

Fiscal Year:	FY 2013	Task Last Updated:	FY 10/26/2012
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Project Title:	Duke NSCOR: Lung Cancer Risk from HZE Ions		
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:	None		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	27710-0001	Congressional District:	1
Comments:			
Project Type:	GROUND	Solicitation / Funding Source:	2010 Space Radiation NSCOR/Virtual NSCOR NNJ10ZSA002N
Start Date:	01/01/2011	End Date:	12/31/2015
No. of Post Docs:	3	No. of PhD Degrees:	1
No. of PhD Candidates:	3	No. of Master' Degrees:	0
No. of Master's Candidates:	0	No. of Bachelor's Degrees:	0
No. of Bachelor's Candidates:	0	Monitoring Center:	NASA JSC
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Flight Assignment:			
Key Personnel Changes/Previous PI:			
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Grant/Contract No.:	NNX11AC60G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

The goal of the Duke NSCOR is to understand mechanisms of high charge and energy (HZE) ion-induced lung cancer. To accomplish this goal, the Duke NSCOR has brought together experts in radiation biology, lung cancer development, lung injury and repair, radiation dosimetry, and education. We will combine sophisticated mouse genetics, in vivo lineage tracing, ex vivo isolation of lung epithelial progenitor cells, and analyses of lung cancers induced by HZE nuclei to dissect mechanisms of HZE ion-induced lung cancer. We will integrate 3 separate projects to understand how the cell of origin influences lung cancer development after HZE ion exposure, identify mechanisms of cellular response to HZE ions in different progenitor populations in the lung, and define how and when the p53 tumor suppressor, which is the most commonly mutated gene in human lung cancer, regulates HZE ion-induced carcinogenesis in the lung. We anticipate that our hypothesis-based research will ultimately lead to the development of better models for HZE ion carcinogenic risk assessment for individual astronauts and novel approaches to prevent HZE ion-induced lung cancer through biological countermeasures.

Rationale for HRP Directed Research:

Lung cancer causes more than one million cancer deaths each year and is the leading cause of cancer death worldwide. Despite advances in the detection and treatment of lung cancer, lung cancer prevention presents a major unmet need. While many lung cancer cases are preventable as they are due to smoking, it is estimated that 25% of lung cancer cases worldwide involve never smokers. Though multiple risk factors including exposure to radiation from radon gas have been implicated, no clear-cut cause has emerged to explain the relatively high incidence of lung cancer in never smokers. Lung cancers arising in never smokers demonstrate different mutation patterns and frequencies when compared to cancers arising in smokers, suggesting that lung cancer arising in never smokers is a clinically distinct disease. Indeed, lung cancers in never smokers respond differently to targeted cancer therapies. Further research into the mechanism of lung cancer development in never smokers is needed so that more successful strategies for prevention and treatment of lung cancer can be developed. By studying the mechanisms of lung cancer initiation and development, the Duke NSCOR is generating new knowledge that can be used to develop novel approaches for the prevention and treatment of lung cancer.

Research Impact/Earth Benefits:

Lung cancer can be divided into two major forms: small-cell lung cancer and non-small cell lung cancer. Both non-small cell lung cancers and small cell lung cancers have developed in survivors of the atomic bombs in Japan. Similarly, both types of lung cancer arise in smokers. Cancers arising in never smokers preferentially develop in the distal airways and are of the adenocarcinoma histological subtype, which is a type of non-small cell lung cancer. Recently, genomic sequencing technology has been utilized to identify the most commonly mutated genes in adenocarcinomas. Based on this analysis, the two most commonly mutated genes in adenocarcinomas are Trp53, which encodes the tumor suppressor p53, and the oncogene Kras. The Duke NSCOR is utilizing sophisticated genetically engineered mouse models to study the role of p53 and Kras in non-small cell lung cancer. For example, we are studying how mutations in Kras in different kinds of cells in the lung affect lung cancer development with exposure to space radiation. We are also studying mice with an additional copy of p53 or inducible p53 suppression to investigate the timing and mechanism by which p53 suppresses Kras-driven lung adenocarcinoma progression after space radiation exposure. In addition, we are developing a mouse model of radiation-induced small-cell lung cancer. Together these studies will provide new insights into how lung cancer forms, where lung cancers develop, and how Kras and p53 mutation promote lung cancers. As we answer these questions using experiments with space radiation, we expect that our results will not only help us understand how lung cancer develops on earth, but will also provide new insights into preventing and treating lung cancer.

In addition to studying lung cancer development, the Duke NSCOR is also studying lung progenitor cell injury and repair after exposure to either terrestrial or space radiation. Injury and inflammation of the lung are key components of many diseases in people including emphysema, asthma, and lung fibrosis. Furthermore, patients receiving radiotherapy for either primary lung cancer or other neoplasms of the thoracic region (e.g. breast cancer) undergo lung tissue remodeling and declining lung function that is directly related to the dose and location of radiation exposure. By exploring which lung cells are injured by space radiation and how these injured lung cells are repaired, we anticipate that this knowledge may also lead to a better understanding of how lung diseases besides cancer develop and strategies that may be employed to moderate the effects of radiotherapy on lung tissue remodeling. This information may ultimately be used to develop novel approaches for the prevention and treatment of these lung diseases, and the improvement of public health.

In our second year of funding, the Duke NASA Specialized Center of Research (NSCOR) continued to perform the experiments proposed in our application. During 2012, members of the Duke NSCOR twice travelled to Brookhaven National Laboratory to expose mice to space radiation at the NASA Space Radiation Laboratory. We have made significant progress towards determining the acute effects of this space radiation on lung progenitor cells. In addition, we have initiated several long-term experiments to determine the effect of space radiation exposure on lung cancer risk. On March 7, 2012, the UTSW NSCOR visited Duke, and we exchanged data and established opportunities for collaboration. In addition, we have sent mice and cells to the Emory NSCOR for collaborative projects. From July 7-11, 2012, Duke hosted the Annual NSCOR Meeting and the 23rd Annual NASA Space Radiation Investigators Workshop. Project 1. The role of the tumor suppressor p53 in space radiation-induced lung cancer. David Kirsch, M.D., Ph.D., Lead

We have proposed to study the role and timing of the tumor suppressor p53 in radiation-induced lung cancer using mice with an extra copy of p53 (Aim 1) and reversible knockdown of p53 (Aim 2). In addition, we are developing a model of radiation-induced small cell lung cancer (Aim 3).

For Aim 1, we have confirmed an increased induction of p53 transcriptional targets in mice with an additional copy of p53 (super p53 mice) after both X-ray and 600 MeV/n 56Fe (HZE) irradiation. We have bred mice with 2 or 3 copies of p53 with mice that are predisposed to lung cancer and have exposed 77 of these mice to space radiation at BNL and 23 mice to X-ray irradiation at Duke. We have analyzed the majority of these mice for lung tumor burden six months following radiation. Our preliminary results suggest that space radiation exposure increases the occurrence of lung cancer in these mice. In addition, an extra copy of p53 appears to protect mice from lung tumor initiation. In the coming year, we plan to increase the size of our mouse cohorts to verify these initial findings.

For Aim 2, we have bred mice predisposed to lung cancer in which p53 expression can be knocked down using a doxycycline-inducible RNA interference system. Using these mice, we will temporarily knockdown p53 during space radiation exposure to investigate the temporal role of p53 in HZE radiation-induced lung cancer. We will irradiate our

first cohort of these mice in November 2012.

For Aim 3, we have irradiated 42 mice with fractionated space radiation at BNL and are following them for the development of small cell lung cancer. We have already observed several mice with lung tumors after radiation. In the coming year, we plan to irradiate mice with varying susceptibility to small cell lung cancer with both single dose and fractionated HZE and low-LET (X-ray) radiation to evaluate the effect of space radiation exposure on lung tumor initiation.

Project 2. The role of cell of origin in space radiation-induced lung cancer. Mark Onaitis, M.D., Lead

We have proposed to study the cell of origin of K-RasG12D-induced lung cancer in response to space radiation. Our aims include studying the effects of HZE radiation on mice in which K-RasG12D is inducibly expressed in different cell types of the lung: Clara cells (Aim 1), basal cells (Aim 2), and Type II cells (Aim 3).

For Aim 1, we have now radiated 27 CC10-CreER; lsl K-RasG12D mice and have 28 CC10-CreER; lsl K-RasG12D controls that were sham irradiated. Analysis of tumor formation in these mice is ongoing. We will continue to irradiate more cohorts of these mice in the next year.

For Aim 2, we have had difficulty breeding mice. Recently, we identified successful breeding pairs. Therefore, we are now expanding this colony and will begin irradiating these mice this year.

For Aim 3, we have now radiated 14 SPC-CreER; lsl K-RasG12D mice and have 6 SPC-CreER; lsl K-RasG12D mice that were sham irradiated as controls. The mice have been sacrificed and the lungs fixed. We are currently analyzing sections of the lungs to assess for phenotypic differences. Many more of these mice will be irradiated in the next year. Because the K-RasG12D mutant mice develop widespread tumors causing death of the mouse within 24 weeks after tamoxifen administration, as an alternative approach, we have begun irradiating CC10-CreER; floxed NF1 or floxed Ink4A/Arf mice in order to assess the effects of radiation in a less penetrant model.

Project 3. Effects of space radiation and p53 signaling on lung progenitor cells. Barry Stripp, Ph.D., Lead

The focus of this project is to compare direct and non-target effects of X-rays and HZE radiation on the clonogenic and repair capacity of lung epithelial progenitor cells, and to determine the impact of p53 deficiency on these responses. We have shown that region-specific progenitor cells maintain the specialized epithelium of mouse and human airways and have developed novel mouse models to functionally investigate their behavior in vivo and in vitro. An important feature of our in vitro model used to assess the clonogenic behavior of epithelial progenitor cells is the use of a three-dimensional culture environment in which epithelial cells are co-cultured with stromal support cells to restore critical elements of the in vivo microenvironment.

Task Progress:

For Aim 1 we have used in vivo lineage tracing and novel in vitro models that recapitulate epithelial-stromal interactions seen in small airways, to determine how either 320 kVp X-ray or 600 MeV/n 56Fe particles (HZE) impact clonal expansion of epithelial progenitor cells. Lineage tracing coupled with morphometry was used to establish that whole body exposures to either X-ray or HZE were associated with dose-dependent increases in the probability that epithelial progenitor cells expanded to yield large clone sizes within airways. However, in vivo clonal expansion of epithelial progenitor cells was not associated with a significant change in the epithelial proliferative index. Ongoing experiments are using double labeling methods to define the effects of radiation dose and type on the pool size of epithelial progenitor cells in vivo, and to determine how lung injury resulting from either ozone or influenza virus impacts the rate of progenitor cell expansion following IR exposure. These studies are important as we show that the effects of IR exposure are latent within the epithelium of airways. We predict that the effects of radiation exposure and differences between dose and type of IR, on epithelial progenitor cells will be amplified by environmental triggers that cause epithelial cell injury. In vitro experiments performed over the past funding period have revealed direct effects of either X-ray or HZE exposure on lung progenitor cells following whole-body exposures. Our ability to couple lineage tracing of epithelial progenitor cells with in vitro clonal behavior has provided a sensitive measure of moderate to low-dose effects. In vitro exposure of either isolated epithelial progenitor cells or stromal cells used in 3D co-cultures has provided preliminary insights into direct versus non-target effects of radiation exposure on the clonogenic behavior of epithelial progenitor cells. In collaborative studies with Dr. Jerry Shay and the UTSW NSCOR we are coupling in vitro exposure models with drug screens to identify radio-protective molecules and pathways impacting progenitor cell responses to either X-ray or HZE radiation.

For Aim 2, we have established lines of mice allowing application of either in vivo or in vitro assays to assess behavioral changes of epithelial progenitor cells to IR exposure that accompany loss of p53 function. Initial experiments are focusing on X-ray exposures with HZE exposures at NSRL/BNL planned for 2013.

Core A: Administrative Core. David Kirsch, M.D., Ph.D., Lead. Duke NSCOR Administrators: Michelle Cooley and Sue Yager

The Administrative Core (Core A) provides overall management of the NSCOR award by ensuring that projects make satisfactory progress. During the second year of funding, the Administrative Core has monitored project progress by conducting biweekly Duke NSCOR meetings, an annual Internal Advisory Committee Meeting, and multiple teleconferences with NASA. Minutes were recorded at these meetings in order to ensure that tasks were completed in a timely manner. Core A made travel arrangements for the Duke NSCOR team to travel to Brookhaven National Laboratory in Spring and Fall of 2012 in order to expose mice to high energy ionizing radiation. Travel arrangements were also made for all of the meetings described above to facilitate communication between the Duke NSCOR and other NASA investigators. Furthermore, Core A organized the visit by the UTSW NSCOR on March 7, 2012, which was held at the R. David Thomas Center at Duke. Core A also provided administrative support for credentialing Duke NSCOR investigators to work at BNL and for submitting and renewing the animal protocols at Duke and BNL. Core A provided budget oversight for the Duke NSCOR. Project expenditures were monitored by Erin Dillard. Ms. Dillard met monthly with David Kirsch M.D., Ph.D. to review spending and fiscal matters for each NSCOR project and Core. Marcia Painter assisted with ordering supplies and financial accounting for the Duke NSCOR.

Core B: Physics Core. Terry Yoshizumi, Ph.D., Lead

The Physics Core (Core B) provides comprehensive measurements of radiation dose (dosimetry) and oversees the radiation safety of experiments performed by investigators in the Duke NSCOR for experiments with X-rays. By performing routine dosimetry measurements on the standard small animal X-Ray irradiator, the Physics Core provides

	<p>quality control for radiation exposure experiments. In addition, members of the physics core participate and present physics reports in the monthly NSCOR meeting.</p> <p>Core C: Education Core. Rochelle Schwartz-Bloom, Ph.D., Lead</p> <p>The Education Core (Core C) is developing an online problem-based unit to teach high school students about radiation in space by incorporating principles of physics, chemistry, and biology. The unit contains a hypothetical scenario in which a group of young astronauts are selected to travel to Mars in the year of 2040. The astronauts must learn about the types of radiation they will encounter in space (compared to on earth), the damage these high energy particles and cosmic rays can cause to their DNA molecules, how their bodies can deal with the damage using a protein called p53, and what would happen if their p53 gene has a mutation. They also learn how mutations in p53 genes can increase the risk of cancer, especially of the lung. The astronauts will meet some “virtual” scientists (the PIs of projects 1-3) who study these topics and whose research findings are crucial to the development of a successful space program that includes a trip to Mars. The educational unit will be field-tested in local high schools for impact on content knowledge and interests in science.</p>
Bibliography Type:	Description: (Last Updated: 03/11/2021)
Abstracts for Journals and Proceedings	<p>Lee CL, Blum JM, Moding EJ, Kim Y, Kirsch DG. "The tumor suppressor p53 acts during total-body irradiation to promote lymphoma development." 58th Annual Meeting of the Radiation Research Society, San Juan, Puerto Rico, September 30 – October 3, 2012.</p> <p>58th Annual Meeting of the Radiation Research Society, San Juan, Puerto Rico, September 30 – October 3, 2012.</p> <p>Presentation Number: PS1-39. , Oct-2012</p>
Abstracts for Journals and Proceedings	<p>Moding EJ, Woodlief LZ, Lee CL, Ma Y, Kirsch DG. "Role of p53 in Lung Carcinogenesis after Exposure to Space Radiation." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11 2012.</p> <p>23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11 2012. , Jul-2012</p>
Abstracts for Journals and Proceedings	<p>Lee CL, Blum JM, Moding EJ, Woodlief L, Borst L, Kim Y, Kirsch DG. "The tumor suppressor p53 acts during total-body irradiation to promote lymphoma development. " 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11 2012.</p> <p>23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. , Jul-2012</p>
Abstracts for Journals and Proceedings	<p>Futtner C, Shan L, Onatits M. "High LET Radiation Does Not Alter Short-Term Tumor Pattern in K-Ras-expressing Bronchiolar and Alveolar Cells." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012.</p> <p>23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. , Jul-2012</p>
Abstracts for Journals and Proceedings	<p>Farin AM, Manzo ND, Terry KL, Stripp BR. "Modeling Cell-Intrinsic Effects of Low vs High LET Ionizing Radiation on Lung Epithelial Progenitor Cells." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012.</p> <p>23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. , Jul-2012</p>
Abstracts for Journals and Proceedings	<p>Manzo ND, Farin AM, Terry KL, Stripp BR. " Proliferative and Clonogenic Potential of Lung Progenitor Cells Exposed to Ionizing Radiation." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012.</p> <p>23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. , Jul-2012</p>
Abstracts for Journals and Proceedings	<p>Rodrigues AE, Nguyen G, Li Y, Das SK, Kirsch DG, Yoshizumi T. "Dose verification in small animal image guided radiation therapy: A dose comparison between TG-61 based look-up table and MOSFET method for various collimator sizes." 2012 North Carolina Health Physics Society 2012 Spring Meeting, Raleigh, NC, March 15-16, 2012.</p> <p>North Carolina Health Physics Society 2012 Spring Meeting, Raleigh, NC, March 15-16, 2012. , Mar-2012</p>
Abstracts for Journals and Proceedings	<p>Rodrigues A, Nguyen G, Li Y, Choudhury KR, Kirsch D, Das S, Yoshizumi T. "Dose Verification in a Small Animal Image-Guided Radiation Therapy X-Ray Machine: A Dose Comparison Between TG-61 Based Look-Up Table and MOSFET Method for Various Collimator Sizes." AAPM (American Association of Physicists in Medicine) 54th Annual Meeting, Charlotte, NC, July 29 - August 2, 2012.</p> <p>AAPM (American Association of Physicists in Medicine) Annual Meeting, Charlotte, NC, July 29 - August 2, 2012.</p> <p>http://www.aapm.org/meetings/2012AM/PRAbs.asp?mid=68&aid=17954 , Aug-2012</p>
Articles in Other Journals or Periodicals	<p>Moding EJ, Kirsch DG. "Genetically modified mouse models of lung cancer." The Health Risks of Extraterrestrial Environments. January 2012. , Jan-2012</p>
Articles in Peer-reviewed Journals	<p>Newton J, Oldham M, Thomas A, Li Y, Adamovics J, Kirsch DG, Das S. "Commissioning a small-field biological irradiator using point, 2D, and 3D dosimetry techniques." Medical Physics. 2011 Dec;38(12):6754-62. PubMed PMID: 22149857 , Dec-2011</p>
Awards	<p>Lee CL. "Second place in the poster competition in the post-doc category for: Lee CL, Blum JM, Moding EJ, Woodlief L, Borst L, Kim Y, Kirsch DG. The tumor suppressor p53 acts during total-body irradiation to promote lymphoma development. 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11 2012." Jul-2012</p>
Awards	<p>Moding EJ. "Second place in the poster competition in the graduate student category for: Moding EJ, Woodlief LZ, Lee CL, Ma Y, Kirsch DG. Role of p53 in Lung Carcinogenesis after Exposure to Space Radiation. 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11 2012. " Jul-2012</p>
Awards	<p>Lee CL. "Marie Curie Lecture Award for: Lee CL, Blum JM, Moding EJ, Kim Y, Kirsch DG. The tumor suppressor p53 acts during total-body irradiation to promote lymphoma development. 58th Annual Meeting of the Radiation Research Society, San Juan, Puerto Rico, September 30 – October 3, 2012." Oct-2012</p>

Awards	Rodrigues AE. "NC Health Physics Society Student Paper Competition- First Prize for: Rodrigues AE, Nguyen G, Li Y, Das SK, Kirsch DG, Yoshizumi T. Dose verification in small animal image guided radiation therapy: A dose comparison between TG-61 based look-up table and MOSFET method for various collimator sizes. North Carolina Health Physics Society 2012 Spring Meeting, Raleigh, NC, March 15-16, 2012." Mar-2012
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