

Fiscal Year:	FY 2017	Task Last Updated:	FY 06/26/2017
PI Name:	Brenner, David Ph.D.		
Project Title:	Physical and Biological Modulators of Space Radiation Carcinogenesis: Mechanistically- Based Model Development for Space Radiation Risk Assessment		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:	TechPort:	Yes	
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:	djb3@cumc.columbia.edu	Fax:	FY
PI Organization Type:	UNIVERSITY	Phone:	(212) 305-5660
Organization Name:	Columbia University		
PI Address 1:	Center for Radiological Research		
PI Address 2:	630 W. 168th St.		
PI Web Page:			
City:	New York	State:	NY
Zip Code:	10032	Congressional District:	13
Comments:			
Project Type:	GROUND	Solicitation / Funding Source:	Directed Research
Start Date:	08/26/2016	End Date:	08/25/2020
No. of Post Docs:	1	No. of PhD Degrees:	
No. of PhD Candidates:		No. of Master' Degrees:	
No. of Master's Candidates:		No. of Bachelor's Degrees:	
No. of Bachelor's Candidates:		Monitoring Center:	NASA JSC
Contact Monitor:	Simonsen, Lisa	Contact Phone:	
Contact Email:	lisa.c.simonsen@nasa.gov		
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	June 2017 report: n/a		
COI Name (Institution):	Hei, Tom Ph.D. (Columbia University Center for Radiological Research)		
Grant/Contract No.:	NNX16AR81A		
Performance Goal No.:			
Performance Goal Text:			
Task Description:	<p>This project is designed to use state-of-the-art mechanistic modeling of the experimental data from NASA Specialized Center of Research (NSCOR) programs and other available data as a basis to generate HZE (high energy particle) related cancer risk and uncertainty estimates in humans. There are four components: First, development of practical mechanistically motivated models, emphasizing the significance of individual radiation sensitivity. Second, based on model-based analysis of our and other NSCOR experimental data, estimate site-specific and consensus quality functions for HZE ions. Third, generate realistic uncertainty estimates for these estimates. Finally, our results and uncertainties will be critically compared with the current NASA projections and uncertainties.</p> <p>In order to answer the critical question of how to reliably estimate heavy ion-induced cancer risks in astronauts embarking on long-distance space exploration missions such as a flight to Mars, we are developing a mechanistically-motivated mathematical model that can predict radiogenic carcinogenesis as function of dose and dose</p>		

	<p>rate using both targeted effect (TE) and non-targeted effect (NTE) contributions. Importantly, such models are needed to predict low dose rate risks based on data at higher dose rates because the very low heavy ion dose rates relevant for space missions are difficult to achieve in terrestrial experiments. Our goal is to calibrate the carcinogenesis model using available human and animal data and to generate scaling factors such as the recently proposed radiation effects ratio (RER), which compares carcinogenic effectiveness of heavy ions and gamma rays at the dose of interest. The scaling factors would then be used to estimate human heavy ion-induced cancer risks, based on human gamma-ray-induced risks. An important focus of our work is generation of realistic uncertainties for model parameters and predictions, which ultimately translate into realistic uncertainties on astronaut risk estimates.</p>
Rationale for HRP Directed Research:	<p>This research is directed because it contains highly constrained research, which requires focused and constrained data gathering and analysis that is more appropriately obtained through a non-competitive proposal. The timing of this work supports current efforts by the Risk Assessment project to quantify uncertainties due to radiation quality factors and use of the dose and dose-rate effectiveness factor (DDREF). Work is highly synergistic with on-going work in the Furnace NSCOR as well as in assessing tissue-specific quality factors and DDREF specific to GI (gastrointestinal) cancers. The study will integrate data from multiple NSCORs (NASA Specialized Centers of Research).</p>
Research Impact/Earth Benefits:	<p>Cancer is the second leading cause of death in the United States, exceeded only by heart disease (http://www.cdc.gov/). One of every four deaths in the United States is due to cancer. Almost 1.7 million new cancer cases are estimated to occur in the US in 2017, and over 600,000 people are estimated to die from cancer during this year (http://www.seer.cancer.gov). Considering this high frequency of cancer in the American population, even a small increase by space radiation would have a major impact on planning and design of future long-range (e.g., interplanetary) manned space missions. Reliable estimation of the cancer risks resulting from space radiation is, therefore, very important for space exploration.</p>
Task Progress:	<p>Heavy ion bombardment can be much more carcinogenic than exposure to sparsely-ionizing radiation such as gamma-rays, and therefore heavy-ion induced carcinogenesis is an important challenge for long-distance human space exploration such as manned missions to Mars. Because the very low heavy ion dose rates relevant for space missions are difficult to achieve in terrestrial experiments due to constraints on time and resources, mechanistically-motivated mathematical models are needed to predict low dose rate risks relevant for space missions based on data at higher dose rates.</p> <p>Here we present such a model, which quantifies both TE and NTE contributions. NTE can dominate at low doses/dose rates encountered in space. To estimate an important model parameter – the dose rate at which NTE are 50% activated – we fitted the model to lung carcinogenesis data in radon-exposed miners, which are very useful for heavy ion risk estimation because they contain information on human carcinogenesis induced by densely-ionizing radiation at doses and exposure durations that overlap the range expected during space exploration missions. To calibrate the model for highly-energetic space-relevant heavy ions (C, Si, Fe) we used data from mouse experiments. We then generated model-based radiation effects ratios (RER) values, which compare carcinogenic effectiveness of heavy ions and gamma rays, at doses/dose rates expected during space exploration. The RER is a new metric, conceptually similar to a relative risk, which is useful for risk scaling when dose-effect relationships are complex. We used RER values to scale human gamma ray-induced cancer risks to estimate heavy ion cancer risks in astronauts.</p> <p>We sought to address the following question: is the carcinogenic effectiveness of heavy ions at the very low dose rates encountered in space substantially different from that at the high dose rates used in terrestrial experiments? For example, is there a direct dose rate effect (i.e., reduction in carcinogenic effectiveness at low dose rates), or an inverse one (i.e., a possible increase in carcinogenic effectiveness)? Providing quantitative answers to such questions by generating RER and risk estimates and uncertainties is important for the planning and design of new terrestrial experiments and – ultimately – manned missions in space.</p> <p>Our mechanistically-motivated model of densely-ionizing radiation carcinogenesis was able to describe the shapes of the dependences of lung cancer risk in radon-exposed miners on dose rate (exposure duration) and dose. Consistently with the data, the model predicted an inverse dose rate effect – an increase in cancer risk from a given densely ionizing radiation dose when this dose was delivered at a lower dose rate, i.e., over a longer duration.</p> <p>The model-based interpretation of this phenomenon is as follows. When the exposure is protracted over a longer period, the duration of NTE signal activation is prolonged and NTE-driven carcinogenesis therefore increases. In other words, over a range of doses/dose rates that are sufficient to cause nearly maximal susceptible cell activation, there is an inverse dose rate effect for cancer risk from NTE. At very low doses, however, ionizing particle tracks are too sparse and occur too rarely to maintain high NTE signal levels because NTE signals induced by one track have time to decay away before the next track traverses the target area. Under such conditions reducing the dose rate causes a direct dose rate effect – NTE-driven carcinogenesis at a given dose decreases with decreasing dose rate.</p> <p>The model parameter responsible for the dose rate dependence of the NTE contribution to cancer risks is the dose rate at which NTE signal levels reach 50% of maximal. The fit to the radon-exposed miner data suggested that this parameter is small. Consequently, substantial NTE activation was predicted at dose rates relevant for a mission to Mars. The combination of dose and dose rate expected for a Mars mission lies close to the transition from direct to inverse dose rate effects, according to model predictions. For such exposure scenarios, the model predicted a small and not statistically-significant inverse dose rate effect, relative to an acute exposure with the same total dose.</p> <p>Compared with gamma-rays, the estimated carcinogenic effectiveness (RER) of heavy ions at space-relevant doses and dose rates was ~33, with considerable uncertainties. This large RER value and uncertainties, and their dependence on dose rate, were caused by NTE. If NTE terms were absent from the model, RER would be equal to the ratio of TE dose response slopes for ions vs gamma-rays, which would be approximately 1.7 in this case, and there would be no dependence of RER on dose rate. When the RER was used to scale human gamma-ray risks to heavy ions, the estimated heavy ion-induced sex-averaged colon cancer risk for a 40-year-old astronaut was ~2.8%, with considerable uncertainties. The uncertainties are fundamentally caused by paucity of information about NTE response at very low dose rates.</p> <p>Important components of the current modeling efforts include the following: (1) The radiation carcinogenesis model</p>

included both TE and NTE. The latter can be particularly important at the low doses and dose rates of densely-ionizing radiation encountered during space exploration. (2) The model was able to fit the shapes of dose/dose rate dependencies observed in a valuable data set of human cancer risks after protracted densely-ionizing radiation exposure – lung cancers in radon-exposed miners. (3) Carcinogenesis data from animal experiments using space-relevant heavy ions (C, Si, Fe) at appropriate energies were also used to calibrate the model. (4) Monte Carlo simulations and error propagation were used to realistically approximate the errors associated with model parameters and other output. (5) Model predictions were used to scale human gamma-ray-induced cancer risks to heavy ions at doses/dose rates expected during space missions using a recently-developed metric: radiation effects ratio (RER).

Although several simplifying assumptions were used in the modeling, the resulting predictions were consistent with other data sets that were not used in the current analysis: (1) No strong dose rate effects were predicted. This is consistent with animal experimental data using heavy ions at tested dose rates. (2) NTE signals were predicted to be long-lasting, with decay rates on the order of months-years. This is consistent with data that show long-term consequences of irradiation such as chronic inflammation, oxidative stress, and genomic instability.

Our modeling approach and its application to human and animal radiation carcinogenesis data quantify and help to explain the complex effects of dose rate on the dose responses for densely-ionizing radiation such as galactic cosmic rays. Whereas most cellular damage induced by sparsely-ionizing radiation such as gamma-rays is rapidly repaired, leading to direct dose rate effects, damage induced by densely-ionizing radiation is more difficult to repair and often induces NTE. Persistent activation of NTE signaling during/after irradiation can result in inverse dose rate effects.

Our results suggest that the carcinogenic effectiveness of heavy ions at space-relevant dose rates and at high dose rates used in terrestrial experiments may be comparable. The model predicts a small inverse dose rate effect, but the uncertainties overlap a scenario with no dose rate effect.

Bibliography Type:	Description: (Last Updated: 06/28/2023)
Abstracts for Journals and Proceedings	Shuryak I, Fornace AJ, Datta K, Suman S, Kumar S, Sachs RK, Brenner DJ. "Scaling human cancer risks from low LET to high LET when dose-effect relationships are complex." Presented at 2017 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 23-26, 2017. 2017 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 23-26, 2017. , Jan-2017
Articles in Peer-reviewed Journals	Shuryak I, Fornace AJ Jr, Datta K, Suman S, Kumar S, Sachs RK, Brenner DJ. "Scaling human cancer risks from low LET to high LET when dose-effect relationships are complex." Radiat Res. 2017 Apr;187(4):476-82. Epub 2017 Feb 20. https://doi.org/10.1667/RR009CC.1 ; PubMed PMID: 28218889 , Apr-2017