Fiscal Year:	FY 2012	**Task Last Updated:**	FY 11/03/2011
PI Name:	Goukassian, David A M.D., Ph.D.		
Project Title:	Evaluation of Space Radiation-induced Myocardial and BM-derived EPC Damage and Assessment of Associated Long-term Degenerative Cardiovascular Risks		
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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Comments:	NOTE: PI moved to Icahn School of Medicine at Mount Sinai from Temple University in October 2018.		
Project Type:	GROUND	**Solicitation / Funding Source:**	2010 Space Radiobiology NNJ10ZSA001N
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No. of PhD Candidates:	1	**No. of Master' Degrees:**	
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NASA JSC
Contact Monitor:	Cucinott1a, Francis	**Contact Phone:**	281-483-0968
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Yan, Xinhua (Caritas St. Elizabeth's Medical Center Of Boston, Inc.)		
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Task Description:	The main objectives of our proposal is to determine space radiation-dependent short- and long-term degenerative cardiovascular (CV) risks on the molecular, cellular, and tissue levels in the heart as the primary organ and bone marrow (BM)-derived endothelial progenitor cells (EPC) first, as a primary space radiation target and second, as a possible significant contributor to degenerative CV risks, later on in life. Our central hypothesis is that low-dose space radiation-induced DNA damage repair is inefficient in BM-derived EPC and this may lead to increased mutagenesis with subsequent long-term loss of endothelial function of BM-derived EPCs. This may then pose significant degenerative CV risk on physiologic homeostasis in the aging heart and on the regeneration and neovascularization processes in the heart under pathologic conditions such as acute myocardial infarction (AMI). Comparisons will be made between two types of low-dose radiation - proton versus iron and single versus fractionated exposures. In short-term in vitro studies (minutes, hours, and up to 30 days after exposure) will evaluate in ex-vivo expanded EPCs and cardiomyocytes DNA damage and repair as well as radiation-induced bystander effects (irradiated cells emit signals to "un-hit" cells), angiogenic gene expression in EPCs. In short-term in vivo studies in the heart we will evaluate acute damage (inflammation and cell death), DNA damage, and repair kinetics. In our long-term studies (3, 6, 9, and 12 months after exposure) we will evaluate oxidative stress and antioxidant defense in BM-derived EPCs, alterations in several EPC endothelial functions, number of circulating peripheral blood EPCs, and cardiomyocyte contractility. In the last part of our studies we will assess CV risks as a result of low-dose radiation plus aging and CV risks under pathological condition -- radiation plus aging plus adverse CV event (i.e., AMI). Here we will evaluate post-AMI survival, alterations in cardiac physiology (echocardiography), infarct size, inflammation, cardiac regeneration, neovascularization, and mobilization of EPCs from BM. Our studies will address two high-priority research topics of this specific solicitation and NASA research interests for degenerative risks to the heart -- (1) development of murine models to estimate risks for degenerative heart diseases; (2) determine the progression rates and latency periods for space radiation-related degenerative CV risks as a function of radiation type (proton vs. heavy ion), exposure frequency (single vs. fractionated), age, and age plus adverse CV event.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	In terms of Earth-based applications the information gained from our studies will have benefit for people on Earth who are (1) undergoing therapeutic radiation in the proximity of the heart (breast, esophageal, lung cancers, etc.) for cancer treatment (direct “hit” effect); (2) who are undergoing therapeutic radiation elsewhere in the body (prostate, colon, skin, liver cancers, etc.) for cancer treatment (non-targeted effects) that may affect heart years and decades after these treatment. In addition, our studies will also provide novel insights into the alterations in cardiac function processes on the molecular and cardiac physiology levels that may allow for estimation of degenerative risks to cardiovascular system in the civilian population exposed to full body low-dose radiation due to accidental exposures (Chernobyl, Fukushima, etc.) and cancer patients undergoing very frequent imaging tests (i.e., full body Computer Tomography, PET Scans, etc.). Our studies will address two high-priority research topics for NASA research interests for degenerative risks to the heart - (1) development of murine models to estimate risks for degenerative heart diseases; (2) determine the progression rates and latency periods for space radiation-related degenerative CV risks as a function of radiation type (proton vs. heavy ion), exposure frequency (single vs. fractionated), age and age plus adverse CV event.
Task Progress:	We have made a significant progress in the several directions in our research work during the first year of the funding. We found that: (1) There is a different time course of changes in skeletal muscle (used as an initial model system) Ca2+ homeostasis in response to a single dose of proton and 56Fe irradiation. Specifically, our results indicate that both proton and 56Fe irradiations resulted in detectable increase in [Ca2+]i as well as in reduction of action potential evoked Ca2+ release from the sarcoplasmic reticulum (a cellular compartment). The time course of the observed changes was dependent on the type of radiation, that is - 56Fe radiation produced an increase in [Ca2+]i at the 24hr time point which then declined back to near normal levels, whereas Proton irradiation did not have an effect at the 24hr or 48hr time point, but resulted in a robust increase in [Ca2+]i by 72 hrs. We conclude that ionizing radiation may affect the functional state of skeletal muscle without a presence of obvious histological changes. (2) Full body 0.15 Gy Iron irradiation affects survival and proliferation of bone marrow (BM)-derived endothelial progenitor cells (EPCs). Specifically, our results reveale that 2, 5, and 24 hrs after full-body irradiation there was 2-6-fold increase in EPC cell death (apoptosis) with the peak 6-fold increase in EPC death at 5hrs. The cells death was decreased by 14 days. However, by day 28 there was a second significant 4-fold increase in EPC cell death, indicating that there is a bimodal (early 5 hrs and delayed 28 days) increase in BM-derived EPC cell death after a single 0.15 Gy Iron radiation. Proliferation analysis of BM-derived EPCs revealed no changes in the rate of proliferation up to 7 days post-Iron irradiation. However, there was ~45 increase in the rate of EPC proliferation on day 14, but the rate of EPC proliferation was decreased twice on day 28. Taken together these data suggest that early increase in BM-derived EPC cell death may be a direct effect of radiation, whereas later increase in cell death and decrease in proliferation could be a result of non-targeted effects. We conclude single low dose of Iron irradiation may have long-lasting effect on survival and proliferation of BM-derived EPCs and may induce delayed non-targeted effects. (3) Tumor necrosis factor (TNF)-TNF receptor 1 (R1)/p55 or TNFR2/p75 receptor-ligand (TNF protein) interactions inhibit early and increase delayed radiobiological bystander responses in BM-derived EPCs. Specifically, we found that in wild type (WT) naive (non-irradiated) EPC the peak of detectable mean DNA damage foci (double strand breaks-DSB in the absence of a direct radiation hit) were at 24 hrs, whereas in both TNFR1 and TNFR2 knockout (KO) DSBs were the lowest at 24 hrs. This finding indicates that ligand (TNF) - receptor (p55 or p75) interactions inhibit early (within a day) radiobiological bystander responses in BM-derived EPCs in medium transfer experiments. Interestingly, compared to WT EPCs, delayed (5 days) bystander responses in naive EPCs were amplified in p55KO and p75KO cells, suggesting significant role for TNF protein and its receptors interactions in mediating delayed bystander responses. ELISA analysis of protein levels of 8 angiogenic and 8 inflammatory genes in conditioned cell growth medium (collected from irradiated EPCs) 5 days post-radiation showed 2-16-fold increases at day 3-5 in cumulative levels of following proteins - TNF, IFNr, IL6, EGF, MIP-1, GM-SCF, Rantes , p IL1, IL1, G –CSF, MCP-1, SCF in p55KO and p75KO vs WT. Each of these proteins alone or in combination may be a causative factor in inducing DSB in the absence

	of the actual ionizing radiation. We conclude that radiobiological bystander effects may be regulated (decreased or increased) through modification of TNF signaling via TNFR1/p55 or TNFR2/75, suggesting this strategy may be used to develop mitigating agent(s) for prevention of delayed non-targeted effects. (4) Low dose gamma radiation-induced early responses in the heart and BM-derived EPCs. Specifically, we evaluated the effect of a full-body single dose 1 Gy gamma-irradiation [low linear energy transfer (LET) type of radiation] on the formation of double strand breaks (DSB) in BM-derived EPCs and in the heart in C57/Bl6J mice. Our studies revealed that within 24 hrs the decay of DSB foci was slow in mouse EPCs, which may be indicative of inefficient or delayed DNA DSB repair. There was an increase in the percent of BM-derived EPCs with DSB foci and increase in DSB per cell over 7 days post-radiation, indicating a possibility of significant radiobiological bystander responses in EPCs. In medium transfer experiments (collection of cell medium from irradiated cells and treatment of naïve non-irradiated cells with this medium after filtration) BM-derived EPCs exhibit significant bystander responses in vitro. We found significant decrease in DSB in irradiated mouse heart resident endothelial cells (EC) and non-EC cells, indicating considerable DNA DSB repair, however with slower than usual repair kinetics reported for other primary cells, i.e., fibroblasts, leukocytes. We also found that radiation-induced increase in cytoplasmic [Ca2+]i concentration was sustained for longer periods of time. This was accompanied by a partial loss of mitochondrial membrane potential, which most likely resulted from mitochondrial calcium overload and subsequent activation of the permeability transition (PT) pore. Moreover, full body 1 Gy gamma-radiation led to a substantial loss of mitochondrial membrane potential for at least seven days, suggesting that if sustained for longer periods of time this may alter mitochondrial membrane integrity, affecting energy production in the cells, therefore diminishing muscle contractile function. We conclude that longitudinal studies using low-dose proton and heavy ion (HZE) radiation studies are warranted to determine space radiation-induced long-term Excess Relative Risks (ERR) for cardiovascular diseases.
Bibliography Type:	Description: (Last Updated: 03/06/2024)
Abstracts for Journals and Proceedings	Sasi S, Park D, Wage J, Goukassian DA. "Full body 0.15 Gy Iron Irradiation Affects Survival and Proliferation of BM-derived EPCs. " Presented at the 22nd Annual NASA Space Radiation Investigators' Workshop, League City, TX, September 18-21, 2011. Abstract Book. 22nd Annual NASA Space Radiation Investigators' Workshop, League City, TX, September 18-21, 2011. http://www.dsls.usra.edu/meetings/radiation2011/pdf/7108.pdf , Sep-2011
Abstracts for Journals and Proceedings	Sasi S, Park D, Enderling H, Fox JL, Hahnfeldt P, Hlatky L, Goukassian DA. "TNF-TNFR1/p55 or TNFR2/p75 Receptor-Ligand Interactions Inhibit Early and Increase Delayed Radiobiological Bystander Responses in BM-derived EPCs." Presented at the 22nd Annual NASA Space Radiation Investigators' Workshop, League City, TX, September 18-21, 2011. Abstract Book. 22nd Annual NASA Space Radiation Investigators' Workshop, League City, TX, September 18-21, 2011. http://www.dsls.usra.edu/meetings/radiation2011/pdf/7079.pdf , Sep-2011
Abstracts for Journals and Proceedings	Shtifman A, Pezone MJ, Sasi S,Wage J, Walsh KX, Goukassian DA. "Different Time Course of Changes in Skeletal Muscle Ca2+ Homeostasis in Response to a Single Dose of Proton and 56Fe Irradiation." Presented at the 22nd Annual NASA Space Radiation Investigators' Workshop, League City, TX, September 18-21, 2011. Abstract Book. 22nd Annual Space Radiation Investigators' Workshop, League City, TX, September 18-21, 2011. http://www.dsls.usra.edu/meetings/radiation2011/pdf/7084.pdf , Sep-2011
Abstracts for Journals and Proceedings	Sasi SP, Shtifman A, Levy E, Yan X, Walsh KX, Hahnfeldt P, Hlatky L, Goukassian DA. "Low Dose Radiation-Induced Early Responses in the Heart and Bone Marrow-derived EPC: Implications for Long-term Cardiovascular Risks." Presented at the International Symposium for Radiation Research and Medical Physics, Fudan University, Shanghai, China, May 30-June 2, 2011. Abstract Book. International Symposium for Radiation Research and Medical Physics, Fudan University, Shanghai, China, May 30-June 2, 2011. , May-2011
Patents	U.S. Provisional Application No.: 61/514,008. U.S. Provisional Application, August 2011. Aug-2011 Goukassian DA. "Compositions and Methods for the Treatment of Radiation Exposure."