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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:			
Research Impact/Earth Benefits:	<p>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.</p> <p>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.</p> <p>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.</p>		

Task Progress:	<p>In our third year of funding, the Duke NASA Specialized Center of Research (NSCOR) continued to perform the experiments proposed in our application. We have developed two robust models of radiation-induced lung cancer, which we are currently using to determine the effect of space radiation exposure on lung cancer risk. Two members of the Duke NSCOR presented at the Heavy Ion in Therapy and Space Radiation Symposium in Chiba, Japan from May 15-18, 2013. One of the graduate students from the Duke NSCOR attended the 2013 NASA Space Radiation Summer School from June 3-21, 2013. On September 10, 2013, we held an internal advisory meeting with Duke University experts on radiation and lung biology. Through these activities and from our research projects, members of the Duke NSCOR have gained new information about the effects of space radiation on normal lung tissue and lung cancer development.</p> <p>Project 1. The role of the tumor suppressor p53 in space radiation-induced lung cancer. David Kirsch, M.D., Ph.D., Lead</p> <p>We 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 proposed to develop a model of radiation-induced small cell lung cancer (Aim 3).</p> <p>For Aim 1, we completed irradiation and analysis of lung tumor development in KrasLA1 mice predisposed to lung cancer bearing normal levels of p53 or an extra copy of p53. We observed that p53 suppresses lung tumor initiation in the absence of radiation, but that an extra copy of p53 does not affect the proliferation of low grade lung tumors or the expression of pERK, which is a negative prognostic marker. Exposure to neither terrestrial radiation nor space radiation impacted lung tumor initiation in our model. However, our results suggest that space radiation may increase the grade of lung tumors.</p> <p>For Aim 2, we have validated an in vivo knockdown system that enables temporal regulation of p53 expression in the lungs of mice. We plan to use this system in combination with the model of radiation-induced lung cancer that we have developed in Aim 3 to decrease p53 expression temporarily during radiation exposure or permanently during and following radiation exposure to investigate the timing of p53-mediated tumor suppression.</p> <p>For Aim 3, we confirmed that exposure to terrestrial and space radiation accelerates lung tumor formation in a genetically engineered mouse model of small cell lung cancer and adenocarcinoma. This model will be valuable for determining the relative biological effectiveness with which terrestrial and space radiation cause lung cancer to develop. In the future, we plan to expose these mice to varying doses of terrestrial and space radiation to determine whether space radiation is more effective at causing lung cancer.</p> <p>Project 2. The role of cell of origin in space radiation-induced lung cancer. Mark Onaitis, M.D., Lead</p> <p>We 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 600 MeV/n 56Fe (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).</p> <p>For Aim 1, we have now irradiated 29 CC10-CreER; Isl K-RasG12D mice and have 29 CC10-CreER; Isl K-RasG12D controls that were sham irradiated and the lungs analyzed 8 weeks post irradiation. Preliminary results suggest that HZE radiation may increase tumor burden, but the results are not yet statistically significant (p=0.089). We will continue to irradiate more cohorts of these mice in the next year to increase our power. Additionally, for comparison of 600 MeV/n 56Fe to terrestrial forms of radiation, we have so far exposed 13 CC10-CreER; Isl K-RasG12D mice to 320 kVp X-rays at Duke University. Analysis of tumors formed from X-ray exposed mice is ongoing.</p> <p>For Aim 2, we generated K5-CreER; Isl K-RasG12D mice and treated them with tamoxifen. Unfortunately, these mice quickly developed tumors in the forestomach and lip. Therefore, we have not been able to characterize the impact of HZE radiation in this model.</p> <p>For Aim 3, we have now radiated 14 SPC-CreER; Isl K-RasG12D mice and have 6 SPC-CreER; Isl K-RasG12D mice that were sham irradiated as controls. The mice have been sacrificed and the lungs fixed. Unfortunately, we found that this model was leaky in that many of the mice developed confluent tumors in the lung even before radiation exposure. Therefore, we have not been able to characterize the impact of HZE radiation in this model.</p> <p>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; NF1lox/flox; Ink4A/Arf flox/flox mice in order to assess the effects of radiation in a less penetrant model.</p> <p>Project 3. Effects of space radiation and p53 signaling on lung progenitor cells. Barry Stripp, Ph.D., Lead</p> <p>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.</p> <p>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. We are currently analyzing the results from the Spring 2013 BNL run, where we exposed mice to HZE and then exposed them to ozone upon return to Duke. 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 quality of radiation, on epithelial progenitor cells will be amplified by environmental triggers that cause epithelial cell injury.</p> <p>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.</p> <p>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 fall 2013 and spring 2014. We will be looking at in vivo clonal expansion following HZE in fall 2013 and are currently breeding mice to study in vitro colony forming efficiency for spring 2014.</p> <p>Core A: Administrative Core. David Kirsch, M.D., Ph.D., Lead. Duke NSCOR Administrators: Michelle Cooley, Erin Dillard (Jan-August), Lisa Hall (September to present), Marcia Painter</p> <p>The Administrative Core (Core A) provides overall management of the NSCOR award by ensuring that projects make satisfactory progress. During the third year of funding, the Administrative Core has monitored project progress by conducting Duke NSCOR meetings once to twice a month, 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 2013 in order to expose mice to 56Fe ions. Travel arrangements were also made for the annual Radiation Research Society Meeting. Moreover, the Administrative Core arranged travel to the day-long meeting in Arlington, VA for the NSCOR Mid-Term Review.</p> <p>Duke NSCOR administrators served as liaisons between the project groups to guide BNL and Duke training and credentialing of new investigators, ensure timely and accurate submission and renewal of IACUC protocols, NSCOR progress reports as well application for the NSRL Beam Time Request for 2014. Core A provided budget oversight for the Duke NSCOR. Erin Dillard monitored project expenditures. Ms. Dillard met monthly with Dr. Kirsch to review spending and fiscal matters for each NSCOR project and Core. Marcia Painter assisted with the financial accounting for the Duke NSCOR.</p> <p>Core B: Physics Core. Terry Yoshizumi, Ph.D., Lead</p> <p>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 provided quality control for radiation exposure experiments. Members of the physics core participate and present physics reports at regularly-scheduled NSCOR meetings. The Core ensures the timely incorporation of new dosimetry technology to provide state-of-the-art dosimetry support.</p> <p>Forthcoming publications:</p> <ol style="list-style-type: none"> <li>1. Stanton IN, Belley MD, Nguyen G, Rodrigues A, Li Y, Kirsch DG, Yoshizumi TT, and Therien MJ. Europium-Doped Yttrium Oxide Nano-Scintillators That Display a Linear Emission Intensity to X-Ray Radiation Flux; Integration into a Fiber-Optic Dosimeter Prototype. Analytical Chemistry 2013 (under review).</li> <li>2. Belley MD, Wang C, Nguyen G, Gunasingha R, Chao NJ, Chen BJ, Dewhirst MW, Yoshizumi TT. Towards an Organ Based Dose Prescription Method for the Improved Accuracy of Murine Dose in Orthovoltage X-ray Irradiators. Medical Physics 2013 (under review).</li> </ol> <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>
	<p>Bibliography Type: Description: (Last Updated: 03/11/2021)</p>
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	<p>Onaitis MW. "The Duke Lung Cancer NSCOR: Mouse Models." HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013.</p> <p>HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. Session 2: Cancer Risk, , May-2013</p>
	<p>Farin AM, Manzo ND, Terry KL, Stripp BR. "Evidence for Direct and Non-target Effects of Ionizing Radiation on the Clonal Behavior of Lung Epithelial Progenitor Cells." Keystone Symposia: Lung Development, Cancer and Disease, Taos, New Mexico, February 4-10, 2013.</p> <p>Keystone Symposia: Lung Development, Cancer and Disease, Taos, New Mexico, February 4-10, 2013. , Feb-2013</p>
	<p>Wang C, Chao N, Dewhirst M, Leon P, Yoshizumi T. "Quality assurance of biological x-ray irradiators: measurement of the Beam Quality Index (BQI)." 59th Annual Meeting of the Radiation Research Society, New Orleans, LA, September 14-18, 2013.</p> <p>Proceedings of 59th Annual Meeting of the Radiation Research Society, New Orleans, LA, September 14-18, 2013. Presentation number: PS6-41.</p> <p><a href="http://www.abstractsonline.com/Plan/ViewAbstract.aspx?skcye=33a6dc9-138c-4696-876c-35bbb907a8d6&amp;cKey=876da85c-5c96-46b8-6794-dc13c679c6cb&amp;mKey=f11c994cc-9545-4dc7-8580-d74360f68373">http://www.abstractsonline.com/Plan/ViewAbstract.aspx?skcye=33a6dc9-138c-4696-876c-35bbb907a8d6&amp;cKey=876da85c-5c96-46b8-6794-dc13c679c6cb&amp;mKey=f11c994cc-9545-4dc7-8580-d74360f68373</a> ; accessed 11/4/13, , Sep-2013</p>
	<p>Wang C, Yoshizumi T. "Assessment of Timer Error of a Small Animal X-Ray Irradiator: Derivation of the Ramp-up Exposure and Stable Exposure Rate." 46th Mid Year Health Physics Society, Scottsdale, Arizona, 27-30 January 2013.</p> <p>Mid Year Health Physics Society, Scottsdale, Arizona, 27-30 January 2013. Final Program, p. 35. <a href="http://hps.org/documents/2013_hps_midyear_meeting_final_program.pdf">http://hps.org/documents/2013_hps_midyear_meeting_final_program.pdf</a>, Jan-2013</p>

Abstracts for Journals and Proceedings	Stanton IN, Belley MD, Chang XS, Yoshizumi TT, Therien MJ. "A sub-millimeter, nano-material based fiber-optic device for in/ex vivo radiation dosimetry; linear accelerator x-ray and electron beam validation." Joint Workshop: Technology for Innovation in Radiation Oncology, National Institutes of Health (NIH), Bethesda, MD, . June 13-14, 2013. Joint Workshop: Technology for Innovation in Radiation Oncology, National Institutes of Health (NIH), Bethesda, MD, . June 13-14, 2013. , Jun-2013
Abstracts for Journals and Proceedings	Belley MD, Cornwall-Brady MR, Burkhart M, Dewhirst MW, Yoshizumi TT, Down JD. "Regional Microdosimetric Variations in Bone Marrow for Photon Irradiation at Different Energies." 59th Annual Meeting of the Radiation Research Society, New Orleans, LA, September 14-18, 2013. Proceedings of 59th Annual Meeting of the Radiation Research Society, New Orleans, LA, September 14-18, 2013. Presentation number: PS7-28. <a href="http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=b9997513-7168-467e-a7bd-6214b96cb56e&amp;cKey=38dae7c7-abb47-45d9-a4f3-1ab9bdcdd06&amp;mKey=01e994ce-9545-4ec7-8580-d74360fa8373">http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=b9997513-7168-467e-a7bd-6214b96cb56e&amp;cKey=38dae7c7-abb47-45d9-a4f3-1ab9bdcdd06&amp;mKey=01e994ce-9545-4ec7-8580-d74360fa8373</a> ; accessed 11/4/13. , Sep-2013
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