Fiscal Year:	FY 2010	**Task Last Updated:**	FY 09/08/2009
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:**	09/30/2011
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 9/30/2011 per C. Guidry/JSC (8/10) 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 Brca1. The research impact of this study will be to provide information on the mechanism of cataract induction in radiosensitive subpopulations.
Task Progress:	To date, increased incidence and earlier onset of cataracts 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. The research reported here seeks to expand the library of genes involved in DNA repair and checkpoint control beyond Atm, and also to investigate the possible importance of mutations in more than one gene. Attention focused on two genes, Brca1 and Rad9, haplo-insufficiency for which had previously been shown to confer radiosensitivity on cells cultured in vitro. In these studies, the endpoints scored were oncogenic transformation in mouse embryo fibroblasts and apoptosis in mouse thymocytes. These systems were chosen because they give rapid results and are relatively inexpensive, but can be used to choose genes that are likely to be worth the long-term investment of studying them with the in more relevant, but labor-intensive and expensive, end-point of cataract development. Animals heterozygous for Atm, Brca1 or Rad9, as well as wild-type animals, were exposed to either 5 or 25 mGy of 1,000 MeV/amu 56Fe in the BNL NASA Space Radiation Laboratory (NSRL). In addition, double heterozygous animals, Atm/Rad9 and Atm/Brca1, were created by cross-breeding single heterozygotes, and exposed to the same doses of heavy ions. Animals are examined biweekly to classify the extent and stage of lens opacification as it develops, and because the doses used were so low, observations are continued for over a year post-irradiation. During the past year we have completed the study of Atm combined with Brca1, which involved over 200 animals scored for over a year. The study of Atm combined with Rad9 is 50% completed. The first batch of 120 animals was irradiated in 2008 and have been examined for almost one year. A second batch is scheduled to be irradiated in the Fall of 2009, with the study ending in late 2010. To summarize, haplo-insufficiency for both genes studied to date, namely Atm and Brca1, resulted in radiation-induced cataracts that appeared earlier and at a higher grade than in wild type animals. Since mutations and/or polymorphisms are present in the homologues of these genes in the human population, this suggests the existence of a radiosensitive sub-population of a few percent The study of the double heterozygotes also raises an interesting point. Animals heterozygous for both Atm and Brca1 were no more radiosensitive that animals heterozygous for a single gene, suggesting no additive effect as far as these genes are concerned. There are two important consequences of the existence of a radiosensitive sub-population. First it would distort the shape of the dose-response relationship for end-points such as carcinogenesis. Linearity between dose and effect would no longer be the case if a fraction of the population is radiosensitive. Second, it would be unethical to place a radiosensitive individual in a situation where they may be exposed to a significant dose of radiation. It is entirely possible that other genes will be identified that will add to the potential pool of genes determining the size of the radiosensitive human sub-population.
Bibliography Type:	Description: (Last Updated: 10/26/2023)
Articles in Peer-reviewed Journals	Hall EJ. "Is there a place for quantitative risk assessment? " Journal of Radiological Protection, 2009 Jun: 29(2A): A171-84. PubMed PMID: 19454800 , Jun-2009
Articles in Peer-reviewed Journals	Su F, Smilenov L, Ludwig T, Zhou L, Zhu J, Zhou G, Hall EJ. "Heterozygosity for Atm and Brca1 influence the balance between cell transformation and apoptosis." International Journal of Radiation Biology (Submitted, May 2009). , May-2009
Articles in Peer-reviewed Journals	Zhou G, Smilenov LB, Lieberman HB, Hall EJ. "Radiosensitivity to high energy iron ions is influenced by heterozygosity for Atm, Rad9 and Brca1." Advances in Space Research (Submitted, June 2009). , Jun-2009

Articles in Peer-reviewed Journals	Neriishi K, Blakely EA, Kleiman NJ, Shore RE, et al. "Meeting Report: Radiation Cataractogenesis Workshop 2009, Hiroshima, Japan." Radiat. Res., (Submitted, July 2009). , Jul-2009