Fiscal Year:	FY 2018	**Task Last Updated:**	FY 06/25/2018
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Project Title:	Physical and Biological Modulators of Space Radiation Carcinogenesis: Mechanistically- Based Model Development for Space Radiation Risk Assessment		
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Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:		**TechPort:**	Yes
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Comments:			
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Task Description:	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. 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		

	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.
Rationale for HRP Directed Research:	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 Fornace NSCOR as well as in assessing tissue-specific quality factors and DDREF specific to GI (gastronintestinal) cancers. The study will integrate data from multiple NSCORs (NASA Specialized Centers of Research).
Research Impact/Earth Benefits:	Cancer is the second leading cause of death in the United States, exceeded only by heart disease (https://). It accounts for one of every four deaths in the United States. More than 1.7 million new cancer cases and over 600,000 cancer-related deaths are predicted to occur in the US in 2018 (https://). Considering this high frequency and lethality of cancer, even a small increase by space radiation would have a major impact on planning and design of future interplanetary manned space missions. Accurate estimation of space radiation-related cancer risks is, therefore, very important for NASA mission planning.
Task Progress:	Heavy ion bombardment can be much more carcinogenic per unit dose 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. Mechanistically-motivated mathematical models are needed to predict low dose rate risks relevant for space missions based on data at higher dose rates, which are more easily achievable in terrestrial experiments. We developed such a model, which quantifies targeted and non-targeted radiation effects. An important goal for using the model was to estimate dose rate effects (DRE) for heavy ion exposures at doses and exposure times relevant for a Mars mission, relative to much shorter (effectively acute) exposure times at the same dose. For tractable model development, we assumed that traversal of a cell by densely ionizing radiation such as the core of a heavy ion track can cause the release of NTE signals. Under continuous irradiation, such as during a space mission, the signal concentration is expected to quickly (in much less time than the duration of exposure) reach a steady-state equilibrium value in the target organ(s), which is proportional to the radiation dose rate. This concentration determines the equilibrium probability for cells susceptible to NTE signals to enter into and remain in an “activated” state, e.g., a state of perturbed signaling, altered gene expression, and/or oxidative stress. We assume, for simplicity, that two components contribute to the excess cancer yield due to NTE: (1) the effects of cell activation during irradiation, which occur over the irradiation time, and (2) the cumulative (integrated) effects of cell activation after irradiation is finished and NTE signals are decaying. We also assume that the TE contribution to the heavy ion-induced cancer risk is proportional to dose and independent of dose rate, and that cell killing effects (which are unlikely to be dramatic at doses relevant for space missions) of heavy ions are also dose rate independent. We fitted the model to lung carcinogenesis data in radon-exposed miners and rats. These data sets are valuable because they provide information on human and animal lung carcinogenesis induced by protracted exposure to densely ionizing radiation at doses and exposure durations that overlap the range expected during space exploration missions. In addition, radiation energy deposition patterns in cell nuclei in the bronchial epithelium are similar for radon and several types of space-relevant heavy ions such as iron. The model was able to describe the shapes of dose and dose rate dependencies observed in data sets of human and animal cancer risks after protracted densely ionizing radiation exposure. We generated model-based DRE estimates, relative to acute exposures, on heavy ion-induced carcinogenesis at doses/dose rates expected during a Mars mission. A small and not statistically-significant DRE was predicted for human data and for combined human and rat data. 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. Consequently, scaling factors for heavy ion carcinogenesis estimated from moderate/high dose rate experimental data may be applicable for scaling human gamma-ray-induced cancer risks to heavy ions at situations relevant for space exploration. However, animal experiments using multiple small dose fractions and/or very low dose rates of densely ionizing radiation are needed to reduce prediction uncertainties by better quantifying NTE responses at space-relevant dose rates.
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