have identified a number of genes whose 3' regions are highly methylated. This in fact, may be regulatory mechanism for miRNA expression and will be followed up on.
Bibliography Type:	Description: (Last Updated: 06/10/2025)
Articles in Peer-reviewed Journals	Fabre KM, Ramaiah L, Dregalla RC, Desaintes C, Weil MM, Bailey SM, Ullrich RL. "Murine Prkdc polymorphisms impact DNA-PKcs function." Radiat Res. 2011 Apr;175(4):493-500. Epub 2011 Jan 25. PMID: 21265624 , Apr-2011