Fiscal Year:	FY 2016	**Task Last Updated:**	FY 09/10/2016
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Project Title:	NSCOR: Mechanisms underlying the risk of HZE particle-induced solid tumor development		
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) **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:**	2010 Space Radiation NSCOR/Virtual NSCOR NNJ10ZSA002N
Start Date:	01/01/2011	**End Date:**	06/30/2016
No. of Post Docs:	3	**No. of PhD Degrees:**	1
No. of PhD Candidates:	2	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	6
No. of Bachelor's Candidates:	17	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 6/30/2016 per NSSC and S. Monk/LaRC (Ed., 12/31/15)		
Key Personnel Changes/Previous PI:	No change		
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Grant/Contract No.:	NNX11AC30G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

Our NASA Specialized Center of Research (NSCOR) proposal entitled “Mechanisms underlying the risk of HZE particle-induced solid tumor development” (NNX11AC30G) was effective January 1, 2011 and completed June 30, 2016. There were two main goals of the Emory University NSCOR: (i). Evaluate how high of high charge and energy (HZE) particles (as a special component of space radiation) to induce lung tumorigenesis; (ii) Elucidate the mechanism underlying HZE particle-induced lung tumorigenesis.
Primary Goal (Risk Estimation): Emory NSCOR executed 8 beam exposures at Brookhaven National Laboratory (BNL) and NASA Space Radiation Research Laboratory (NSRL) (Fall 2011; Spring/Fall 2012, 2013, and 2014; Spring 2015) that included mice and cell irradiation. We have used 1340 in total mice and irradiated 1110 mice whole body to iron (600 MeV/n), silicon (300 MeV/n), oxygen (600 MeV/n), and x-ray (320 KeV) with either single dose (1 Gy) or fractionated doses (0.2 Gy x 5 at 24 h interval). At 1.5 years post irradiation, the incidents of lung tumorigenesis were analyzed and subsequently revealed that wild type C57BL/6J mice with an extremely low spontaneous lung tumorigenesis background induced more lung tumorigenesis at 1.5 years after exposure to high-LET (linear energy transfer) radiation (particularly to silicon) than low-LET radiation (such as x-rays). These results have been published (Radiat Res 2015, 183:233-239).

Secondary Goal (Mechanistic Studies): Four synergized scientific projects of our NSCOR investigated how HZE particle-induced lung tumorigenesis, studied the mechanism underlying how mammalians respond to HZE particle-induced DNA damage, which contributes to the development of lung tumor. HZE exposure elicits complex DNA damage that follows a broader cell/tissue stress response that likely includes changes in expression of tumor suppressor proteins, persistent elevation of reactive oxygen species, and alterations in the pattern of DNA methylation. HZE particle-induced broader stress response amplifies the carcinogenic risk from a primary DNA damage event, which served as the central hypothesis of the Emory NSCOR. The key investigators have used genetic, epigenetic, and biochemical approaches to address the stress responses in HZE particle-induced DNA damage and the nature of the damage linked to lung tumorigenesis. Our accomplishments pertaining to the mechanistic studies are reflected in our publications.

The administrative core executed the overall Emory NSCOR coordination. In conjunction with the NASA mid-term review, this core organized two Emory NSCOR retreats during 2013 February and 2015 January where the NSCOR team as well as our external consultants (experts in high-LET radiation field and other related cancer field) participated, which enabled fruitful discussions to ensure our NSCOR closely followed the NASA-NSCOR initiative. The Emory NSCOR had an education component that facilitated summer student involvement and public education. The education component was unique for our ESCOR, which was based on NASA encouragement and supported by the School of Medicine and the Winship Cancer Institute of Emory University ($50,000/ year, $250,000 total). Please see the Education Component achievement section for details. Together, 26 peer-reviewed publications and 53 published abstracts for proceedings resulted from the mechanistic studies and risk estimation experiments as described in the scientific projects and animal/radiation core.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

Our NSCOR research impact on Earth is reflected as follows:
1. Contribution towards lung cancer prevention. Lung cancer is the leading cause of cancer death among men and women. Through studying the mechanism underlying space radiation-induced lung tumorigenesis, the Emory NSCOR research discovered new roles of some genes in lung tumorigenesis, which not only facilitated a better understanding of lung carcinogenesis but also provided strategies for improving lung cancer prevention. For example, we discovered a new mechanism to explain GPRC5A as a lung tumor suppressor by revealing that GPRC5A at the endoplasmic reticulum (ER) membrane suppresses synthesis of the secreted or membrane-bound proteins including a number of oncogenes, the most important one being Egfr. Our findings indicate that under-expressed GPRC5A during lung tumorigenesis enhances any transcriptional stimulation through an active translational status, which can be used to control oncogene expression and potentially resulting related disease. Since it is known that vitamin A can stimulate GPRC5A expression, our results suggest that taking vitamin A would help prevent radiation-induced lung tumorigenesis. This work was published in Nature Communication 2016.

2. Contribution to cancer radiotherapy. DNA damage, particularly DNA double strand breaks (DSB), is not only a severe threat to genomic stability but is also the major reason radiotherapy kills tumor cells. Therefore, understanding the mechanism underlying DNA DSB repair will benefit both cancer prevention and cancer treatment. Through studying the mechanism underlying the repair of space radiation-induced DNA DSB, our NSCOR research contributed to new discoveries to help better understand the nature of DNA DSB repair. One example, Ape1 (a base repair enzyme) plays an important role in generating small DNA double strand fragments by digesting the damaged base in cluster DNA damage sites, which contributes to high LET radiation-induced high relative biological effectiveness (RBE). This discovery does not only help us to reduce space radiation induced DNA damage by using an Ape1 inhibitor but also suggests that we can use an Ape1 activator to increase the efficiency of high-LET radiotherapy (such as carbon ion radiotherapy) on tumor killing. This work was published in JBC 2014.

2-1. Overall major achievements:
Major achievement 1: Our team demonstrated for the first time that wild type C57BL/6J mice with an extremely low spontaneous lung tumorigenesis background can induce more lung tumorigenesis at 1.5 years after whole body exposure to high-LET radiation (particularly to silicon) than low-LET radiation (such as x-rays).

Importance of this achievement: All previous studies (published and unpublished) including our initially planned experiments pertaining to radiation-induced lung tumorigenesis used mice with a highly spontaneous lung tumorigenesis background. Our results using the mice with a highly spontaneous lung tumorigenesis background revealed that these mice do not adequately resemble healthy astronauts or estimate the risk of space radiation-induced lung tumorigenesis. Fortunately, our wild type C57BL/6J control mice provided us with valuable data and demonstrated that high-LET radiation (particularly silicon) versus low-LET radiation (such as x-rays) have a higher risk of inducing lung tumorigenesis. Lung cancer is the most prevalent fatal cancer among men and women worldwide. Lung cancer is believed to be one of the major risks of HZE-particle exposure-induced carcinogenesis, although a quantitative and mechanistic understanding of this risk needs further study. Our published data (including positive and negative results) provide an important platform to continue studying the extent of the risk of existing space radiation-induced lung

tumorigenesis. In addition, we can follow our studies to determine whether and how different qualities (LET) of radiation affects lung tumorigenesis. These results will not only provide important information that will aid in the facilitation of the NASA Mars project, but will also provide the public with useful information concerning lung carcinogenesis and the benefits of cancer prevention.

Major achievement 2: Our team has identified that Ape1 (a base repair enzyme) plays an important role in generating small DNA double strand fragments by digesting damaged base in cluster DNA damage sites, which contributes to high LET radiation-induced high relative biological effectiveness (RBE).

Importance of this achievement: Space radiation from HZE-particles with high-LET is different from terrestrial low-LET radiation. Understanding the mechanism by which mammalian cells respond to space radiation-induced DNA damage is a key issue for us to determine the risk of space radiation on astronauts' health at any endpoint. Such results suggest that we can use this mechanism to identify a space radiation countermeasure by searching for an Ape1 enzyme inhibitor with low toxicity to reduce high-LET radiation-induced DNA damage and thereby reduce space radiation-induced health risks. These results have been published: JBC 2014, 289:30635-30644 (see Cumulative Bibliography hyperlink).

2-2. Major achievements per component

Project 1: Elucidate the mechanism underlying HZE particle-induced lung carcinogenesis by determining the nature of the damage and the roles of some key genes in lung carcinogenesis. We demonstrated how changed miRNA expression, such as miR-34a (a tumor suppressor) and miR-21 (an oncogene), after radiation contribute to lung tumorigenesis. Project 1 also demonstrated that miR-21 highly expresses in irradiated and human cells as well as different tissue from irradiated mice. In addition, Project 1 identified some new miR-21 targets linked to lung tumorigenesis. Furthermore, and most important, project 1 showed that the high levels of miR-21 in lung tumors from irradiated mice correlated with the miR-21 level in serum from the same mice. These results indicate that the miR-21 serum level might serve as a useful biomarker to predict the risk of space radiation-induced lung tumorigenesis, which is worthy of continued follow-up studies to confirm since, if proven, the miR-21 level in serum can be easily detected in astronauts to predict lung tumorigenesis risk. We demonstrated a new GPRC5A mechanism that serves as a lung tumor suppressor by revealing that GPRC5A at the endoplasmic reticulum (ER) membrane suppresses synthesis of the secreted or membrane-bound proteins including a number of oncogenes, the most important one being Egfr. The ER-located GPRC5A disturbs the assembly of the eIF4F-mediated translation initiation complex on the mRNA cap through directly binding to the eIF4F complex with its two middle extracellular loops. Particularly, suppression of EGFR by GPRC5A contributes significantly to preventing ionizing radiation (IR)-induced lung tumorigenesis. Thus, GPRC5A deletion enhances IR-promoted EGFR expression through an increased translation rate, thereby significantly increasing the lung tumor incidence in Gprc5a-/- mice. Our findings indicate that under-expressed GPRC5A during lung tumorigenesis enhances any transcriptional stimulation through an active translational status, which can be used to control oncogene expression and potentially resulting related disease. Since it is known that vitamin A could stimulate GPRC5A expression, our results suggest that taking vitamin A would help prevent radiation-induced lung tumorigenesis. This work has been published in Nature Communication 2016.

We demonstrated a new mechanism explaining why high-LET radiation induces chromosome translocation more efficiently than low-LET radiation. Previously, with the aid of NASA funding, we demonstrated that high-LET radiation compared to low-LET radiation generated more DNA double strand break (DSB) fragments (< 40 bp) that affect Ku/DNA-PKcs from properly binding and interfere with the efficiency of non-homologous end-joining (NHEJ) but do not affect homologous recombination repair (HRR) and, thus, result in high RBE for cell killing (DNA Repair, 2008, 7:725-733). Following this study, we further found that high-LET radiation-induced more DNA fragments are the major reason for high-LET radiation vs low-LET radiation to generate more chromosome translocations. In collaboration with project 2, we designed a series of reporters to demonstrate this important discovery and a manuscript will be submitted soon. This discovery will provide a mechanism to explain why high-LET radiation vs low-LET radiation more efficiently induces genomic instability and tumorigenesis since chromosome translocation is a key marker and a major reason for carcinogenesis.

Project 2: Determine whether HZE-particle radiation exposure results in hyper-reliance on error-prone DNA repair pathways and promotes lung-tumorigenesis. A history of exposure to HZE particle radiation compromises the ability to accurately repair future DNA damage, a phenomenon termed the mutagenic repair phenotype. This increases the risk of oncogenic chromosome rearrangements in a setting where occasional encounters with HZE particles occur in the context of ongoing exposure to low-LET components of the galactic cosmic ray field. However, because the mutagenic repair phenotype is a non-targeted effect attributable to cell-cell signaling, it might also be possible to suppress it through pharmacologic interventions as an HZE particle radiation countermeasure. Mutagenic repair phenotype observed following direct irradiation of a reporter cell line. The experimental approach is to test whether a history of HZE radiation exposure influences the fidelity (and not just the efficiency) of the response to future DNA damage. We term this effect the "mutagenic repair phenotype." Work used a tumor cell line that had been engineered to report mutagenic repair of enzymatically-induced DNA double-strand breaks. We exposed replicate cultures to HZE particle radiation and challenged at intervals by expression of a rare-cutting nuclease that cuts within integrated reporter transgenes. In this system, deletion of a sequence within one of the reporter transgenes leads to green fluorescence, and translocation between two transgenes integrated into different chromosomes leads to red fluorescence. An increase in the frequency of nuclease-induced deletions and translocations indicates a breakdown in the fidelity of DNA double-strand break repair.

Using this system, we demonstrated that irradiation with 600 MeV/u 56Fe increases nuclease-induced translocations by up to 3-fold in a dose-dependent manner. It increases deletions by a more modest but nevertheless significant factor. The effect persists for up to two weeks and is associated with the presence of markers of chronic DNA damage. The effect is not seen with low-LET X or gamma-rays at any dose tested.

To further explore the influence of ion species and LET, we tested 1000 MeV/u 48Ti and 300 MeV/u 28Si. Irradiation with 48Ti increases the frequency of nuclease-induced translocations by 3-fold, although the duration of the effect is shorter than for 56Fe, and there is no change in the frequency of nuclease-induced deletions. Irradiation with 28Si does not affect the frequency of nuclease-induced translocations or deletions. Thus, induction of the mutagenic repair phenotype is dose and LET dependent.

Results are potentially significant for carcinogenesis in the space radiation environment, where occasional encounters with HZE particles occur in the context of more frequent encounters with energetic (low-LET) protons or helium nuclei. The findings indicate the existence of a mechanism whereby an initial encounter with an HZE particle degrades the

ability to repair DNA double-strand breaks induced during subsequent encounters with low-LET particles, increasing cumulative risk of oncogenic chromosome rearrangements.

Mutagenic repair phenotype observed in bystander cells. We again performed experiments in which replicate cultures of reporter cells were exposed to HZE particle radiation. Rather than challenging them directly with rare-cutting nuclease, however, we co-cultured the irradiated cells at intervals with radiation-naïve reporter cells expressing the rare-cutting nuclease. We measured the relative frequency of nuclease translocations and deletions at predetermined sites within a reporter cassette. We performed experiments with two ions with different LET values (1000 MeV/u 48Ti and 600 MeV/u 56Fe) and with low-LET radiation as a reference. We observed increases in nuclease-induced translocations (up to 3-fold) and deletions (up to 1.5-fold) in the radiation-naïve reporter cells. No effect was seen when low-LET irradiated cells were co-cultured with the radiation-naïve bystanders. Results indicate that HZE-irradiated cells release a signal into the medium that results in a breakdown in the fidelity of DNA double-strand break repair in neighboring cells. In an attempt to identify the signal, we performed genome expression profiling. HZE irradiation of the reporter cells induces a characteristic set of mRNAs encoding secreted factors, including IL-1b, Il-6, and IL-8. However, these same mRNAs were also induced by low-LET radiation, which does not evoke the mutagenic repair phenotype. With separate NASA funding, we are currently exploring the hypothesis that extracellular vesicles, rather than secreted factors, serve as carriers of the mutagenic repair signal.

Results are again significant for carcinogenesis in the space radiation environment, where the HZE particle fluence is low. Because the mutagenic repair phenotype occurs as the results of a non-targeted effect, a single HZE particle has the potential to compromise the fidelity of repair not only in cells traversed by the radiation track, but also in nearby cells that are not directly traversed. In theory, it might be possible to suppress the mutagenic repair signal as a strategy to mitigate radiation risk. Further characterization of the signal will be required to establish the feasibility of such an approach.

Mutagenic repair phenotype observed for endogenous genes in near-normal lung epithelial cells. Experiments described thus far were performed using a tumor cell line bearing reporter transgenes, which permits facile and very accurate measurements of deletion and translocation frequencies. It was of prime importance to demonstrate whether the phenomenon is also seen in lung epithelial cells, which are the relevant target for lung carcinogenesis. It was also important to demonstrate whether it was seen, not only with artificial reporter genes, but also with endogenous, cancer-relevant proto-oncogenes. Such experiments had not been feasible at the start of the NSCOR project. However, they became feasible with the advent of CRISPR/Cas9 technology, which permits the introduction of targeted DNA double-strand breaks virtually anywhere in the genome.

We adopted an approach based on the introduction of simultaneous double strand breaks in the endogenous ALK and EML4 loci. Faithful DSB repair regenerates the original, unrearranged locus, whereas mutagenic DSB repair leads to a paracentric inversion, with overexpression of an oncogenic EML4-ALK fusion. This is the single most common chromosomal rearrangement in human nonsmall cell lung cancer and has previously been shown to act as a driver of lung carcinogenesis in a mouse model. We developed a Taqman PCR assay for precise quantification of inversion frequency in CRISPR/Cas9 expressing human bronchial epithelial cell populations.

Initial results indicate that exposure to 48Ti radiation leads to an increase in CRISPR/Cas9 nuclease-induced EML4-ALK rearrangements in derivatives of the near-normal human epithelial cell line, HBEC3-KT. We are continuing to characterize and optimize the system with support from an individual NASA award.

Task Progress:

Project 3: Determine the nature of the HZE-particle induced ROS stress response, whether it contributes to HZE particle-induced lung carcinogenesis. This project focused on elucidating mechanisms underlying two prevalent phenotypes resulting from exposure to low and high LET radiation, namely reactive oxygen species (ROS) production and persistent genomic instability. Our initial studies in a non-cancerous human epithelial cell line (HBEC3KT) defined their temporal expression and LET dependence, determining that ROS levels and genomic instability persist within the progeny of irradiated cells proliferating in vitro for up to two weeks following exposure to 1 Gy x-rays (320 keV) or 1Gy 56Fe ions (600 MeV). While we did not observe radiation quality effects for ROS levels, micronuclei increased with an approximate RBE of 4 when these parameters were measured at day 7. We identified p38MAPK and ATM as molecules necessary to sustain these phenotypes. We further tested the role of pro-inflammatory responses in the ROS increases and genomic instability. We found that Fe induced IL-8 with an RBE of 4, by a mechanism dependent on IL-1alpha, which also induced the release of GM-CSF and GRO alpha. This IL-1alpha-dependent response however does not affect ROS production or genomic instability. ROS increases and genomic instability are elicited by multiple types of HZE ions, including Oxygen, Silicon, Iron as well as proton in a range of LET: 17 keV/µm, 70 keV/µm, and 175 keV/µm, respectively in in vitro exposed mouse and human bronchial epithelial cells and in the lungs of whole body irradiated mice. To further investigate the broader context of these phenotypes, we conducted a label-free global proteome analysis, which confirmed some of our previous findings from candidate-based approaches and revealed changes in novel pathways, implicating several nuclear proteins as potential mediators of genomic instability. These findings are of significance because such persistent phenotypes result from protracted biological responses to the initial exposure. Further mechanistic studies should allow identification of biomarkers to indicate individual responses to radiation exposure to assess risk and provide actionable targets to mitigate and/or prevent late effects.

Project 4: Determine the scope of HZE-particle radiation-induced alterations in DNA methylation patterns, whether these alterations contribute to lung carcinogenesis. We characterized the acute impact and long-term persistence of space radiation exposure on DNA methylation at 485,512 CpG sites using an array-based approach (Illumina Human Methylation 450K platform), and compared the effects of low LET (X-ray) vs. high LET (Ti, Fe, Si) radiation exposure. An in-house analytic pipeline was developed and used to identify DNA methylation changes significantly associated with dose, ion, and time. We showed for the first time that exposure of immortalized bronchial epithelial cells to HZE particle radiation induces stable and persistent changes to the epigenome, reflected in site-specific changes in DNA methylation. The radiation-induced changes to DNA methylation patterns are both LET- and quality-dependent; with each insult having a unique impact on the epigenome with regards to the direction, distribution, and specific CpG sites affected. Remarkably, the Fe-induced DNA methylation ‘signature’ uniquely reflects a cancer-specific DNA methylation pattern observed in primary human lung cancers. Taken together these data suggest that a stable imprint of prior space radiation exposure is reflected in the epigenome, and may prove useful as a biomarker of individual lung cancer risk.

Our work has also established a new paradigm for thinking about the influence of HZE particle exposure by probing the relationship between local chromatin environment and propensity towards space radiation-induced epigenome alterations. Using existing genome-wide histone modification profiles, RNA polymerase II binding profiles and other

chromatin features from the ENCODE project, we determined the chromatin structure surrounding the radiation-sensitive CpG sites. This analysis revealed that the Fe-affected sites were more likely (OR=1.3-1.5 fold) to occur in areas with a more “open” chromatin structure, including promoters and distal regulatory elements (enhancers), but were depleted from the transcribed regions of genes. Consistent with a propensity for enhancers, Fe-affected sites were enriched in regions that are accessible to DNaseI and marked by acetylated histone H3 lysine 27 (H3K27ac), a mark of active enhancers. In contrast, Si -affected sites were depleted from genes altogether and were more likely to occur in the condensed chromatin environments found in the intergenic spaces. These data indicate that ions of different charge and LET impart a unique epigenetic imprint on the genome and further implicate local chromatin environment as a key determinant of the underlying susceptibility to, or persistence of, space radiation-induced DNA methylation changes.

Our data raise the exciting possibility that the long-term consequences of space radiation exposure are rooted in the epigenetic reprogramming at distal regulatory elements or enhancers, regions that influence gene expression from a distance and harbor the vast majority of allelic sequence variation associated with human cancer risk. Indeed, the majority of DNA sequence polymorphisms that have been linked to cancer risk in population-based studies are not within gene coding regions, but rather are enriched in known or suspected enhancer regions. DNA methylation status at distal enhancers is a far better indicator of the inter-tumor heterogeneity in gene expression than that of promoters and can be used as a surrogate to predict enhancer activity even in the absence of information about chromatin features. HZE particle induced changes at such regions could underlie the inter-individual variation in biological responses to HZE particle radiation exposure and ultimately in long-term disease risk. A better understanding of the epigenetic imprint left by the components of space radiation and the extent to which this reflects cancer risk sets the stage for the future use of epigenetic signatures to monitor the cumulative impact of space radiation exposure among astronauts in deep space.

Moving forward, our goal is to define HZE particle-specific epigenomic imprints manifest in enhancers and other non-genic parts of the genome. The Illumina 450K methylation array has been useful for our prior work in humans, and allows direct comparison to tumor tissue data in the TCGA project. However, it has limited coverage of non-genic regions and there is no corresponding array for the mouse. Thus, we have developed technology “reduced-representation bisulfite sequencing” (RRBS) that allows for the assessment of methylation at 2.7M (mouse) and 4.1M (human) CpGs (10-20% of the genome). This covers 98% of annotated human/mouse promoters and ~50% of enhancers, among other non-coding regions. Our team has developed a powerful new statistical approach, DSS, to identify differentially methylated CpG sites (DMSs) and regions (DMRs) between unexposed and exposed samples. Parallel RNAseq (TruSeq library preparation, paired-end sequencing) and differential expression analysis can be performed, allowing gene expression correlates. We have applied this approach to identify DMRs in mouse lung bronchial epithelial cells exposed to 1.0 Gy 28Si or 56Fe, and identified differentially methylated regions and correlated this with gene expression changes. We are thus poised to define HZE-particle induced epigenomic alterations at distal regulatory elements, as well to expand these studies to tissues from mice exposed to HZE ions.

Education component: The education component was unique for our ESCOR team, which was based on NASA encouragement and supported by School of Medicine and Winship Cancer Institute of Emory University ($50,000/ year, $250,000 total). The major goal of this component was to educate the student population as well as the public. The accomplished tasks were as follows:

(1) Public Outreach

A. Emory NSCOR Website. We developed a full website for the NASA Emory NSCOR project. The content contains information about the research done by the project leaders and general information about radiation and radiation biology. The website contains information about the research being done (and the researchers performing the work), educational materials for students and the public, and allows participants to keep up with events related to the Emory NSCOR.Video interviews with the project leaders are presented on the site. Relevant video clips (and additional links) have been placed on the CancerQuest website (http://www.cancerquest.org) to leverage the existing user base of CancerQuest.

B. Radiation Education Materials for Students and the Public. We developed and disseminated a radiation curricular unit designed for middle and high school. The unit includes a PowerPoint® presentation, vocabulary list, and more. All material is designed to meet the Georgia Science Standards. The PowerPoint® is also very well suited for education of the general public.

C. Facebook® Our Facebook® page has 32,000 fans and has been used to promote research related to the work of the Emory-NSCOR, our educational materials, Emory NSCOR events, and radiation biology research.

(2) Student Engagement: training of undergraduate researchers via the Summer Undergraduate Research at Emory (SURE) program

One goal of the education unit was to encourage students to pursue science technology and mathematics (STEM) careers. To achieve this, we worked with the Emory SURE Program. SURE is a 10-week long research program. The program is administered by the Emory College Center for Science Education. Participation of underrepresented minorities is strongly encouraged by the Emory SURE program and a minimum of 50% of SURE participants are members of these populations (including ethnic/racial groups, economically disadvantaged, first generation college students, and disabled students).

Emory NSCOR summer research students participate in all SURE activities and present their work via posters at the conclusion of the program. Emory NSCOR researchers hosted 17 different students in their laboratories. Two of those students worked for more than one summer.

(3) Internal Communication/Research Facilitation through Blackboard®

The Emory NSCOR utilized an Emory-sanctioned system, Blackboard®, to host pertinent grant-related documents including meeting agendas and minutes, and lists of shared reagents/cell lines. Access to the system was restricted to those individuals currently working on the project.

Administrative Core major achievements: Apart from coordinating the different components of Emory NSCOR through weekly email and monthly face-to-face meetings, the most important activities for this administrative core were to organize two successful retreats in February 2013 and January 2015. All internal advisory board (IAB) and external advisory board (EAB) members attended the Emory NSCOR retreats as well as all project-related personnel. EAB members included Carlo Croce, MD, Professor and Chair, Depts. of Human Cancer Genetics, Molecular Virology,

	Immunology and Medical Genetics; Director, Human Cancer Genetics Program, Ohio State University Medical Center (For Project 1). George Iliakis, PhD, Professor, Director, Institute of Medical Radiation Biology, University of Duisburg-Essen, Medical School, Essen, Germany (For Project 2). Peter O'Neill, PhD, Professor, Gray Institute for Radiation Oncology & Biology, Department of Oncology, University of Oxford, Oxford, UK (For Project 3). Marco Durante, PhD, Professor, GSI-Biophysik, Darmstadt – Germany (For Project 4). The EAB/IAB members previewed their respective project materials and during these retreats, the Emory NSCOR project leaders reported their progress and EAB/IAB listened and provided valuable comments that greatly enhanced the team's ability to follow the major track of the NASA Space Radiation Element requirements and to more efficiently carry out the designed experiments. Our NSCOR team benefitted significantly from the retreats and the retreats were institutionally supported. Animal/Radiation Core major achievements: Apart from the major overall achievement 1 as described above (demonstrating for the first time that wild type C57BL/6J mice with an extremely low spontaneous lung tumorigenesis background can induce more lung tumorigenesis at 1.5 years after whole body exposure to high-LET radiation (particularly to silicon) than low-LET radiation), the animal/radiation core also served to facilitate a summary describing important lessons learned during our three-year animal experiments. The most important lesson being that mice with high spontaneous lung tumorigenesis: either over-expressed with oncogene or deficient in tumor suppressors are not good models for evaluating the risk of high-LET radiation-induced lung tumorigenesis. This summary is represented in detail in our publication (Life Science Space Research 2016, 9: 48-55). This publication provides NASA and affiliated scientists who study risk of space radiation-induced lung tumorigenesis with valuable lessons. This paper has been cited in the news section by the NASA supported online journal, "The Health Risks of Extraterrestrial Environments (THREE)."
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