Fiscal Year:	FY 2009	**Task Last Updated:**	FY 08/06/2008
PI Name:	Hall, Eric J Ph.D., D.Sc.		
Project Title:	Mechanisms of Ocular Cataracts		
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) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	10032	**Congressional District:**	15
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2004 Radiation Biology NNH04ZUU005N
Start Date:	10/04/2005	**End Date:**	09/30/2010
No. of Post Docs:	0	**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:	Cucinott1a, Francis	**Contact Phone:**	281-483-0968
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Flight Program:			
Flight Assignment:	NOTE: Received no-cost extension to 9/30/2010 per J. Dardano/JSC (8/09)		
Key Personnel Changes/Previous PI:	Personnel unchanged		
COI Name (Institution):	Brenner, David Ph.D. (Columbia University) Smilenov, Lubomir (Columbia University) Kleiman, Norman (Columbia University)		
Grant/Contract No.:	NNJ05HI38G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Radiation standards in space have followed a somewhat different path from those on the ground. Exposures in space are potentially much higher than terrestrial irradiation due to galactic cosmic radiation, trapped radiation belts near the earth and solar particle events. Radiation exposures in space are relatively difficult to reduce and impossible to eliminate entirely. At the same time, other risks to humans in the hostile environment in space may be more acute or drastic than those of radiation. This puts a different perspective on radiation hazards and is one reason, together with the limited number of individuals involved, why larger annual dose limits have been tolerated for astronauts than are recommended for radiation workers on the ground, (though career limits of risk have been roughly equalized). The purpose of radiation protection is to prevent deterministic effects of clinical significance and limit stochastic effects to levels that are acceptable, modulated by societal concerns. The deterministic effect already observed in some astronauts is an earlier onset of ocular cataracts. The hypothesis upon which this proposal is based is that heavy ions mediate their cataractogenic effect through errors in differentiation resulting from damage and/or misrepair of irradiated cells . Aberrantly dividing and/or differentiating cells in the pre-equatorial region of the lens epithelium eventually migrate to the lens where they become opaque lens fiber cells. We propose to investigate the mechanisms of cataractogenesis by looking at cataract formation in animals haploinsufficient for one or more genes involved in DNA repair and/or checkpoint control.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The hypothesis upon which this proposal is based is that heavy ions mediate their cataractogenic effect through errors in differentiation resulting from damage and/or misrepair of irradiated cells. We propose to investigate the mechanisms of cataractogenesis by looking at cataract formation in animals haploinsufficient for one or more genes involved in DNA repair and/or checkpoint control, including Atm, rad9 and BRCA. The research impact of this study will be to provide information on the mechanism of cataract induction in radiosensitive subpopulations.
Task Progress:	Our research is directed at understanding how low doses of heavy ion (high-LET) exposure, similar to that received by astronauts in space, results in cataract in a genetically defined mouse model system. More specifically, we seek to understand whether individuals with one good and one bad copy of gene(s) involved in DNA repair and/or cell cycle checkpoint control (Atm, Brca1 or Rad9) are more susceptible to cataract development. These studies provide an opportunity to investigate the influence(s) of genetic factors on radiosensitivity in a rodent model that has great relevance and similarity to human response to radiation exposure and determination of appropriate human exposure guidelines. Findings in this animal model are likely to be important to the development of appropriate guidelines for national space radiation risk policy. To date, increased incidence and earlier onset of cataract are the only long-term degenerative effects observed in astronauts exposed to space radiation. Furthermore, considerable uncertainty surrounds the relationship between radiation dose and cataract development, which is of concern to the risk assessment community. Previous NASA funded studies from our laboratory demonstrated that mice haplo- insufficient for Atm (one good copy and one bad copy of the Atm gene) develop high-LET (heavy-ion) radiation induced cataracts earlier and with more severity than wild type animals. This leads to speculation that the unexpected observation of cataractogenesis in the astronaut core might be explained by individual genetic susceptibilities and predispositions. Our group received a multi-year NASA grant funded to investigate the mechanisms of heavy ion induced cataractogenesis in mice that are haplo-insufficient for one or more genes involved in DNA repair and/or checkpoint functions. Animals singly or double heterozygous for Atm, Brca1 and/or Rad9, as well as wildtype animals, were exposed to either 5 or 25 cGy of 1,000 MeV/amu 56Fe in the BNL NASA Space Radiation Laboratory (NSRL). Many of the animals irradiated in mid to late 2007 and early 2008 are still being examined biweekly to classify the extent and stage of lens opacification. For example, we irradiated approximately 80 rad9/ATM in Fall 2007 with 5 cGy of 56Fe and approximately 120 Brca1/ATM mice with 56Fe in Spring 2008 averages below 1.0, a cataract stage half that of the double heterozygous mutants. While it is too early to unfold the data in detail, preliminary results indicate that, even at these low doses of heavy ions, irradiated animals are developing lens opacification characteristic of radiation exposure and that some mutant genotypes develop cataract faster than irradiated wild-type animals. Many more Atm-Brca1 double heterozygous animals appear to have reached stage 1.5 cataracts than either Brca1 or Atm singly heterozygous animals. The degree of opacification in wild-type, control animals still averages below 1.0, a cataract stage half that of the double heterozygous mutants. Throughout the coming year, we will continue to examine these animals as well as begin to examine various measures of DNA damage and repair, cell death, mitochondrial function and other cytological endpoints in lens epithelial cells obtained from irradiated animals at the end of their lifespans. To summarize, these studies are among the first to study the effect(s) of multiple haplo-insufficiency on biological response in a highly organized tissue. We believe they will shed considerable light on the genetic control and cellular mechanisms of heavy ion induced cataractogenesis. More significantly, our preliminary results suggest that double heterozygotes are more sensitive to the cataractogenic effects of ionizing radiation than single heterozygotes or wild-type controls. This finding is likely to have important implications for both radiosensitive subsets of the human population and for the astronaut core.
Bibliography Type:	Description: (Last Updated: 10/26/2023)
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Abstracts for Journals and Proceedings	Hall EJ. " Invited talk: Neutrons Secondary to Proton Therapy: Problems and Solutions." PTCOG Meeting, Jacksonville, FL, May 19-24, 2008. PTCOG Meeting, Jacksonville, FL, May 19-24, 2008. , May-2008
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