Fiscal Year:	FY 2009	**Task Last Updated:**	FY 08/04/2008
PI Name:	Burma, Sandeep Ph.D.		
Project Title:	Molecular and Cellular Effects of Heavy Ion Fragmentation due to Shielding		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation Biology		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **ARS**:Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs) (2) **Cancer**:Risk of Radiation Carcinogenesis (3) **CNS**:Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure (4) **Degen**:Risk of Cardiovascular Disease and Other Degenerative Tissue Effects From Radiation Exposure and Secondary Spaceflight Stressors		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	burma@uthscsa.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	210-450-8981
Organization Name:	University of Texas Health San Antonio		
PI Address 1:	Department of Neurosurgery, Department of Biochemistry and Structural Biology		
PI Address 2:	7703 Floyd Curl Drive, MC7843, Room 102F		
PI Web Page:			
City:	San Antonio	**State:**	TX
Zip Code:	78229	**Congressional District:**	21
Comments:	NOTE: Formerly at University of Texas Southwestern Medical Center at Dallas until fall 2019.		
Project Type:	GROUND	**Solicitation / Funding Source:**	2004 Radiation Biology NNH04ZUU005N
Start Date:	10/01/2005	**End Date:**	09/30/2010
No. of Post Docs:	1	**No. of PhD Degrees:**	
No. of PhD Candidates:	2	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA ARC
Contact Monitor:	Cucinott1a, Francis	**Contact Phone:**	281-483-0968
Contact Email:	noaccess@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: Received NCE to 9/30/2010 per A. Chu/ARC (8/09) NOTE: Changed Division and Discipline/Program to HRP as of FY2006, per program changes at that time, per JSC/A. Chu-ARC (jvp 4/2009)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):			
Grant/Contract No.:	NNA05CS97G		
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Task Description:	Galactic cosmic rays (GCRs) represent a major risk to human crews on long-term missions outside the Earth's magnetic field. The GCR consists of protons, helium nuclei and HZE (High Z and Energy) particles such as iron. Understanding the radiobiology HZE particles is of enormous interest as the energy of these particles can be sufficient in many cases to penetrate the spacecraft hull and interior materials. While traversing through matter, high energy radiation fragments into a large number of secondary particles with generally lower energy but with higher ranges and biological effects than the incident cosmic rays. Therefore, an exact knowledge of the biological effects of shielding is important not only for understanding the risks to humans on space flights but also for determining optimal shielding for space crafts. Previous studies have used relatively late end points such as chromosome aberrations and cell survival to elucidate the biological consequences of fragmentation due to shielding. The early response of a mammalian cell to ionizing radiation has recently been very clearly elucidated at the molecular level in the context of the relocation and modification of damage-responsive factors and these very early events have a very important bearing on the repair of DNA damage and the ultimate fate of the cell. In this proposal we aim to study the biological effects of shielding using these pertinent early molecular responses as end points. Specific Aims are: 1) To test the hypothesis that shielded heavy ions may result in more complex DNA damage to the cells as compared to unshielded heavy ions, 2) To test the hypothesis that the molecular response to shielded radiation is different from that induced by unshielded radiation, and 3) To test the hypothesis that shielded radiation may have more deleterious effects on the cell as compared to unshielded radiation and to elucidate the mechanisms involved in repair of DNA damage. Studies carried out in NSRL at Brookhaven National Laboratory during 2006 and 20007 (NSRL6A-7B) indicate that significant differences exist between DNA damage caused by unshielded Fe particles versus particles that have passed through different shielding materials. Our studies have also begun to elucidate the molecular and cellular consequences of the fragmentation of HZE particles during passage through shielding materials.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Galactic cosmic rays (GCRs) represent a major risk to human crews on long-term missions outside the Earth's magnetic field. The GCR consists of protons, helium nuclei and HZE (High Z and Energy) particles such as iron ions. Understanding the radiobiology of HZE particles is of enormous interest as the energy of these particles can be sufficient in many cases to penetrate the spacecraft hull and interior materials. While traversing through matter, HZE particles fragment into a large number of secondary particles with generally lower energy but with higher ranges and biological effects than the incident cosmic rays. Therefore, an exact knowledge of the biological effects of shielding is important not only for understanding the risks to humans on space flights but also for determining optimal shielding for space crafts. Previous studies have used relatively late end points such as chromosome aberrations and cells survival to elucidate the biological consequences of fragmentation due to shielding. The early response of a mammalian cell to ionizing radiation has recently been very clearly elucidated at the molecular level especially, the relocation and modification of damage-responsive factors at DNA-damage sites and these very early events have a very important bearing on the repair of DNA damage and the ultimate fate of the cell. In this proposal, we are studying the biological effects of shielding using these pertinent early molecular responses as end points. With these approaches, we can not only verify the immediate biological effects of beam fragmentation through shielding but can also estimate the efficacy of shielding materials.
Task Progress:	Background and Significance. Galactic cosmic rays (GCRs) represent a major risk to human crews on long-term missions outside the Earth's magnetic field. The GCR consists of protons, helium nuclei and HZE (High Z and Energy) particles such as iron ions. Understanding the radiobiology of HZE particles is of enormous interest as the energy of these particles can be sufficient in many cases to penetrate the spacecraft hull and interior materials. While traversing through matter, such as spacecraft shielding, an HZE particle may undergo either of two changes: 1) the particle may lose velocity as it traverses the shield thereby becoming more ionizing (increased LET) and, thus, more deleterious OR 2) the particle may fragment into a large number of secondary particles which are generally less ionizing (decreased LET) but result in a more complex radiation field. The net effect of shielding (whether beneficial or detrimental) is thus a trade off between loss of velocity and fragmentation. This is largely influenced by the composition of the shield with high Z shields resulting in loss of velocity (thus increased LET) and more hydrogenous shields such as polyethylene (CH2) favoring fragmentation (thus decreased LET). While the physical aspects of interaction of HZE particles with shielding matter are somewhat understood what is not known at all is the extent and complexity of DNA damage induced by these particles after shield traversal. This is important not only for understanding the risks to humans on space flights but also for determining optimal shielding for spacecrafts. Specific Aims: 1) To test the hypothesis that shielded heavy ions may result in more complex DNA damage to the cells as compared to unshielded heavy ions, 2) To test the hypothesis that the molecular response to shielded radiation is different from that induced by unshielded radiation, and 3) To test the hypothesis that shielded radiation may have more deleterious effects on the cell as compared to unshielded radiation and to elucidate the mechanisms involved in repair of DNA damage. Brief summary of progress. In experiments carried out during the first two years of the project we were able to establish the methods that would be required for successful completion of the project. We were also able to obtain preliminary results that allowed us to estimate the feasibility of the proposed objectives. In the third year (2007-2008), significant progress was made in most of the proposed aims of the project, resulting in a manuscript that was accepted for publication in DNA Repair. These results are detailed below along with plans for the coming year. Detailed summary of progress. Ions of high atomic number and energy (HZE particles) pose a significant cancer risk to astronauts on prolonged space missions. The properties of these particles can be drastically altered during passage through spacecraft shielding, therapy beam modulators, or the human body. In this project, we have used pertinent responses to DNA double-strand breaks (DSBs) to understand the consequences of energy loss versus nuclear fragmentation of Fe ions during passage through shielding or tissue-equivalent materials. Phosphorylation of histone H2AX and recruitment of 53BP1 were used to generate 3D reconstructions of DNA damage in human cells and to follow its repair. Human cells are unable to repair a significant portion of DNA damage induced by Fe ions. DNA-PK and ATM are required, to different extents, for the partial repair of Fe-induced DNA damage. Aluminum shielding has little effect on DNA damage or its repair, confirming that the hulls of the Space Shuttle and the International Space Station afford scant protection against these particles. Lead shielding, on the other hand, exacerbates the effects of Fe ions due to energy loss during particle traversal. In sharp contrast, polyethylene (PE), a favored hydrogenous shield, results in DNA damage that is more amenable to repair presumably due to Fe ion fragmentation. Human cells are indeed able to efficiently repair DSBs induced by chlorine ions and protons that represent fragmentation products of Fe.

	Interestingly, activation of the tumor suppressor p53 in these cells is uniquely biphasic and culminates in the induction of high levels of p21(Waf1/Cip1), p16(INK4a) and senescence-associated beta-galactosidase activity. Surprisingly, these events occur even in the absence of ATM kinase implying that ATR may be a major responder to the complex DNA damage inflicted by Fe ions. Significantly, fragmentation of the Fe beam through PE attenuates these responses and this, in turn, results in better long-term survival in a colony forming assay. Our results help us to understand the biological consequences of ion fragmentation through materials and provide us with a biological basis for the use of hydrogenous materials like PE as effective space shields. Future plans. The long-term goal would be evaluate the contribution of Fe particles with or without shielding to carcinogenesis using models currently being developed in my laboratory. As a model system, we have used “primed” astrocytes bearing some (but not all) of the mutations that would lead to the development of glioblastomas (aggressive brain tumors). These “pre-initiated” cells normally do not form tumors in nude mice. We find, however, that irradiation of these cells with Fe ions results in tumor formation. We can, therefore, use this model system to evaluate the effectiveness of relevant shielding materials.
Bibliography Type:	Description: (Last Updated: 04/27/2023)
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