Fiscal Year:	FY 2014	**Task Last Updated:**	FY 06/04/2014
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
Start Date:	01/01/2011	**End Date:**	12/31/2014
No. of Post Docs:	4	**No. of PhD Degrees:**	
No. of PhD Candidates:	0	**No. of Master' Degrees:**	2
No. of Master's Candidates:	2	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:	3	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: Extended to 12/31/2014 per NSSC information and PI (Ed., 6/3/14) NOTE: Extended to 5/31/2014 per NSSC information (Ed., 12/4/13)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Yan, Xinhua (Genesys Research Institute)		
Grant/Contract No.:	NNX11AD22G		
Performance Goal No.:			
Performance Goal Text:			
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) 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 treatments.
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 completed seven sub-projects within the scope of our main project. Each of the summaries below represent progress for the particular sub-project.
SUB-PROJECT 1. CARDIAC HISTOLOGY (UP TO 3 MONTHS AFTER A SINGLE 1H- AND 56FE-IR). We evaluated the effect of a single low-dose full body exposure to 50 cGy, 1 GeV 1H, and 15 cGy, 1 GeV/n 56Fe IR on the formation and decay of p-H2AX foci, inflammation (CD68 staining), and oxidative DNA damage (8-oxo-deoxy-dGuanosine ELISA) in the hearts of 8-9 months old (at the time of initial IR) C57BL/6NT mice over 28 days post-IR. CD68 staining and 8-oxo-de-oxy dGuanosine ELISA was also performed at 2 and 3 months.

Summary for SUB-PROJECT 1:

• 56Fe IR-induced mean p-H2AX foci are HIGHER IN NON ECS, including CM vs. heart ECs, and the decay of 56Fe IR-induced p-H2AX foci is SLOWER IN CM vs. ECs.

• 56Fe IR-induced inflammatory responses are cyclical and longer-lived in the heart.

• 56Fe-IR-induced oxidative damage responses are longer lasting in the heart.

SUB-PROJECT 2. CARDIOMYOCYTES MICROARRAYS (DAYS 1, 3, 7, 14, AND 28 POST-IRs). Isolation of Left Ventricular (LV) Cardiomyocytes. Primary mouse LV cardiomyocytes (CM) were isolated to examine the temporal response following in vivo exposure to 15 cGy, 1 GeV/n 56Fe ions, or 50 cGy, 1GeV 1H. Early time points were collected 1 or 3 days after IR along with non-IR controls. Three additional isolations were made at 7, 14, or 28 days after IRs.

Summary for SUB-PROJECT 2:

• At 50cGy, 1 GeV/n dose of 1H-IR, gene expression in CM is NOT affected over 28 days.

• At 15 cGy, 1 GeV/n dose of 56Fe-IR, cardiomyocytes exhibit a time dependent change in gene expression that results in an overall increase in the activity of inflammatory, free radical scavenging, and CV development and function genes 7 and 28 days post-IR.

• Two weeks after a single 56Fe-IR, the activation of several developmental transcription factors (TBX5, GATA4, MEF2C) that are required for the maintenance of cardiac homeostasis strongly suggest ACTIVATION OF CARDIO-PROTECTIVE RESPONSES IN 56FE-IR HEARTS, ONLY.

SUB-PROJECT 3. LONGITUDINAL STUDIES, RADIATION + AGING, 1 AND 3 MONTHS POST-IR. We evaluated the effect of a single, low-dose, full body 50 cGy, 1GeV 1H, and 15 cGy, 1GeV/n 56Fe IR in the hearts of 8-9 months old C57BL/6NT mice over 1 and 3 months post-IR. The survival between control, 1H, and 56Fe up to 3 months post-IR was 95-98% (N=100/treatment group), and no statistical difference was observed between control and either of the IR groups up to 3 months. IR-induced alterations in cardiac function were assessed by echocardiography (ECHO) and hemodynamic (HEMO) measurements and activation of signaling pathways by protein analyses.

Summary for SUB-PROJECT 3:

• Low dose, full body, single 56Fe and 1H-IR induced effects on myocardium are of long duration 56Fe-NEGATIVE, 1H-POSITIVE.

• 56FE-IR, BUT NOT 1H-IR, affects CV homeostasis under normal aging conditions.

• The significant NEGATIVE effects on systolic and diastolic heart functions post-56Fe-IR are associated with altered Ca2+ and cardiac contractility signaling, increased cardiac hypertrophy signaling, and decreased p38 MAPK signaling.

• These 56Fe-IR-mediated NEGATIVE CV developments are indicative of INCREASED RISK for cardiac dysfunction during aging, and also AN INCREASED RISK FOR IMPAIRED RESPONSES TO AN ISCHEMIC EVENT, such as heart attack.

SUB-PROJECT 4. LONGITUDINAL RADIATION + AGING + ADVERSE CV EVENT (Acute Myocardial Infarct). We evaluated the effect of a single, low-dose, full body 50 cGy, 1GeV 1H, and 15 cGy, 1GeV/n 56Fe IR in the hearts of 8-9 months old C57BL/6NT mice over 3 months in Radiation + Aging + AMI. IR-induced alterations in cardiac function were assessed by echocardiography (ECHO) and hemodynamic measurements (HEMO). Acute myocardial infarct (AMI) was induced by ligation of the left anterior descending (LAD) coronary artery 1 and 3 months post-IR, and mice were monitored over 28 days post-AMI. Post-surgical mortality (1-2 days following the surgery) was 14±1.5% at 1 month, and 11±6% for 3 months, respectively (p=NS, between all three groups). In remaining mice post-AMI survival after LAD ligation was not significantly different between control, 1H, and 56Fe groups at 1 and 3 months post-IR and up to 28 days post-AMI (100%, 100% and 88±13% survived AMI surgery, respectively, p=NS).

Summary for SUB-PROJECT 4: • A single, low dose, full body 1H-IR 3 months prior to AMI is BENEFICIAL, whereas 56Fe is DELETERIOUS for recovery after AMI.

• Low dose HZE particle, 56Fe-IR, has long-lasting NEGATIVE effect on degenerative CV risks in case of adverse CV event (e.g., heart attack).

• Multiple signaling pathways that regulate survival, proliferation, and angiogenesis ARE INHIBITED IN 56FE-IR and ACTIVATED IN 1H-IR HEARTS 3 MONTHS POST-AMI.

SUB-PROJECT 5. SURVIVAL OF BONE MARROW PROGENITOR CELL POPULATIONS UP TO 10 MONTHS AFTER PROTON AND IRON IR. After a full body, single 50 cGy 1H- and 15 cGy 56Fe-IR (both ions at 1 GeV/n) mice (C57BL/6NT) were sacrificed at 1, 2, 4, 8, 12, 28, and 40 weeks post-IR. BM cells were subjected to density gradient centrifugation to isolate mononuclear cells (MNCs). MNCs were triple-stained with FITC-labeled RAM34 (consists of CD34, c-kit, and Sca1), PE-Cy7-labeled AC133, and PE-labeled hematopoietic Linminus cocktail then sorted for Early-Multi-Potent Progenitor cells (E-MPP) and Late-MPP (L-MMP).

Summary for SUB-PROJECT 5:

• Despite an initial 1H-IR-induced increase in the number of BM multipotent progenitor (MPP) cell populations, both 1H-IR and 56Fe-IR have profound and long-lasting (28-40 weeks) NEGATIVE effects, >50% DECREASES in the number of early- and late-MPPs.

• The function of the surviving fraction of E-MPPs and L-MPPs and implications for the cardiac homeostasis, as well as cardiac repair and regeneration, remains unknown.

FRACTIONATED/SEQUENTIAL 1H AND 56Fe IR STUDIES. During GCR each cell in an astronaut's body is being traversed by a 1H about every 3 days and HZE nuclei about every few months. Hence, the traversal sequence of cells with an ion in space is random and 99% of the space IR environment consists of 1H and 2He63. Therefore, a scenario that a cell in human body may be hit first with several 1H particles then with HZE or an HZE then several 1H should be equally probable. We present here the first set of preliminary data for fractionated/sequential mix ion IR regimens in the hearts of 8-9 months old C57BL/6NT mice over 1 and 3 months.

SUB-PROJECT 6. FRACTIONATED/SEQUENATIAL RADIATION + AGING (1 AND 3 MOUSE-MONTHS AGING). We evaluated the effect of low-dose fractioned and sequential IR dose regimens in the following groups: Group 1- Control; Group 2 - 1H 17 cGy x 3 every 2 days; Group 3 - 1H 17 cGy x 3 every 2 days/56Fe 15 cGy; Group 4 - 56Fe 15 cGy/1H 17 cGy x 3 every 2 days at the energy of 1 GeV/n, for both ions.

Summary for SUB-PROJECT 6:

• 1H+1H+1H-IR – at the dose of 17 cGy x 3 and the energy of 1 GeV/n and 1H+1H+1H/56Fe-IR - at the dose of 1H 17 cGy x 3 / 56Fe 15 cGy x 1 and an energy of 1 GeV/n for both ions, does NOT reveal negative effects on the heart function.

• 56Fe/1H+1H+1H-IR – at the dose of 56Fe 15 cGy x 1 / 1H 17 cGy x 3 and an energy of 1 GeV/n for both ions, revealed significant INCREASE IN POST-IR MORTALITY, INCREASED CARDIAC FIBROSIS, REDUCED RELAXATION, AND CONTRACTILE FUNCTIONS in the heart of the surviving fraction of mice.

SUB-PROJECT 7. FRACTIONATED/SEQUENATIAL RADIATION + AGING + ACUTE MYOCARDAIL INFARCT (1 AND 3 MOUSE-MONTHS AGING). We evaluated the effect of low-dose fractioned and sequential IR dose regimens on post-AMI recovery after fractionated-sequential 1H and single 56Fe-IR regimens in the following groups: Group 1- Control; Group 2 - 1H 17 cGy x 3 every 2 days; Group 3 - 1H 17 cGy x 3 every 2 days/56Fe 15 cGy; Group 4 - 56Fe 15 cGy/1H 17 cGy x 3 every 2 days at the energy of 1 GeV/n, for both ions.

Summary for SUB-PROJECT 7: Fractionated 1H-IR alone or 56Fe/1H+1H+1H-IR regimens DO NOT have significant negative effect on post-AMI survival and cardiac function at 1 month post-IR. However, when fractionated 1H-IR was followed by a single 56Fe-IR, there are several NEGATIVE developments: (a) there is a 24% DECREASE in post-AMI survival at 1 month; (b) LV EDP in DECREASED at 1 month (altered relaxation function); (c) post-AMI cardiac fibrosis is INCREASED. These findings are indicative of significant negative effects for post-AMI recovery of 1H+1H+1H/56Fe-IR regimen in the surviving fraction of mice in this group.

MAJOR CONCLUSIONS, FRACTIONATED/SEQUENTIAL 1H AND 56FE IR: Our preliminary findings in mix ion IR studies strongly suggest dramatically different biological responses due to diverse sequence and fractionation of 1H vs. single 56Fe-IR.

• In IR + AGING group - 56Fe/1H+1H+1H-IR regimen revealed SIGNIFICANT NEGATIVE effects on the heart during aging, whereas 1H+1H+1H/56Fe-IR and 1H+1H+1H-IR had NO NEGATIVE effect, at least up to 3 months post-IR.

• In IR + AGING + AMI group, in contrary to IR + AGING group, 1H+1H+1H/56Fe-IR regimen presented SIGNIFICANT DEGENERATIVE CV RISK for the recovery of the heart after AMI, whereas both, 56Fe/1H+1H+1H-IR and 1H+1H+1H-IR had NO NEGATIVE effect on AMI recovery at least up to 1 month post-IR.

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