FY 2014 Task Last Updated	: FY 10/31/2013
Kirsch, David M.D., Ph.D.	
Duke NSCOR: Lung Cancer Risk from HZE Ions	
Human Research	
HUMAN RESEARCH	
HUMAN RESEARCHRadiation health	
TechPort:	No
(1) SR:Space Radiation	
None	
None	
None	
None	
david kirsch@duke.edu Fax	: FY
UNIVERSITY Phone	: 919-681-8586
Duke University	
450 Research Dr	
Box 91006, LSRC Bldg. Room B230	
Durham State	: NC
27710-0001 Congressional District	: 1
Ground Solicitation / Funding Source	: 2010 Space Radiation NSCOR/Virtual NSCOR NNJ10ZSA002N
01/01/2011 End Date	: 12/31/2015
3 No. of PhD Degrees	: 1
4 No. of Master' Degrees	: 0
0 No. of Bachelor's Degrees	: 0
0 Monitoring Center	: NASA JSC
Simonsen, Lisa Contact Phone	:
lisa c simonsen@nasa.goy	
Bloom, Rochelle Ph.D. (Duke University) Yoshizumi, Terry Ph.D. (Duke University) Onaitis, Mark M.D. (Duke University) Stripp, Barry (Cedars-Sinai)	
NNX11AC60G	
The goal of the Duke NSCOR is to understand mechanisms of high charge and energy (HZE) ion-induced biology, lung cancer development, lung injury and repair, radiation dosimetry, and education. We will con cells, and analyses of lung cancers induced by HZE nuclei to dissect mechanisms of HZE ion-induced lung cancer development after HZE ion exposure, identify mechanisms of cellular response to HZE ions in diffi the most commonly mutated gene in human lung cancer, regulates HZE ion-induced carcinogenesis in the better models for HZE ion carcinogenic risk assessment for individual astronauts and novel approaches to	lung cancer. To accomplish this goal, the Duke NSCOR has brought together experts in radiation bibne sophisticated mouse genetics, in vivo lineage tracing, ex vivo isolation of lung epithelial progenitor s cancer. We will integrate 3 separate projects to understand how the cell of origin influences lung rent progenitor populations in the lung, and define how and when the p53 tumor suppressor, which is lung. We anticipate that our hypothesis-based research will ultimately lead to the development of prevent HZE ion-induced lung cancer through biological countermeasures.
Lung cancer causes more than one million cancer deaths each year and is the leading cause of cancer death presents a major unmet need. While many lung cancer cases are preventable as they are due to smoking, it factors including exposure to radiation from radio gas have been implicated, no clear-cut cause has emerg never smokers demonstrate different mutation patterns and frequencies when compared to cancers arising lung cancers in never smokers respond differently to targeted cancer therapies. Further research into the m prevention and treatment of lung cancer can be developed. By studying the mechanisms of lung cancer into novel approaches for the prevention and treatment of lung cancer. Lung cancer can be divided into two major forms: small-cell lung cancer and non-small cell lung cancer here provention and and lead lung cancer and be developed. By studying the mechanisms of lung cancer in bombs in Japan. Similarly, both types of lung cancer arise in smokers. Cancers arising in never smokers p type of non-small cell lung cancer. Recently, genomic sequencing technology has been utilized to identify radiation. We are also studying mice with an additional copy of p33 or inducible p33 suppression to invest after space radiation exposure. In addition, we are developing a mouse model of radiation-induced small- clung cancers develop, and how Kras and p33 mutation promote lung cancers. As we answer these question how lung cancer develops on earth, but will also provide new insights into preventing and treating lung can rak eky components of many diseases in people including emphysema, asthma, and lung fibrosis. Furthere region (e.g. breast cancer) undergo lung tissue remodeling and declining lung function that is directly relat radiation we these injured lung cells are repaired, we anticipate that this knowledge may also lead to employed to moderate the effects of radiotherapy on lung tissue remodeling. This information may ultimat the improvement of public health.	worldwide. Despite advances in the detection and treatment of lung cancer, lung cancer prevention is estimated that 25% of lung cancer cases worldwide involve never smokers. Though multiple risk de to explain the relatively high incidence of lung cancer in never smokers. Ing cancers arising in in smokers, suggesting that lung cancer arising in never smokers. Income cancers arising in in smokers, suggesting that lung cancer arising in never smokers. Income cancers arising in in smokers, suggesting that lung cancer arising in never smokers is a clinically distinct disease. Indeed, echanism of lung cancer development in never smokers is needed so that more successful strategies for itation and development, the Duke NSCOR is generating new knowledge that can be used to develop both non-small cell lung cancers and small cell lung cancers have developed in survivors of the atomic efferentially develop in the distal airways and are of the adenocarcinoma histological subtype, which is a the most commonly mutated genes in adenocarcinomas. Based on this analysis, the two most e oncogene Kras. The Duke NSCOR is sutilizing sophisticated genetically engineered mouse models to in Kras in different kinds of cells in the lung affect lung cancer development with exposure to space giate the timing and mechanism by which p53 suppresses Kras-driven lung adnocarcinoma progression ell lung cancer. Together these studies will provide new insights into how lung cancer forms, where susing experiments with space radiation, we expect that our results will not only help us understand acer. jury and repair after exposure to either terrestrial or space radiation. Injury and inflammation of the lung acer. diverts receiving adiotherapy for either primary lung cancer or other neolsams of the thoracic ed to the dose and location of radiation exposure. By exploring which lung cells are injured by space a better understanding of how lung diseases besides cancer develop and strategies that may be ely be used to develop novel approaches for the pre
	Sinch. Duröl M.D., Ph.D.   Sinch. Duröl M.D., Ph.D.   Sinch. Duröl M.D., Ph.D.   Maran Research   UMAN RESEARCH   RMAN RESEARCH   Since   Sin

	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 onormal lung tissue and lung cancer development. Project 1. The role of the tumor suppressor p53 in space radiation-induced lung cancer. David Kirsch, M.D., Ph.D., Lead We proposed to study the role and timing of the tumor suppressor p53 in radiation-induced lung cancer using mice with an extra conv 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).
	For Anit 1, we compreted inflation in a langest of lange unior development in KrassLAT indee prediposed to lang cancel ocaring normal reversion pp 50 an extra coty of p35. We observed that p35 suppresses lange tumor initiation in the absence of radiation, but that are extra coty of p35 does not affect the proliferation of low grade lange tumors or the expression of pERK, which is a negative prognosite marker. Exposure to neither terrestrial radiation nor space radiation impacted lange tumor initiation in une model. However, our results suggest that space radiation may increase the grade of lang tumors.
	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 enacer 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.
	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.
	We proposed to study the cell of origin in opport Rankof 12D-induced lung clamer in many charge radiation. Our aims include studying the effects of 600 MeV/n 56Fe (HZE radiation) on mice in which KP proc 12D is include lung clamerated in differential lung clame of the lung clame clamerated and the studying the effects of 600 MeV/n 56Fe (HZE radiation) on mice in which KP proc 12D is include lung clamerated in differential lung clame of the lung clamerated and the studying the effects of 600 MeV/n 56Fe (HZE radiation) on mice in which KP proc 12D is include lung clamerated in differential lung clamerated and the lung clamerated and the studying the effects of 600 MeV/n 56Fe (HZE radiation) on mice in which KP proc 12D is include lung clamerated in differential lung clamerated and the lung clamerated and the studying the effects of 600 MeV/n 56Fe (HZE radiation) on mice in which KP proc 12D is include lung clamerated and the lung clamerated and
	For Aim 1, we have now irradiated 29 CC10-CreER; IsI K-RasG12D mice and have 29 CC10-CreER; IsI K-RasG12D controls that were sham irradiated and the lungs analyzed 8 weeks post irradiation. Preliminary results suggest that HZE radiation may increase tumor but the results are not yet statistically significant ( <b>p</b> =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; IsI K-RasG12D mice to 320 kVp X-rays at Duke University.
	Analysis of tumors formed from X-ray exposed mice is ongoing. For Aim 2, we generated K5-CreER; Isl K-RasG12D mice 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.
	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.
	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, NF116x/Ilox; Ink4A/Arf flox/Ilox mice in order to assess the effects of radiation in a less pneutrant model.
	Project 5. Effects of space radiation and p55 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
Task Progress:	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 vitor. An important feature of our in vitor model used to assess the clonogenic behavior or 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.
	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 MeVn 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 radiation dependent within the epithelial ord in virus. 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 envirus in virus.
	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 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 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.
	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
	The National State of Conce (Conce Net Conce Net Conce Net Conce Net Conce Net Net Conce Net Net Net Net Net Net Net Net Net Ne
	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.
	Core B: rhysics Core. 1erry 1 osnizum, 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 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 ensured.
	Fortheoming publications:
	<ol> <li>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>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</li> </ol>
	Orthovoltage X-ray Irradiators. Medical Physics 2013 (under review). Core C: Education Core. Rochelle Schwartz-Bloom. Ph.D., Lead
	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 "wirtual" sciencitist (the P1s 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.
Bibliography Type:	Description: (Last Updated: 10/09/2024)
Abstracts for Journals and Proceedings	Moding EJ, Min HD, Lee CL, Williams N, Woodlief L, Ma Y, Kirsch DG. "Dissecting the Function of p53 in Lung Carcinogenesis Following Fractionated Exposure to X-rays and 56Fe." HITSRS2013Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. HITSRS2013Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. Session 2: Cancer Risk, Poster-02-13. , May-2013
Abstracts for Journals and Proceedings	Onaitis MW. "The Duke Lung Cancer NSCOR: Mouse Models." HITSRS2013Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. HITSRS2013Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. Session 2: Cancer Risk., May-2013
Abstracts for Journals and Proceedings	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. Keystone Symposia: Lung Development, Cancer and Disease, Taos, New Mexico, February 4-10, 2013. , Feb-2013
Abstracts for Journals and Proceedings	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. Proceedings of 59th Annual Meeting of the Radiation Research Society, New Orleans, LA, September 14-18, 2013. Presentation number: PS6-41. http://www.astrnetsentine.com/Plant/lewAbstract.acpr/3sKy=33a6cfuel-138c-4606-876e-35bbb007a8d6&cKg=8266u85c-5c96-46b8-b704-dc13c679e4cb&mKg=01c904ce-9545-4ec7-8580-d74360fa8373 : accessed 11/41/3 Sper-2013
Abstracts for Journals and Proceedings	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. Mid Year Health Physics Society, Scottsdale, Arizona, 27-30 January 2013. Final Program, p. 35. http://hps.org/documents/2013.hps_mid/year_meeting_final_program.pdf, Jan-2013

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.
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. http://www.abstractsonice.com/Plant/View/Abstract.aspx?sKey=b0907513.7168.4671e-a7kid-6514b96cb56e&cKey=38due767-abd74540-adTL-1abf9bcded06&mKey=01c994ce-9545_4ee7.8580-d74360fa8373 ; accessed 11/4/13. , Sep-2013
Articles in Peer-reviewed Journals	Rankine LJ, Newton J, Bache ST, Das SK, Adamovics J, Kirsch DG, Oldham M. "Investigating end-to-end accuracy of image guided radiation treatment delivery using a micro-irradiator." Phys Med Biol. 2013 Nov 7:58(21):7791-801. Epub 2013 Oct 18. http://dx.doi.org/10.1088/0031-9155/58/21/7791. PubMed PMID: 24140983, Nov-2013