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| **Fiscal Year:** | FY 2020 | **Task Last Updated:** | FY 12/03/2019 |
| **PI Name:** | Edwards, John Ph.D. | | |
| **Project Title:** | Countermeasures to Radiation Induced Cardiomyopathy | | |
| **Division Name:** | Human Research | | |
| **Program/Discipline:** | | | |
| **Program/Discipline--Element/Subdiscipline:** | | | |
| **Joint Agency Name:** | | **TechPort:** | No |
| **Human Research Program Elements:** | (1) **SR**:Space Radiation | | |
| **Human Research Program Risks:** | (1) **Cancer**:Risk of Radiation Carcinogenesis | | |
| **Space Biology Element:** | None | | |
| **Space Biology Cross-Element Discipline:** | None | | |
| **Space Biology Special Category:** | None | | |
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| **Comments:** | | | |
| **Project Type:** | GROUND | **Solicitation / Funding Source:** | 2017-2018 HERO 80JSC017N0001-BPBA Topics in Biological, Physiological, and Behavioral Adaptations to Spaceflight. Appendix C |
| **Start Date:** | 02/01/2019 | **End Date:** | 01/31/2021 |
| **No. of Post Docs:** | | **No. of PhD Degrees:** | |
| **No. of PhD Candidates:** | 1 | **No. of Master' Degrees:** | |
| **No. of Master's Candidates:** | 3 | **No. of Bachelor's Degrees:** | |
| **No. of Bachelor's Candidates:** | | **Monitoring Center:** | NASA JSC |
| **Contact Monitor:** | | **Contact Phone:** | |
| **Contact Email:** | | | |
| **Flight Program:** | | | |
| **Flight Assignment:** | | | |
| **Key Personnel Changes/Previous PI:** | December 2019 report: Have added one Research Assistant. | | |
| **COI Name (Institution):** | Eisenberg, Carol Ph.D. ( New York Medical College )<br>Rota, Marcello Ph.D. ( New York Medical College ) | | |
| **Grant/Contract No.:** | 80NSSC19K0436 | | |
| **Performance Goal No.:** | | | |
| **Performance Goal Text:** | | | |

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| **Task Description:** | The present application seeks to study the long-term consequences of cosmic radiation exposure. Space travel increases solar particle radiation exposure which is significantly elevated once travel moves beyond low Earth orbit. This includes a combination of high-energy protons and heavy ions such as 56Fe, 28Si, and 16O. The adverse risk of radiation-induced heart failure is also evident as a long-term consequence of accidental radiation exposure or cancer treatment. Survivors of cancer are also at risk for other adverse health outcomes including abnormal pulmonary function, endocrine disorders, neurocognitive impairment, and osteoporosis. All of these organ systems are characterized by a low turnover of cells and it is likely that an accelerated cell death and/or the failure of regeneration by the pluripotent cells may be the underlying cause of organ failure. Although this application will focus on heart failure, our findings will have implications for many organ systems.<br>Our preliminary studies observed degradation of cardiovascular function in a model of cosmic radiation (High-Linear Energy Transfer) exposure. Mice were exposed to 50 cGy (Fe56) at 3 months of age and then studied at 24 months of age. Degradation of cardiac function was evident by significant decreases in myocardial contractility and relaxation. Concomitant with this were significant changes in mitochondrial and stem/progenitor cell function. In the present ground based application, we propose to evaluate the impact of High-Linear Energy Transfer (LET); to identify the pathway to heart failure; and evaluate three distinct protocols as potential countermeasures.<br><br>Hypothesis: Radiation-induced cardiomyopathy is the result of a cell specific failure. Cell specific failure is the result of an inability to maintain the balance of repair/replacement that ultimately leads to activation of degradation pathways and accelerated cell loss. This study will utilize both cultured cells as well as Swiss Webster mice to be randomly assigned to control or single heavy ion high-LET exposure groups. Phase 1 will use single exposures to high-LET exposure of 1) 56Fe (50 cGy) or 2) Proton (200 cGy). Phase 2 will utilize a mixed field exposure following the guidelines of the Human Exploration Research Opportunities (HERO) Announcement (80JSC017N0001-BPBA; Appendix C). All exposures will be performed at the NASA Space Radiation Laboratory at Brookhaven National Laboratory. We plan to study three distinct countermeasures including 1) MitoTempo, 2) Metformin, and 3) Lisinopril. MitoTempo is an antioxidant that partitions to the mitochondria. Metformin, an antidiabetic mainstay, has more recently been shown to have significant anticancer properties. Lisinopril, an inhibitor of the angiotensin system, has been shown to mitigate radiation injuries from Low-LET exposure. Evaluations will be made on several levels, to include 1) Determination of cardiovascular function, 2) Identification of cell specific failure, and 3) Intracellular determination of damage focusing on genomic and mitochondrial DNA damage. Cell failure in terms of metabolic failure, accelerated senescence, as well as DNA damage will be determined. A number of investigations in Space Biology are currently ongoing at New York Medical College (NYMC) and collaborations and sharing of resources will enhance the research products derived from funding this application.<br><br>Radiation induced cardiomyopathies are observed months or years after exposure. The present application will separate the insult from the consequences. Our preliminary findings demonstrated significant degradation of cardiac function similar to the accelerated aging phenotype observed with chemotherapy. It may not be relevant that any single cell dies but that the balance of cell death and cell replacement is upset. Although focused on the heart, these investigations will have widespread application to other organ systems and collectively serve the long term health and well being of flight crews. |
| **Rationale for HRP Directed Research:** | |
| **Research Impact/Earth Benefits:** | Space travel has many dangers including chronic exposure to cosmic radiation. Cosmic radiation has a higher level of energy than the typical x-ray a person would receive in the dentist's office. And as such it is more damaging. On Earth, the magnetosphere and our atmosphere absorbs nearly all of the energy from this form of radiation. However, as one ascends to the upper levels of our atmosphere the levels of exposure increases. And once the astronauts are beyond low Earth orbit this goes up even more. Currently it is estimated that the mission to Mars will expose the flight crew levels beyond the allowable lifetime limit for radiation exposure.<br>The focus of this NASA funded research project is to develop countermeasures to cosmic radiation exposure with the goal of protecting flight crews on long duration missions. However, the findings of this project will also benefit those with more Earth bound problems. Radiation therapy has been used for the treatment of cancer for many years, and it has long been known that these survivors are at risk for other illnesses related to their treatment. Proton Therapy is an increasingly popular radiation protocol for cancer treatments. This protocol generates similar types of radiation and energy levels that are part of the cosmic radiation spectrum. We also know that airline pilots and flight attendants have a small but significantly higher risk of cancer that is directly attributable to the chronic exposure to cosmic radiation during the course of their careers. And unfortunately we live in an age when terrorists might eventually gain access to weapons that will generate very high radiation exposures. Hopefully this won't happen but the lessons learned from the present investigation will have overlap to the nuclear countermeasures that others are studying. The results from the current project will hopefully contribute knowledge base that other fields will find useful. |
| | Countermeasures to Radiation Induced Cardiomyopathy--The major goal of this project is to develop countermeasures to prevent long-term cardiovascular degradation as a consequence of space flight due to cosmic radiation exposure. It focuses on the use of small molecules from a commercially available FDA (Food & Drug Administration) approved library, in addition to molecules identified by NASA personnel as high priority compounds. These drugs are part of other ongoing investigations and their inclusion will be useful in making comparisons across platforms. With regard to the Map to Human Research, this project primarily addresses two Risks and to a lesser extent one other. All are designated as High LxC for longer endurance missions or long-term health and wellbeing.<br><br>The heart is a heterogeneous organ. Although cardiomyocytes are relatively radio-resistant they comprise only 50-60% by cell number of the whole heart. Other cell types include smooth muscle, endothelial cells, fibroblasts, and cardiac progenitor cells. The radio sensitivity of these different cell types is unknown. Clinically, radiation-induced cardiac dysfunction leading to heart failure remains a significant problem. This is of even greater concern if chemotherapy is part of the treatment protocols. Analysis of heart transplantation patients found cancer treatment as the underlying cause in 2-3% of all heart transplant cases.<br><br>Countermeasures fall into three categories--Radio protectors are given prophylactically or concurrently to prevent damage. Radiation therapeutics are those that stimulate repair or regeneration processes. Radionuclide eliminators discorporate or block absorption of internalized radionuclides. This project will focus on radio protectors with the hope |

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| | of developing protocols that will diminish the need for radiation therapeutics.<br><br>Drug screening will be performed on two levels: 1) broad screening using analysis that allows for high throughput, and 2) focused analysis of high value target molecules. The hierarchy for success will be: 1) ability to protect cellular function, 2) ability to protect cell viability, 3) ability to ameliorate radiation induced senescence, 4) ability to protect DNA. An FDA-approved drug library from MedChem Express was chosen over other commercially libraries because it includes a larger number drugs directed towards DNA damage, anti-inflammation, and has been cited in a number of recent drug screens. The complete FDA approved library available from MedChem Express of more than 1500 drugs was reduced to 725 drugs, by selecting against drugs that were antibiotics or anti-parasitic. Priority was given to drugs that indicated role for DNA repair, were anti-oxidant, or anti-inflammatory. The MedChem Express library also included 8 of 9 drugs identified by NASA as high value.<br><br>Progress Report<br><br>NASA Space Radiation Laboratory (NSRL) Run 19B was our first run at NSRL and H9c2 cells (originally derived from the heart) were exposed to a total of 75 cGy using a simplified 5-ion GCR protocol developed by NASA at the NSRL facility. One pass through the library using 10 microM of each drug included tests for mitochondrial function, cellular senescence, and anti-oxidant capacity was accomplished. Of 725 drugs, more than 150 showed some improvement over the untreated GCR exposed cells, while more than 500 showed degradation of function or were ineffective. A composite score was developed for each drug and the top 160 were prioritized for further testing. In the broadest terms, what we learned from 19B was that drugs used in chemotherapy, the treatment of HIV infections, as well as the antifungal drugs were not useful and likely detrimental. The "statins" generated ambiguous results.<br><br>For NSRL 19C Run, the H9c2 and RBL-2H3 mast cell lines were exposed to a total of 75 cGy using a simplified 5-ion GCR protocol developed by NASA at the NSRL facility. Following GCR exposure cells were moved on to test plates and treated for 7 days using 1 microM of each drug. Cells were tested for viability, oxidant stress, cellular senescence, and mitochondrial function. Z-scores were calculated and a composite score was developed for each drug. |
| **Task Progress:** | Within the160 drugs, 33 are considered to have some anti-inflammatory capacity. 5 of the 5-HT3 antagonists considered useful were 5-HT3 specific, while for others the specificity was not indicated. Most of the other 5-HT antagonists that were not deemed effective were those that bound to other 5-HT isoforms or also bound to other serotonergic receptors. This suggests that the 5-HT3 specific pathways maybe of some importance. The 5-HT3 receptors are Ca+2 activated small K+ channels and used clinically for the treatment of nausea and vomiting. Some groups have reported that 5HT3 antagonism may ameliorate the effects of damaging radiation.<br><br>12 of 25 angiotensin converting enzyme inhibitors or AT1 antagonists were observed to be effective, while no AT2 antagonists appeared useful. 10 of 46 drugs identified as interacting with histamine receptors were deemed effective and mostly interacted with the H1 receptor isoform. Another anti-inflammatory inhibitory pathway included 54 COX inhibitors some of which were effective. All of the 7 drugs deemed effective were COX2 inhibitors and none were COX1 specific. The library contained 20 drugs that bound to adrenergic receptors of which 5 were deemed effective, although given their direct impact on blood pressure they are not likely to be useful as countermeasures.<br><br>A common theme among the effective drugs was that they interacted with GPCR/G coupled proteins, a class of signaling proteins that mediate and control cellular function. That COX2 but not COX1, AT1 but not AT2 receptor antagonists, or 5HT3 antagonists but no other 5HT isoforms suggest that some unique pathways were more relevant than others. Collectively they appeared to modulate inflammation and anti-oxidant pathways and this may be useful in the management of cosmic radiation exposure for long duration flight crews.<br><br>Utilization of cultured cells will allow us to expose, monitor, and analyze cells under highly controlled conditions. The data derived from these experiments will also demonstrate the relative robustness of the different cell types to cosmic radiation. And using a relatively pure cell type will allow us to differentiate the responses to different protection protocols, something that cannot be done in animals. Our previous studies have suggested that the terminally differentiated cells may be more sensitive to oxidant stress than pluripotent cells. However, this approach may also be a limitation, in that using a single cell type may miss interactions important at the tissue level. For example, in response to some stresses, mast cells of the heart release histamine and cytokines that are likely to be responsible for accelerated senescence of nearby cells. The counter experiment to these limitations would be to study mast cells using Transwell inserts that permit the co-culture of different cell types.<br><br>The goal of this project is the development of reasonable countermeasures to manage the acute and long-term consequences of High-LET exposure. To that end, we are screening a library of FDA approved drugs, using an approach that will rule in or rule out the tested molecules. The use of cultured cells maintained long-term to narrow down the long list of drugs is cost effective by decreasing the timeline of the project as well as vastly reducing the number of animals that would ultimately be needed to validate our findings. One value added aspect to this approach is the redundancies observed within a class of drugs may be indicative of the relative importance of a specific pathway. Although the use of sequential "mixed" beam irradiation is not completely replicative of space radiation exposure, it is the most cost effective ground based protocol to date. That being said any interpretations of the data would need to be cognizant of these limitations.<br><br>Collectively our results to date are consistent with other studies that modulation of cellular inflammation and anti-oxidant pathways may be useful in the management of cosmic radiation exposure for long duration flight crews. Going forward, we plan to expand the cell types tested to include endothelial, fibroblast, and iPSCs cells, all of which are highly important in the long-term maintenance of the heart. Also we will begin to look more closely at the pathways associated with inflammation as an underlying cause in the transition of a normal healthy cell to a cancerous cell. |
| **Bibliography Type:** | Description: (Last Updated: 07/05/2023) |