Fiscal Year:	FY 2009	**Task Last Updated:**	FY 01/13/2010
PI Name:	Blakely, Eleanor A Ph.D.		
Project Title:	Early Markers of Space-Radiation Induced Human Cataractogenesis		
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:	94720	**Congressional District:**	13
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2007 Space Radiation NNJ07ZSA001N
Start Date:	09/04/2007	**End Date:**	12/22/2010
No. of Post Docs:		**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:	Cucinott1a, Francis	**Contact Phone:**	281-483-0968
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Flight Program:			
Flight Assignment:	NOTE: New end date is 12/22/2010 (previously 9/30/2010) per C. Guidry/JSC (10/2010) NOTE: New end date is 9/30/2010 per C. Guidry/JSC (6/2010)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Chang, Polly (SRI International)		
Grant/Contract No.:	NNJ07HC79I		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The proposed project is a competitive renewal application with research emphasis focused on reducing the risk of radiation-induced cataract in human space travel. A clear understanding of the underlying mechanisms for cataractogenesis is necessary for early diagnosis and mitigation of cataract risks. The hypothesis driving our research is that particle radiation induces early molecular signaling alterations in the lens epithelial cells, which disrupt normal differentiation mechanisms necessary for the maintenance of lens clarity. In order to assess the time course of the expression and the natural history of the developing lesion, two experimental models of the lens are proposed in this application. Differentiating human lens cells in vitro will be used to extend the investigation of molecular mechanisms of action that follow particle radiation induced changes in key marker proteins using beams defined by NASA's operational parameters, eg. low doses and dose-rates of protons or heavy ions. Mice will be irradiated and early lenticular changes associated with molecular aggregation will be followed using an exquisitely sensitive dynamic light scattering method to map the unique signatures of particle radiation-induced lens opacification. Information gathered from these measurements will be used to determine when the lenses will be harvested for protein identification. The results of the proposed research will improve mechanistic understanding underlying variability of dose-rate dependencies for cataract formation, and reduce the uncertainties in cataract risk assessment.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The results of our work will be used to pursue countermeasures that could reduce the risk of cataract. These studies may also contribute to estimations of risk assessment for radiation-induced cataracts among astronauts exposed to particles during space travel, especially during missions into deep space. We may also contribute to the development of countermeasures for radiation-induced cataracts from other occupational and clinical radiation exposures. The biological mechanisms underlying normal lens fiber cell differentiation may also be elucidated. The exact factor(s) responsible for the continued replication of lens epithelial cells in embryos and adults remains to be determined. These studies therefore should shed new light on the process of human lens cell differentiation that has been difficult to explore with animal models in vivo or with human lens cultures in vitro that are either immortalized and/or undergo only limited differentiation.
Task Progress:	The long-term objectives of our project are to elucidate the underlying molecular basis for heavy-ion-induced radiation cataractogenesis, and to obtain a more complete understanding of the normal process of lens cell differentiation. The weight of experimental evidence indicates that the germinative epithelium is the primary target for radiation damage leading to cataract. However, there are potentially three hypotheses for the mechanism of radiation-induced cataractogenesis: 1) the increased genotoxic load of radiation damage leads to cataract through a number of intermediate steps involving altered expression, 2) gene expression is altered without genomic changes (the effect here may be at the level of signaling), or 3) the effect is on protein expression directly. There is of course the possibility that these three hypotheses are not mutually exclusive, and that some combination of these hypotheses is involved. We postulate that cytokines play a role in driving the cell-cycle regulation in lens epithelial cells. The cascades of signals trigger multiple membrane-based events, including alterations in actin cytoskeletal dynamics, integrin extracellular matrix expression, adhesion complex remodeling, intra- and inter-cellular communication, and cell movement. For homeostasis, these interactions are tightly coupled. We have made significant progress in the completion of Specific Aims since our last progress report. In vivo studies Baseline measurements using a novel and proprietary quasi-elastic light scattering (QLS) technique and slit lamp examinations on lens clarity was made in animals prior to a low or a high dose of protons or iron ions at NSRL. After exposure, animals are monitored at regular intervals for body weight changes. Fully dilated animal lenses were evaluated monthly using QLS and slit lamp techniques. To date, we have accumulated 9 months of QLS and slit lamp data from all animals. We have detected corneal abrasions randomly distributed in all study groups. Our collaborator Dr. Lee E. Goldstein has developed an analytical method to deconvolute the non-invasive infrared quasi-elastic light scattering and intensity fluctuation measurements to generate an autocorrelation function tau. The time constant for tau is an indicator of the size of the protein aggregation and light scatting centers in the lens. A computer program has been written to automate the autocorrelation analyses. Preliminary autocorrelation data analysis by Dr. Goldstein's group show very promising early results demonstrating detectable changes in light scattering parameters in lenses that are determined to be clear through the conventional slit lamp techniques. The study is on-going and we expect that the results will be available for tabulation and analysis within the next 6 months. Our current plans are to harvest lenses from all the animals when we observe frank opacities in the high dose groups. Lenses will be ex vivo imaged using the stereo microscopic technique to document lens pathology. Some of the lenses will be frozen for molecular analysis while others will be fixed for immunohistochemistry. In vitro studies HLE cells were irradiated with a range of single doses of 1 GeV/u protons or 1 GeV/u titanium ions. Total RNA, protein and immunoflourescent samples were harvested from sham-treated controls and irradiated samples as a function of time post irradiation. Using a high throughput quantitative RT-PCR approach, we profiled the expression of 84 human genes that are known to be important for cell-cell and cell-matrix interactions. Genes in this panel include extracellular matrix (ECM) proteins associated with basement membrane constituents, collagens, and genes playing a role in ECM structure. Proteases involved in remodeling of the ECM are included as well as their inhibitors. This array also represents molecules important to cell adhesion, including molecules involved in cell-cell and cell-matrix adhesion, transmembrane molecules, and others. Our data indicate that there are both qualitative and quantitative changes in the regulation of extracellular matrix genes after a low or a high dose of protons. Such transcriptional changes are also temporally regulated within a time-frame of up to 8 hrs post irradiation. We have also demonstrated that the quality of radiation plays a role in the transcriptional regulation of expression of ECM-associated genes with a significant number of down-regulated genes after exposure to either 10 cGy or 100 cGy Titanium ion.
Bibliography Type:	Description: (Last Updated: 05/05/2021)

Abstracts for Journals and Proceedings	Blakely EA, Bjornstad KA, Rosen CJ, Bunin D, Moncaster JA, Goldstein LE, Chang PY. "CD44 gene expression in rat lenses in vivo nine months after low-dose particle radiation." NASA Human Research Program (HRP) Investigators' Workshop, League City, Texas, February 2 - 4, 2009. NASA Human Research Program (HRP) Investigators' Workshop, League City, Texas, February 2 - 4, 2009. , Feb-2009
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Significant Media Coverage	Frey MA. "Our work entitled, Radiation Health: Mechanisms of Radiation-Induced Cataracts in Astronauts, was featured in an article covering Research Progress Reports from the NASA Human Research Program in the journal Aviation, Space and Environmental Medicine, 80(6): 575-576, June 2009." Article entitled, "Radiation health: mechanisms of radiation-induced cataracts in astronauts." Aviat Space Environ Med. 2009 Jun;80(6):575-6. PMID: 19522371 , Jun-2009