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| **Fiscal Year:** | FY 2008 | **Task Last Updated:** | FY 12/19/2008 |
| **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 |
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| **No. of Master's Candidates:** | | **No. of Bachelor's Degrees:** | 1 |
| **No. of Bachelor's Candidates:** | | **Monitoring Center:** | NASA JSC |
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| **Flight Program:** | | | |
| **Flight Assignment:** | | | |
| **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.<br>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 | | |

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| | 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:** | Task Progress: Several particle radiation response markers have been identified in our cultured differentiating human lens cell model as potentially having a role in the mechanisms of radiation cataractogenesis. These include cytokines, cyclin-dependent kinase inhibitors, cell adhesion and extracellular matrix molecules. Changes in the levels these markers are dose-dependent, can be initiated rapidly after exposure and can persist up to 12 hours post exposure. An important question is whether or not these gene and protein expression changes observed in human cells in vitro persist to correlate with cataractous changes in lenses of irradiated rodents in vivo.<br>We have recently acquired quantitative PCR (Q-PCR gene expression array data in whole lenses from Sprague-Dawley male and female rats (6-12 weeks of age at time of exposure) irradiated with 600 MeV/u iron ions in our earlier funding period. These lenses were collected nine months after radiation exposure. mRNA isolated from the whole irradiated lenses was analyzed for quantitative changes in gene expression with a Rat Extracellular Matrix and Adhesion Molecules RT2 Profiler Array (SABiosciences, MD). Fold-changes in gene expression were considered significant at the $p < 0.09$ level. Quantitative analysis of 96 genes included in the array were conducted on lens samples obtained from animals exposed to 10 cGy or 100 cGy of 600 MeV/amu iron-ions. The results were normalized to the unirradiated sham-treated control lenses. Each analysis included mRNA of lenses from 4 animals harvested nine months after the irradiation.<br><br>Detailed visual inspection of iron-ion irradiated lenses confirms that the cataractous lesions are multifocal and polymorphic, with anterior cortical opacification, and anterior cortical involvements. Opacities appear to aggregate in the equatorial periphery suggesting likely transition at the lens bow region. In addition, posterior subcapsular catactous (PSC) dots are clearly visible in 50% of the lenses that were examined ex vivo.<br><br>Analyses of individual rat lenses for quantitative gene expression show remarkable reproducibility within control and treatment groups. Results from array analysis revealed that lenses from 10 cGy-iron-ion-irradiated rat lenses showed significant 3- to 4-fold increases in genes in CAM (Cell Adhesion Molecules) & ECM (Extra Cellular Matrix) functional groups in lenses with early cataractous changes nine months after exposure, including > 3-fold changes in the CD44 antigen, a gene that was previously noted in epithelial cells in cataractous human lenses (Nishi et al, IOVS, 1997). On the other hand, 100 cGy-iron-ion-irradiated rat lenses show a completely different gene response. Only 2 genes in the ECM & CAM series were increased 2- to 3-fold in cataractous lenses, and two CAM series genes were significantly down-regulated 2- to 3-fold nine months after exposure.<br><br>The high responsiveness of ECM gene families demonstrated after a low radiation dose to the lens in vivo contrasts with the decreased gene expression seen after a 10-fold higher radiation dose nine months after the exposures. Clearly, different genes are affected at each dose level. It is not yet known how this gene profile correlates with the status of the opacifications observed at each dose at the same time post-exposure.<br><br>We participated in two separate NSRL runs during the first year of this grant. In NSRL08A, HLE cells were grown on matrix-coated plastic tissue culture flasks and irradiated with 1 GeV/u protons or 1 GeV/u titanium. Single doses of 10, 50 or 100 cGy were given. Total RNA and protein extracts from sham-treated control and irradiated samples were harvested at different times after radiation exposure and processed. Samples were also fixed with 4 % paraformaldehyde and stored until analysis. Another cell study was also conducted during NSRL 08C to duplicate the proton experiment performed during the 08A campaign. C57Bl6 male mice were whole-body irradiated during NSRL 08C. Animals were purchased from Charles River Laboratories, shipped to Dr. Lee Goldstein's laboratory at Boston University for baseline quasi-elastic light scattering (QLS) evaluation prior to transporting to the animal facility at BNL. Twenty five animals in each dose/ion group were whole-body exposed with a single 10 or 100 cGy of 1 GeV/u protons or 1 GeV/u Titanium ions. Within a week after exposure, animals were shipped to the animal facility at LBNL for long-term maintenance and evaluations. Planned monthly QLS evaluations and slit lamp video monitoring are in progress. We aim to follow these animals up to 1 year after the radiation exposure. 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 photographed to document lens pathology. Some of the lenses will be frozen for molecular analysis while others will be fixed for immunohistochemistry.<br><br>Work is in progress to show if the early in vitro human lens cell responses within hours after exposure correlate with the persistent in vivo whole rat lens response profile nine months after low doses. Integrin alpha 5 shows good cross-species induction after 1 Gy doses of 600 Mev/amu Iron to rats, and 4 Gy doses to cultured differentiating human lens cells. A comprehensive investigation of the dose-dependent expression of ECM and CAM genes in rat and human lens cells is ongoing. Studies using lower particle fluences are planned. |
| **Bibliography Type:** | Description: (Last Updated: 05/05/2021) |
| **Abstracts for Journals and Proceedings** | Blakely E, Nelson G, Guida P, Rusek A, Sutherland B, Forrette E, Rogers K. "Fifth NASA Space Radiation Summer School." Presented at NASA's Human Research Program Investigators' Workshop, League City, TX, Feb 4-6, 2008. Conference Proceedings, NASA's Human Research Program Investigators' Workshop, League City, TX, Feb 4 - 6, 2008. , Feb-2008 |

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| **Abstracts for Journals and Proceedings** | Blakely EA, Chang PY, Bjornstad KA, Rosen CJ. "Particle Radiation Triggers Premature Lens Fiber Cell Differentiation." Presented at NASA's Human Research Program Investigators' Workshop, League City, TX, Feb 4-6, 2008.<br>Conference Proceedings, NASA's Human Research Program Investigators' Workshop, League City, TX, Feb 4-6, 2008. , Feb-2008 |
| **Abstracts for Journals and Proceedings** | Blakely EA, Bjornstad KA, Rosen CJ, Bunin D, Moncaster JA, Goldstein LE, Chang PY. "Early & Late Expression of Particle Radiation Response Markers." Presented at NASA Investigators Workshop, Philadelphia, PA, June 30 – July 2, 2008.<br>Conference Proceedings, NASA Investigators' Workshop, Philadelphia, PA, June 30 – July 2, 2008. , Jun-2008 |