Fiscal Year: FY 2009  Task Last Updated: FY 02/03/2010

PI Name: Ullrich, Robert Ph.D.  Project Title: NSCOR: Radiation Leukemogenesis

Division Name: Human Research  Program/Discipline: HUMAN RESEARCH

Program/Discipline--Element/Subdiscipline: HUMAN RESEARCH--Radiation health

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

City: Galveston  State: TX  Congressional District: 14

Zip Code: 77555-5302

Comments: NOTE: PI moved to UTMB from Colorado State University in late 2008 (6/2009)

Project Type: GROUND  Solicitation: NSCOR 03-OBPR-02

Start Date: 10/01/2003  End Date: 07/30/2009

No. of Post Docs: 1  No. of PhD Degrees: 2

No. of PhD Candidates: 4  No. of Master's Degrees:

No. of Master's Candidates: 0  No. of Bachelor's Degrees:

No. of Bachelor's Candidates: 0  Monitoring Center: NASA JSC

Contact Monitor: Cucinott1a, Francis  Contact Phone: 281-483-0968

Contact Email: noaccess@nasa.gov

Flight Program:  NOTE: End date changed to 7/30/2009 per J. Dardano/JSC (10/2009)

NOTE: Received NCE to 12/31/2008 (from 9/30/2008) per J. Dardano/JSC (9/2008)

Key Personnel Changes/Previous PI: delete personnel - John Belmont, BCM delete personnel - Wei-Wen Cai, BCM delete personnel - E.J. Ehrhart, CSU delete personnel - Lalitha Nagarajan, UTMDACC add personnel - Jeffery Bacher, Promega

COI Name (Institution): Bailey, Susan (Colorado State University)

Bedford, Joel (Colorado State University)

Story, Michael (University of Texas Southwestern Medical Center)

Weil, Michael (Colorado State University)

Bacher, Jeffery (Promega Corp.)

Grant/Contract No.: NAG9-1569

Performance Goal No.:  

Performance Goal Text: The goal of this program is to provide information required to develop a rational scientific basis for estimation of risks...
The goal of this program is to provide information required to develop a rational scientific basis for estimation of risks for leukemogenesis in humans from exposure to radiation during space flight. This will be accomplished using several coordinated research activities. A key activity will be to develop quantitative data on the relative leukemogenic effectiveness of specific HZE particles and of high-energy protons compared with gamma rays in a mouse model of radiation-induced acute myeloid leukemia (AML). Extrapolation of risks from this mouse model to risks in humans requires additional information, and a major component of research activities in this program are designed to provide such information. A major research effort of this program is focused on studies of cellular and molecular mechanisms and processes involved in radiation-induced AML. These studies will not only improve the basic understanding of the pathogenesis of AML but will also provide information on cellular and molecular markers that may be useful in predicting individuals at increased risk. These activities will focus on the use of molecular and molecular cytogenetic approaches, the development of new model systems, and comparative analyses of murine and human AML to facilitate the translation of results obtained in mice to human AMLs. Problems of extrapolation are not limited to biological factors. There are clear dosimetric differences that also must be considered when extrapolating data obtained from mouse studies to human risks. To address these issues this project also has an important physics and dosimetry component that includes modeling of dose to target cells in murine and human bone marrow.

Rationale for HRP Directed Research:

This research provides information on risks from exposure to ionizing radiation and mechanisms of carcinogenesis. It has also provided insight into potential approaches to chemoprevention of radiation damage.

Research Impact/Earth Benefits:

The Leukemogenesis NSCOR was initiated in September 2003. Its centerpiece was a key project designed to establish an RBE for 1 GeV 56Fe-induced acute myeloid leukemogenesis in CBA mice, and many of the proposed experiments in other projects relied on tumors collected from 56Fe and gamma-ray irradiated mice. 56Fe irradiation of the mice started in March 2004 at the first NSRL run after the NSCOR was formed. In the CBA mouse, the latency of radiation-induced acute myeloid leukemia (AML) is roughly one to two years. Consequently, most of our efforts over the first few years of funding were focused on irradiating mice and monitoring them for morbidity. By late 2007, tumors and tissues from irradiated and aged mice became available for analyses. In light of earlier results for neutron-induced leukemogenesis, the results for 56Fe-induced leukemogenesis study were unexpected. In brief, the RBE for 1 GeV 56Fe-induced AML was essentially 1, suggesting that cell killing effects of this HZE ion may outweigh its transformation effects in the murine radiation-induced AML model system. An additional unexpected finding was that 1 GeV 56Fe irradiated mice had a high incidence of hepatocellular carcinomas (HCC) with an estimated RBE of approximately 50. Taken together these results suggest that HZE ions induce AML and HCC by different mechanisms.

The results from the large scale mouse irradiation leukemogenesis study were complemented by cytogenetic studies of HZE irradiated mouse bone marrow cells. Deletions in chromosome 2 encompassing the PU.1 (Sfpi1 in the mouse) gene are characteristic in murine radiation-induced myeloid leukemias and are likely the initiating events for this type of cancer. In mouse strains that are susceptible to radiation-induced AML, bone marrow cells bearing chromosome 2 deletions can be found one day after radiation exposure and these cells and their descendants persist in the bone marrow, probably for the life of the mouse. Bone marrow cells with chromosome 2 deletions are also evident soon after irradiation of mouse strains that are resistant to radiation-induced AML, but in these strains with chromosome 2 deletions disappear within a month. We found that the RBE for persistent chromosome 2 deletions in 1 GeV 56Fe irradiated bone marrow cells in CBA mice was about 1. We also found that bone marrow cells with 56Fe-induced chromosome 2 deletions did not persist in an AML resistant mouse strain, C57BL/6.

With the availability of leukemic material from AML affected mice we were able to begin the characterization of 1 GeV 56Fe and gamma-ray induced leukemias. The leukemias were assayed for chromosome 2 deletions, mutations in the non-deleted PU.1 gene, microsatellite instability, gene expression, and genomic loss or gain. The data from these assays are currently being analyzed and prepared for publication. However, a preliminary review of the data suggests that 1 GeV 56Fe and gamma-ray induced leukemias have similar molecular and cytogenetic aberrations, pointing to a similar mechanism of induction. AMLs induced by these different radiations cannot be distinguished from one-another by their gene expression profiles.

An additional, smaller scale mouse HZE irradiation leukemogenesis study was initiated in April 2007. Twelve-week-old female BALB/cByJ mice were irradiated with 0.2 Gy of 1 GeV 56Fe ions, 0.5 Gy of 137Cs gamma-rays, or left unirradiated. There were approximately 100 mice per group. These mice were monitored to 800 days of age. All of the mice in the study have been euthanized either because they became moribund or because they reached 800 days. Tissues have been collected from the mice and are being examined by histopathology. The experiment was designed to provide preliminary data on whether the spectrum of tumors that arise in gamma-irradiated female BALB/c mice (mammary, ovarian, and lung tumors) also arise in 1 GeV 56Fe ion irradiated mice of the same sex and strain, and to determine if the high risk for HCC seen in HZE irradiated male CBA mice is also found in HZE irradiated female BALB/c mice.

In order to develop a biological model for radiation-induced AML, the cell type targeted by radiation for neoplastic transformation must be identified. Whether radiation-induced AML arises from a hematopoietic stem cell or a more restricted progenitor of myeloid lineage is currently unknown. We explored this question by using the PU.1 encompassing chromosome 2 deletion in irradiated bone marrow cells as an early marker for potential radiation-induced AML. We performed immunophenotyping combined with in situ hybridization (immunoFISH) to study the persistence of PU.1 containing chromosome 2 deletions in hematopoietic stem cells and lineage specific progenitor cells. Bone marrow cells were harvested from CBA/CaJ mice irradiated with 3 Gy of 137Cs ?-rays 1, 3 and 6 months post-irradiation and assayed by immunoFISH for PU.1 deletions and cell differentiation markers. The preliminary data demonstrated that the frequency of PU.1 deletions were similar in different cell types 1 month after irradiation but increased in the myeloid lineage and decreased in the lymphoid lineage at 3 and 6 months post-irradiation. This result indicates that radiation-induced AML is likely to originate from the more restricted progenitor of the myeloid lineage.

The original funding period for the Leukemogenesis NSCOR ended on September 30, 2008 and was followed by extensions to the end of July 2009. We took advantage of this period to undertake small, short duration experiments and to develop methodology that would be useful in a renewed of the NSCOR program. This work included a preliminary screen of Ras and Raf mutations in HCC arising in gamma-ray and 56Fe ion irradiated mice, and unirradiated controls.
Codons 12, 13 and 61 of H-ras, K-ras and N-ras, and codon 624 of B-Raf were sequenced in representative tumors because these are mutation “hotspots” in chemically induced HCC. H-ras codon 61 mutations were detected in 5 of 6 tumors from unirradiated mice, 1 of 6 tumors from gamma-ray exposed mice, and 5 of 12 tumors from 56Fe irradiated mice. B-Raf codon 624 mutations were detected in one tumor each from gamma-ray and 56Fe ion irradiated mice.

We also developed a PCR-based assay capable of detecting rare bone marrow cells with point mutations in codon 235 of the PU.1 gene in irradiated mice. A second assay based on laser scanning cytometry is also under development. PU.1 codon 235 mutations are found in about 85% of murine radiation-induced AMLs with chromosome 2 deletion and their occurrence is thought to be a key step in leukemogenesis. Once perfected, these assays will allow us to determine the timing of the codon 235 mutation, the cells affected, and whether the mutation occurs preferentially in cells that have suffered a chromosome 2 deletion.

Articles in Peer-reviewed Journals


