Fiscal Year:	FY 2008	**Task Last Updated:**	FY 07/20/2007
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:**	09/30/2009
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:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
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:	To date we have completed the first specific aim, namely to establish stocks of mice heterozygous for the Atm and BRCA1, and also to produce double heterozygotes, i.e. animals haploinsufficient for both Atm and BRCA1. Towards completion of the second specific aim, 287 mice have been enrolled in the study since the Spring 2006 BNL run. These include 28 double heterozygotes, 52 Atm heterozygotes, 46 Brca1 heterozygotes and 98 wild type controls. (Approximately half of the wild-type controls are being utilized for histological and immunohistological preparations.) 24 double heterozygotes, 39 Atm herozygotes, 42 Brca1 heterozygotes and 67 wild types were irradiated with either 5 or 25 cGy of 1,000 MeV/n 56Fe (approximately equal numbers of mice received each of the two doses). Mice are examined weekly by slit lamp examination and monthly by Scheimpflug examination. Cataract stage is scored for each mouse and the genotype or irradiation status of each animal is blinded to the observer. Examination will continue for up to 100 weeks post irradiation unless death and/or disease removes the animal from the study. At present, 103 mice have been examined for approximately 68 weeks, 121 mice for 54 weeks and 63 mice for 40 weeks post examination. Preliminary results for average cataract stage in this study can be calculated using the aggregate data from the four genotypes without revealing information about any particular animal. In general, at any time point, average cataract stage for single and double heterozygotes is greater than that of wild type animals and the oldest such animals are presently approaching an average cataract stage of 2.0 (3.0 is considered blinding and any animal with this score is sacrificed.) Unirradiated control animals have average cataract scores in the range of 1.0-1.5. The code will be broken and the data analysed in approximately one year.
Bibliography Type:	Description: (Last Updated: 10/26/2023)
Articles in Peer-reviewed Journals	Hall EJ, Worgul BV, Smilenov L, Elliston CD, Brenner DJ. "The relative biological effectiveness of densely ionizing heavy-ion radiation for inducing ocular cataracts in wild type versus mice heterozygous for the ATM gene. " Radiat Environ Biophys. 2006 Jul;45(2):99-104. Epub 2006 Jun 24. PMID: 16799786 , Jul-2006
Articles in Peer-reviewed Journals	Hall EJ. "Intensity-modulated radiation therapy, protons, and the risk of second cancers." Int J Radiat Oncol Biol Phys. 2006 May 1;65(1):1-7. Review. PMID: 16618572 , May-2006
Articles in Peer-reviewed Journals	Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, Begg CB, Caporaso N, Chanock S, DeMichele A, Figg WD, Gospodarowicz MK, Hall EJ, Hisada M, Inskip P, Kleinerman R, Little JB, Malkin D, Ng AK, Offit K, Pui CH, Robison LL, Rothman N, Shields PG, Strong L, Taniguchi T, Tucker MA, Greene MH. "Cancer survivorship--genetic susceptibility and second primary cancers: research strategies and recommendations. " J Natl Cancer Inst. 2006 Jan 4;98(1):15-25. Review. PMID: 16391368 , Jan-2006
Articles in Peer-reviewed Journals	Hall EJ. "The inaugural Frank Ellis Lecture--latrogenic cancer: the impact of intensity-modulated radiotherapy." Clin Oncol (R Coll Radiol). 2006 May;18(4):277-82. PMID: 16703744 , May-2006
Articles in Peer-reviewed Journals	Hall EJ. "Cancer caused by x-rays--a random event?" Lancet Oncol. 2007 May;8(5):369-70. PMID: 17466892 , May-2007