Fiscal Year:	FY 2015	**Task Last Updated:**	FY 10/31/2014
PI Name:	Wang, Ya M.D., Ph.D.		
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		
PI Email:	ywang94@emory.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	(404) 778-1832
Organization Name:	Emory University		
PI Address 1:	School of Medicine Radiation Oncology		
PI Address 2:	1365 Clifton Road NE		
PI Web Page:			
City:	Atlanta	**State:**	GA
Zip Code:	30322	**Congressional District:**	5
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:**	
No. of PhD Candidates:	2	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	3	**Monitoring Center:**	NASA JSC
Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
Contact Email:	lisa.c.simonsen@nasa.gov		
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:			
COI Name (Institution):	Doetsch, Paul (Emory University) Orloff, Gregg (Emory University) Sun, Shi-Yong (Emory University) Vertino, Paula (Emory University) Wang, Huichen (Emory University) Dynan, William (Emory University)		
Grant/Contract No.:	NNX11AC30G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

The Emory University-Georgia Health Sciences University NSCOR will investigate the mechanisms by which high charge and energy (HZE) particles, a component of space radiation, induce lung cancer. HZE exposure elicits complex DNA damage, together with 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. The central hypothesis of this NSCOR is that this broader stress response amplifies the carcinogenic risk from a primary DNA damage event. Preliminary studies suggest that a small noncoding RNA, microRNA-21 (miR-21) plays a key role in coordinating the HZE particle-associated stress response. Center investigators will use genetic, epigenetic, and biochemical approaches to address the role of miR-21 dependent and independent stress responses in HZE particle-induced lung cancer. There are four projects:
1. Determine whether the lung cancer suppressor, Gprc5a, protects against HZE particle-induced lung carcinogenesis, and whether miR-21 overexpression blunts this protective effect.

2. Determine whether HZE-particle radiation exposure results in hyper-reliance on error-prone DNA repair pathways, whether miR21 mediates this effect, and whether dysregulation of DNA repair contributes to lung carcinogenesis.

3. Determine the nature of the HZE-particle induced ROS stress response, whether it contributes to HZE particle-induced lung carcinogenesis, and the role of miR-21 in this process.

4. Determine the scope of HZE-particle radiation-induced alterations in DNA methylation patterns, whether these alterations contribute to lung carcinogenesis, and the role of miR-21-dependent targeting of DNA methyltransferase 1 (DNMT1) in this process.

These four projects have a synergy through their collaboration on studying the mechanism underlying how mammalian respond to HZE particle-induced DNA damage, which contributes to tumor development.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

Space radiation from HZE-particles with high-LET is different from radiation with low-LET on Earth. Understanding the mechanism by which mammalian cells respond to space radiation induced the DNA damage is a key issue for us to evaluate the risk of space radiation on astronauts' health at any endpoint. Lung cancer is the most common 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 is lacking. The Emory NSCOR will address this important knowledge gap. In addition, our NSCOR team will answer the question concerning 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.

Overall Progress
The most important progress during the past year is reflected as follows:

1) We have discovered additional mechanism underlying the higher RBE of high-LET radiation when compared with low-LET radiation-induced cell killing: Ape1 in the clustered DNA damage site generated small DNA double strand breaks (DSBs) that contribute to the RBE. These results have been published: JBC 2014, 289:30635-30644. The importance of this work is to create an opportunity to consider about biological approaches that will reduce the risk of space radiation to astronauts.

2) We have found that heavy ions exposure induced higher incidents of lung tumors than x-ray exposure in whole body irradiated wild type mice. This is the first report to reveal that high-LET radiation can generate more lung tumors than low-LET radiation. These results have been resubmitted as a revised manuscript to Radiation Research. The importance of this work will enable us to further study the underlying mechanism and further estimate the risk of space radiation on lung tumorigenesis and reduce the risk.

Other progress: 1) We finished the mid-term evaluation that was organized by NASA's radiation program on October 21, 2013 at NASA headquarters.

On October 21, 2013, the Emory NSCOR key personnel (the leaders of each project and the education component) reported our project progress to the review panel that included Drs. Colin Hill (USC Keck School of Medicine), Raymond Meyn (M.D. Anderson Cancer Center), Phuoc Tran (Johns Hopkins University), Janice Huff (USRA/NASA JSC), Noelle Metting (DOE), and Walter Schimmerling (USRA). We also answered questions raised by the panel members. We expect to obtain the final review report by December, 2013. Again, we believe that the mid-term evaluation will help our NSCOR team to better follow the major goal of NASA radiation program for estimating the risk of space radiation on astronauts' health and exploring approaches to reduce the risk. 2) We have finished the animal radiation exposure for long-term tumorigenesis. In this NSCOR proposal, we used several mouse models to perform the radiation-induced tumorigenesis study. The mouse strains include wild type C57BL/6 mice, miR-21 knock-in mice, Gprc5a-/- mice, miR-21 knock-in, and Gprc5a-/- double mutant mice, miR-21-/- mice. X-ray exposure was performed in the Department of Radiation Oncology, Emory University and the HZE-particle exposure was performed at NASA Space Radiation Laboratory (NSRL), Brookhaven National Laboratory (BNL). We originally planned to sacrifice the mice at 8 months after irradiation; however, due to the fact that no significant tumorigenesis was observed at this time point from 3 irradiated miR-21 mice, we decided to extend the observation period from 8 months to 1.5 years to obtain the results of IR-induced tumorgenesis. Until now, we have finished all animal irradiation. We have obtained some valuable tumorigenesis data. The major discoveries are summarized as follows:

a. Wild C57BL/6 mice at 1.5 years after exposure to 1 Gy (single or fractionated dose) of different types of radiation with different LET (iron, silicon, oxygen and x-ray) showed that without radiation no lung tumorigenesis, low-LET exposure induced < 3% of lung tumorigenesis; however, all these tested HZE particles (iron, silicon, oxygen) induced a higher incidence of lung tumorigenesis than x-ray, the RBE was > 6 and silicon exposure induced more aggressive lung tumors. The manuscript is submitted.

b. MiR-21 knock-in mice without radiation showed a 30-40% lung tumorigenesis, suggesting that miR-21 is an oncogene. After radiation the lung tumor incidents in miR-21 knock-in mice reduced to half, which was related to the

lower level of miR-21 in the irradiated lung tissues. These results confirm the oncogene characteristic of miR-21. We are working on this project and manuscript is expected to be finished by early next year.

c. Gprc5a-/- mice without radiation showed a 10% lung tumorigenesis, confirming that Gprc5a is a tumor supressor. After radiation the lung tumor incidents in Gprc5a-/- mice increased to 30%; however, no difference of lung tumorigenesis was observed between low and high-LET radiation. Combining these results with the data of lung tumorigenesis from miR-21 knock in mice, we conclude that artificial made gene mutation mice may not be good mouse model for observing lung tumorigenesis although these mice could be the good models to identify the real function of these genes in spontaneous carcinogenesis.

d. Gprc5a as a tumor suppressor was previously determined to only exist in lung tissue; however, we discovered that Gprc5a also exists in human and mice thyroid tissue. Therefore, we were interested in determining if Gprc5a plays any role in preventing thyroid tumorigenesis after exposure to low or high-LET radiation. To address this, we examined the incidence of thyroid tumorigenesis in wild and Gprc5a knockout C57BL/6 mice at 1.5 years after exposure to 1 Gy (single or fractionated dose) of different types of radiation with different LET (iron, silicon, oxygen, and x-rays). We found that radiation induced more thyroid tumors in Gprc5a knockout mice than wild type mice. We also found that high-LET radiation induced higher incidents of thyroid tumors than low-LET radiation (x-rays), and silicon ions in particular generated more thyroid tumors in Gprc5a knockout mice. These results indicate that high-LET radiation, particularly silicon ions, has a higher risk than low-LET radiation to generate thyroid tumors and Gprc5a as a tumor suppressor also plays an important role in preventing high-LET radiation-induced thyroid tumors. A manuscript is under preparation and is expected to finish by end of 2014.

Progress from each project: This proposal has four projects and one education component. The progresses from these projects are described as follows:

Project 1:

Major goal: The major goal of this project is to study how radiation-induced DNA double strand breaks (DSBs) contribute to carcinogenesis and how miR-21 dependent and independent miRNAs affect radiation-induced tumorigenesis.

Progress: During the past year, we have reported that miR-34a as a tumor suppressor inhibited high-LET radiation-induced oncogenic transformation. We also reported that different heavier ions with different LET spectrum use a same mechanism for killing cells (interfere with non-homologous end-joining). In addition, we collaborated with project 2 and 3 identified that Ape1 as a base excision repair enzyme contributes to the RBE of high-LET radiation-induced cell killing. We found that the decreased level of Gprc5a and increased EGFR is correlated with an increased frequency of radiation-induced tumorigenesis. These findings provide an important explanation for why DNA DSB repair deficient mice have a high frequency of spontaneous tumorigenesis, and also provides additional explanation concerning why radiation-induced DNA DSBs enhances tumorigenesis. In addition, we are collaborating with Dr. Vertino (project 4) as to how miR-21 affects cell response to HZE particles via targeting DNMT. We plan to complete these studies in the next year.

Next year plan: To study the mechanism underlying the high-LET radiation-induced lung tumorigenesis by analyzing the DNA and RNA changes in the high-LET radiation-induced lung tumors and studying the changed gene functions in tumorigenesis.

Project 2: The hypothesis underlying project 2 is, “exposure to HZE-particle radiation, or altered miR-21 expression status, results in hyper-reliance on error-prone repair pathways, which accounts for the excess relative risk of HZE-particle radiation in lung carcinogenesis.” 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. In prior publications supported by this award, we measured the fidelity of repair in an irradiated population. We have now extended the work to co-cultured bystander cells. We showed that co-culture of HZE-irradiated cells with naïve bystander cells increased the frequency of mutagenic repair in the bystanders. Results are significant because they provide the first evidence that the mutagenic repair phenotype is a non-targeted effect experienced at the population level.

Highlights of the past year include: • Completion of bystander experiments. We measured mutagenic repair by co-culturing directly irradiated and bystander cells, then challenging the bystander population at intervals with a rare-cutting nuclease and measuring the relative frequency of induced 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. Results with Si ions showed increases in both translocations (up to 3-fold) and deletions (up to 1.5-fold). No effect was seen with low-LET radiation. Each experiment was performed in triplicate during two different NSRL campaigns for a total of six independent biological replicates. We are now preparing the results for publication.

• Completion of gene expression experiments showing that 600 MeV/u 56Fe and 1000 MeV/u 48Ti induce a characteristic set of mRNAs encoding secreted factors, including IL-1b, Il-6, and IL-8. We performed additional replicates and tested higher doses of low-LET radiation to obtain a robust, complete data set.

• Development of new approaches to address whether the mutagenic repair phenomenon extends to near-normal human epithelial cells, which are the cells of interest for lung carcinogenesis. This work is in direct response to feedback received at the mid-term review. Initially, we contemplated an approach where we inserted a reporter cassette into a near-normal epithelial cell line. However, with the advent of facile CRISPR/Cas9 technology we decided to adopt an approach based on simultaneous, paired incisions at sites known to undergo rearrangement in human lung cancer (ALK/EML4 and CD74/ROS1). Initial results indicate that CRISPR pairs do stimulate rearrangements (an inversion and a translocation, respectively) under baseline conditions in the HBEC3KT line. We are continuing to characterize and optimize the system and are approved for experiments at NSRL in the Spring 2015 campaign.

Project 3:

Summary the past year progress and next year plan:

DNA damage inflicted by radiation or chemotherapeutic drugs induces a cellular stress response by as yet undefined mechanisms and consequences for cell survival, genomic stability, and carcinogenesis. The goals for Project 3 are to

Task Progress:

determine the nature of HZE particle induced stress response and the resulting DNA damage and genomic instability that contributes to HZE particle induced lung carcinogenesis. In the fourth year we have accumulated a critical mass of experimental results for a second publication (to be submitted to Radiation Research) examining the role of proinflammatory responses induced by Fe with an RBE of 6 on persisting genomic instability phenotypes. We found that Fe particle and proton irradiation as well as higher doses of X-ray induce IL-1a release, which drives the induction of cytokines including GM-CSF, GROa, IL-1a, IL-8. Using a competitive inhibitor for IL-1 activity, human recombinant IL-1 Receptor Antagonist (Anakinra), we show that this response does not influence genomic instability measured by micronucleus and DNA repair foci frequencies. Moreover, we found that in this model, genomic instability is a cell-autonomous phenotype, not modified by factors released into the media by irradiated cells. We started to address the recommendations of our mid-term review by evaluating the presence of these mechanisms in irradiated mouse models in collaboration with Project 1, with the goal of studying the role of the responses persisting beyond the repair of the initial DNA damage and putative intervention strategies we identify in vitro, for in vivo disease development and carcinogenesis. In parallel, we are using in vitro transformation assays to evaluate the potential role of the multiple components of the stress response on cell transformation. For the next year of support we will further characterize the protein expression phenotype of the cells with persisting genomic instability as these could function as biomarkers to identify and quantify the cells that were traversed by a particle at an earlier time as well as reveal further consequences of this phenotype.

Project 4:

Studies and Results: The primary goal of this project is to define the epigenetic “memory” of high LET radiation exposure. We hypothesize that alterations in DNA methylation and chromatin structure resulting from acute radiation exposure and local DNA damage have the potential to become ‘fixed’ if they are subsequently replicated, leading to permanent changes in DNA methylation and potentially new gene expression programs. To test this hypothesis, triplicate cultures of immortalized human bronchial epithelial cells (3KT) were exposed to low LET (X-ray) (onsite at Emory) or HLET radiation of various doses (0, 0.3, 1.0 Gy) and sources (Si, Fe, Ti) at the Brookhaven National Laboratory facility. Samples were collected from a fraction of the exposed population after 48 hrs and the remaining cells were maintained in continuous culture for an additional 20 population doublings (~3 months) with weekly collection for genomic DNA, RNA, and cellular protein. Unexposed cultures underwent the same handling procedures and were maintained in parallel. The methylation status of > 485,000 CpG residues across the human genome was analyzed using the Illumina Infinium Human Methylation 450K platform. Two independent experiments have been performed for the HLET Fe series. We have recently also completed a longitudinal study of Ti exposure at 1.0 Gy.

An analytical pipeline was developed to identify statistically significant changes in DNA methylation associated with dose, source, or time after exposure. A linear mixed-effects model was applied using an in-house tool (‘CpG assoc’) wherein Beta values (methylation level) were treated as the outcome (dependent variable), with various co-variates considered including dose, time elapsed, chip position, and a random effect for chip number. We considered the Ti, Fe, Si, and X-ray exposed cohorts separately in the analyses. Significance was assessed by the Holm, and Benjamini-Hochberg methods, and permutation analyses were incorporated to test for robustness of the results.

Our results indicate that the most significant association is with time; more than 100,000 CpG sites underwent a significant drift in methylation over time in culture, independently of the type or dose of radiation exposure. We estimate this to be an ~0.1 % change in methylation per day, that is, on average 1 in 1000 molecules of DNA switches its methylation status per day. Both hyper and hypomethylation events were observed, but CpG sites whose methylation patterns drift trend in the same direction over time, suggesting a cumulative effect.

We also identified methylation changes that were significantly associated with radiation dose, independent of time. We identified 934 sites whose methylation status was significantly associated with Fe dose (849 hyper; 86 hypo); 299 sites whose methylation status was associated with Si dose (158 hyper, 142 hypo) and 1150 that were associated with X-ray dose (252 hyper; 898 hypo).

Significantly, we find that the effects of radiation on genome-wide methylation patterns were dependent on both LET and on radiation quality. Exposure to Fe ions resulted in a genome-wide trend towards hypermethylation and tended to affect sites that start out with lower DNA methylation levels (mean=21.9%); whereas exposure to X-ray resulted in a genome-wide trend towards hypomethylation and affected sites that tended to start out with a higher methylation level (median=61.9%). Si had an intermediate effect and showed no particular trend in either direction. Importantly, radiation-induced methylation changes were observed early (48h after exposure) and persisted over time, indicating a stable and heritable change had occurred in the epigenome.

Through genome-wide comparative analyses, we also determined that high and low LET exposure tended to affect different genomic compartments, implying that they arise through distinct mechanisms, and have distinct cellular consequences. CpG sites whose methylation status was affected by Fe exposure tended to be enriched in CpG island ‘shores’, the regions surrounding CpG islands that harbor the most variable methylation in the genome, and underrepresented in gene bodies, whereas sites affected by X-ray exposure were enriched in gene bodies and intergenic regions. Sites affected by Si were overrepresented in heterochromatic regions. Interestingly, there was a 1.3 fold enrichment of Fe affected sites in regions with features of distal enhancer elements. Such regions are known to confer cell type specific transcriptional control and are also the source of significant genetic variation associated with diseases including cancer. Recent work suggests that the dynamic regulation of DNA methylation may also contribute to the regulation of gene expression at a distance through enhancer elements.

To probe the significance of our findings with respect to human cancer lung cancer, we compared our observed HLET methylation “signature” with the methylation patterns of primary human lung cancers of different genetic and pathologic backgrounds that have been analyzed as part of the NIH’s Cancer Genome Atlas (TCGA) project. Interestingly, we find that the methylation status of CpG sites affected by Fe exposure in our experimental model are capable of segregating lung cancer from normal adjacent tissue, both for a set of lung adenocarcinomas and a distinct dataset from squamous cell lung carcinomas, suggesting that they represent cancer-specific methylation changes in human lung cancer. Similar analysis showed no such relationship with the sites affected by either X-ray or by Si exposure. Thus, the HLET (Fe) radiation exposure methylation signature reflects a cancer-specific methylation in primary lung cancers. In addition, several Fe sites were identified whose methylation status reliably predicts patient outcomes.

Taken together these data suggest that both HLET and Low LET radiation exposure can induce stable and heritable changes in DNA methylation, but that these effects are distinct in mechanism, and may also have distinct biological consequences related to carcinogenesis. HLET radiation induced methylation changes may prove useful as biomarkers

for long term risk assessment.

Plans for upcoming year

At this point all of our exposure and methylation analyses have been on lung cells in culture. While this has provided fundamental information regarding the role of HLET radiation-induced effects on the epigenome, our ultimate goal is to determine the impact of an altered epigenome on lung cancer risk, and over the long term, to identify methylation biomarkers that might be useful in biodosimetry and risk assessment. To this end, we are in the process of refining the methods to evaluate epithelial cells isolated from bronchial lavage from mice exposed to HLET radiation at the Brookhaven facility. This also requires a shift in technology to examine methylation patterns genome wide using Reduced Representation Bisulfite Sequencing RRBS) methods which provide information on ~1/10 of the genome (and 10x the coverage associated ic coverage (~2M CpG sites) across the mouse genome. These studies are being done in collaboration with Project 1 (Wang).

To determine whether HLET radiation induced DNA damage leaves an epigenetic ‘scar’ that is subsequently perpetuated, or more generally affects DNA methylation in random patterns (due to more global effects like increased cellular ROS), we will attempt clonal studies where individual cells will be isolated immediately after exposure and clonally expanded prior to methylation analysis. We also plan to work with Project 2 to assess DNA methylation and chromatin structural changes and around induced DSBs following the compromised repair observed in flow sorted HLET exposed cells.

Education Component: The main goal of the education and outreach plan is designed to maximize the immediate and long-term impact of the work performed by the NSCOR network (Network), which will greatly enhance the influence of the NASA education programs. For this purpose, the education component has the following activities:

Summary of Education Unit Activities November 2013-September 2014

1) Public Outreach

A. Emory NSCOR Website. This year we created video interviews with all of the Emory NSCOR project PIs and have placed them on the Emory NSCOR website (http://nscor.emory.edu). and in our YouTube channel. We are also placing relevant video clips (and additional links) on the CancerQuest website (http://www.cancerquest.org) to leverage the existing user base of CancerQuest.

We have worked to maintain and expand the Emory NSCOR website 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.

B. Radiation Education for Students and the Public. 1. We are currently finalizing the new curricular unit on lung cancer. The topics covered include risks and prevention of lung cancer, including terrestrial radiation exposures (i.e. radon). The possible effects of space radiation, as researched by NASA NSCORs, will also be covered. 2. We continue to disseminate the radiation curricular unit. 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 34,711 fans (up from ~9,500 last year at this time) and is actively used to promote research related to the work of the Emory-NSCOR, our educational materials, and Emory NSCOR events.

2) Student Engagement

A. Training of Undergraduate Researchers via the SURE program. One goal of the education unit is to encourage students to pursue science technology and mathematics (STEM) careers. To achieve this, we work 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 student, disabled).

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 two full-time SURE student researchers during the summer of 2014 and one half-time (education/outreach) student. Photographs of the Emory NSCOR students at the research symposium are posted on our website.

3) Internal Communication/Research Facilitation

A. Blackboard®. The Emory NSCOR Blackboard® site contains pertinent grant-related documents including meeting agendas and minutes, and lists of shared reagents/cell lines. Access is restricted to those individuals currently working on the project.

4) Administration

A. Participation in Monthly Meeting. Gregg routinely attends and actively participates in monthly Emory NSCOR meetings. The education products are presented and discussed along with the results/plans for the research projects.

B. Attendance/Presentation at NASA NSCOR Reviews. Education and outreach updates are presented at all internal and e external reviews of the Emory NSCOR. The Education unit provides multimedia equipment and support for events, as needed.

5) Future Plans

A. Student Researcher Interviews. We will videotape interviews with the students who worked in the Emory NSCOR laboratories to allow them to discuss their experiences with NASA-funded research. The videos will be placed on our websites and on YouTube. We hope to encourage participation in research by populations currently under-represented in the sciences.

	B. Twitter® Integration. We will add Twitter® to our social media outlets by creating and connecting a Twitter® account to our Facebook® page. This will expand the reach of our posts and drive additional traffic to the Emory NSCOR website C. Website Maintenance and Expansion. We will work to keep the research presented on the website reflective of the work done by our NSCOR and add additional sections to the site addressing advances in radiation and radiation therapy research.
Bibliography Type:	Description: (Last Updated: 07/07/2021)
Abstracts for Journals and Proceedings	Li Z, Hudson FZ, Wang H, Wang Y, Murnane JP, Dynan WS. "A genomic stress response as a novel mechanism leading to chromosomal instability in heavy particle-irradiated cell populations." 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. http://www.hou.usra.edu/meetings/hrp2014/pdf/3138.pdf , Feb-2014
Abstracts for Journals and Proceedings	Werner E, Tang KX, Wang H, Doetsch PW. "The role of persisting phenotypes on radiation-induced genomic instability." 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. http://www.hou.usra.edu/meetings/hrp2014/pdf/3187.pdf , Feb-2014
Abstracts for Journals and Proceedings	Li Z, Zheng X, Wang Y, Dynan WS. "Novel, non-targeted effect of HZE particle radiation on the DNA double strand repair machinery." 60th Annual Meeting of the Radiation Research Society, Las Vegas, Nevada, September 21-24, 2014. 60th Annual Meeting of the Radiation Research Society, Las Vegas, Nevada, September 21-24, 2014. , Sep-2014
Abstracts for Journals and Proceedings	Werner E, Tang KX, Wang H, Doetsch PW. "The role of inflammation in radiation-induced genomic instability." 60th Annual Meeting of the Radiation Research Society, Las Vegas, Nevada, September 21-24, 2014. 60th Annual Meeting of the Radiation Research Society, Las Vegas, Nevada, September 21-24, 2014. , Sep-2014
Abstracts for Journals and Proceedings	Vertino PM. "Islands, Shores, and Beyond: DNA Methylation in Space." Emory University Chromatin Club, Feb 22, 2014. Emory University Chromatin Club, Feb 22, 2014. , Feb-2014
Articles in Other Journals or Periodicals	Wang H, Wang X, Chen G, Zhang X, Tang X, Park D, Cucinotta FA, Yu DS, Deng X, Dynan WS, Doetsch PW, Wang Y. "Distinct roles of Ape1 protein, an enzyme involved in DNA repair, in high or low linear energy transfer ionizing radiation-induced cell killing." J Biol Chem. 2014 Oct 31;289(44):30635-44. http://dx.doi.org/10.1074/jbc.M114.604959 ; PubMed PMID: 25210033. ED. NOTE: Article re-categorized as "Other" since was WITHDRAWN May 2020, see PMID: 32358082; PMCID: PMC7196659 , Oct-2014
Articles in Peer-reviewed Journals	Werner E, Wang H, Doetsch PW. "Opposite roles for p38MAPK-driven responses and reactive oxygen species in the persistence and resolution of radiation-induced genomic instability." PLoS One. 2014 Oct 1;9(10):e108234. eCollection 2014. http://dx.doi.org/10.1371/journal.pone.0108234 ; PubMed PMID: 25271419; PubMed Central PMCID: PMC4182705 , Oct-2014
Articles in Peer-reviewed Journals	Zheng X, Zhang X, Ding L, Lee JR, Weinberger PM, Dynan WS. "Synergistic effect of high charge and energy particle radiation and chronological age on biomarkers of oxidative stress and tissue degeneration: a ground-based study using the vertebrate laboratory model organism Oryzias latipes." PLoS One. 2014 Nov 6;9(11):e111362. eCollection 2014. http://dx.doi.org/10.1371/journal.pone.0111362 ; PubMed PMID: 25375139; PubMed Central PMCID: PMC4222877 , Nov-2014
Articles in Peer-reviewed Journals	Ng WL, Chen G, Wang M, Wang H, Story M, Shay JW, Zhang X, Wang J, Amin AR, Hu B, Cucinotta FA, Wang Y. "OCT4 as a target of miR-34a stimulates p63 but inhibits p53 to promote human cell transformation." Cell Death Dis. 2014 Jan 23;5:e1024. http://dx.doi.org/10.1038/cddis.2013.563 ; PubMed PMID: 24457968; PubMed Central PMCID: PMC4040665 , Jan-2014
Articles in Peer-reviewed Journals	Wang Y. "The effects of space radiation-changed MiRNAs on tumorigenesis." The Health Risk of Extraterrestrial Environments (THREE) website, February 2014. http://three.usra.edu/articles/Ya-Wang-MiRNA.pdf ; accessed 11/11/14. , Feb-2014
Articles in Peer-reviewed Journals	Li Z, Hudson FZ, Wang H, Wang Y, Murnane JP, Dynan WS. "Mutagenic joining of enzymatically induced DNA double-strand breaks, accompanied by persistent unrepaired DNA damage and a secretory protein phenotype, in HZE-exposed human cells." J Radiat Res. 2014 Mar 1;55(Suppl 1):i85-i86. (Proceedings of Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013.) http://dx.doi.org/10.1093/jrr/rrt169 , Mar-2014
Articles in Peer-reviewed Journals	Werner E, Kandimalla R, Wang H, Doetsch PW. "A role for reactive oxygen species in the resolution of persistent genomic instability after exposure to radiation." J Radiat Res. 2014 Mar 1;55(Suppl 1):i14. (Proceedings of Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013.) PMCID: PMC3941489 ; http://dx.doi.org/10.1093/jrr/rrt183 , Mar-2014
Articles in Peer-reviewed Journals	Kennedy EM, Conneely KN, Vertino PM. "Epigenetic Memory of Space Radiation Exposure." The Health Risks of Extraterrestrial Environments (THREE), 2014. https://three.jsc.nasa.gov/articles/Vertino.pdf , Jun-2014
Articles in Peer-reviewed Journals	Li Z, Wang H, Wang Y, Murnane JP, Dynan WS. "Effect of radiation quality on mutagenic joining of enzymatically-induced DNA double strand breaks in previously irradiated human cells." Radiat Res. 2014 Nov;182(5):573-9. Epub 2014 Oct 20. http://dx.doi.org/10.1667/RR13723.1 ; PubMed PMID: 25329962 , Nov-2014
Articles in Peer-reviewed Journals	Wang H, Wang Y. "Heavier ions with a different linear energy transfer spectrum kill more cells due to similar interference with the ku-dependent DNA repair pathway." Radiation Research. 2014 Oct;182(4):458-61. http://dx.doi.org/10.1667/RR13857.1 ; PMID: 25229976 , Oct-2014