Fiscal Year:	FY 2007	**Task Last Updated:**	FY 07/28/2006
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:**	
No. of PhD Candidates:	0	**No. of Master' Degrees:**	
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	
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:	We sadly report the death of Professor Basil Worgul during the year. His place is taken on this project by Dr. Norman Kleiman. The rest of the personnel remains unchanged.		
COI Name (Institution):	Brenner, David J Ph.D. (Columbia University) Smilenov, Lubomir (Columbia University) Kleiman, Norman (Columbia University)		
Grant/Contract No.:	NNJ05HI38G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The only non-cancer degenerative effect so far unequivocally observed in astronauts is the early onset of ocular cataracts. Previous studies have shown that mice haplo-insufficient for Atm develop cataracts earlier than wild type animals exposed to either gamma rays or high energy Fe ions. At a large x-ray dose (4 Gy) the Atm heterozygotes developed vision impairing cataracts 10 or more weeks early than the wild-type counterparts. At a lower dose x-ray dose (0.5 Gy) the Atm heterozygotes developed a low grade cataract, while the wild-type did not. We can conclude from this study that (a) Vision impairing cataracts appear earlier in Atm heterozygotes than in wild-type animals; the acceleration by 10 weeks is an appreciable fraction of the life-span of the animal. (b) At lower doses, low grade cataracts appear in Atm heterozygotes where none appear in wild-type animals. For animals exposed to 0.325 Gy of high energy Fe-59, cataracts again appeared earlier in the Atm heterozygotes and the acceleration is similar to that seen for x-rays. Also, at this dose, vision impairing cataracts occur in Atm heterozygotes, but not in wild type animals. These earlier studies indicated that the susceptibility to cataractogenesis shown by Atm heterozygotes is much greater than for cell killing in cells grown in culture from the same animals, suggesting that errors in differentiation, not cell killing, is the mechanism for cataract formation. When dividing cells in the pre-equatorial region of the lens epithelium are damaged by radiation, they differentiate into fibers that are not translucent as they accrete at the posterior pole of the lens. We now have available mice heterozygous for Mrad9, for the BRCA1 and BRCA2 genes, as well as animals that are heterozygous for pairs of genes believed to be in the same DNA repair pathway, for example Atm/Mrad9, Atm/BRCA1. We propose to irradiate these animals carrying these various genetic deficiencies to a fluence of Fe-59 ions corresponding to one particle traversal per cell nucleus, and score the appearance of cataracts over the life-time of the mice. Data from these experiments will (a) Shed light on the genetic factors that control the susceptibility to radiation induced cataracts, and (b) Identify further sub-groups in the population that are radiosensitive to cataractogenesis. AT heterozygotes comprise 1 to 3% of the US population, RAD9 polymorphisms occur with a similar frequency, while 1 in 250 women carry a BRCA mutation. The combination of these genes, and others that may be identified in the future, add up to a small but significant group of individuals that would develop cataracts earlier and of a higher grade than normal individuals following exposure to high energy heavy ions. Laboratory experiments involving cytological and cytopathological endpoints are designed to elucidate the mechanisms of cataractogenesis in wild type and Atm heterozygous animals in an attempt to understand why the small difference in cell killing due to haploinsufficiency for the Atm protein translates into a large and important difference for cataract formation.
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. In the course of two runs at the Brookhaven Alternating Gradient Synchrotron, this year (06A and 06B) a total of 225 animals have been exposed to either 0.05 or 0.25 Gy of 1 Gev/amu 56Fe ions. The animals were approximately equally divided between wild type, Atm+-, BRCA+- and Atm+- / BRCA+- double heterozygotes. All animals undergo slit-lamp examinations weekly to assess the development of cataracts.
Bibliography Type:	Description: (Last Updated: 10/26/2023)
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	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. PMID: 16799786 , Jul-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	Persaud R, Zhou H, Baker SE, Hei TK, Hall EJ. "Assessment of low linear energy transfer radiation-induced bystander mutagenesis in a three-dimensional culture model. " Cancer Res. 2005 Nov 1;65(21):9876-82. PMID: 16267011 , Nov-2005